Chapter 9
Sex Differences in Nicotine Reinforcement and Reward: Influences on the Persistence of Tobacco Smoking

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Introduction

Current treatments for smoking cessation show limited efficacy, despite the development of new medications, with none producing long-term quit rates of more than 30% in formal clinical trials (Piasecki & Baker, 2001). In an effort to improve cessation, research over the past decade has paid more attention to genetic or other individual differences in smoking persistence and response to treatments (e.g., pharmacogenetics; Munafo, Shields, Berrettini, Patterson, & Lerman, 2005). The focus of this chapter will be on differences in smoking persistence and response to medication as a function of perhaps the most prominent of all individual differences, a smoker's sex. As will be discussed in detail, findings from our laboratory and elsewhere indicate that, compared to the smoking behavior of men, the smoking behavior of women is influenced less by nicotine and more by non-nicotine factors. These results have implications for clinical research and may help explain why women have greater difficulty quitting in general (e.g., Borrelli, Papandonatos, Spring, Hitsman, & Niaura, 2004; Fortmann & Killen, 1994; Scharf & Shiffman, 2004) and with nicotine replacement therapy in particular (Cepeda-Benito, Reynoso, & Erath, 2004; Perkins & Scott, in press Wetter, Kenford, Smith, Fiore, Jorenby, & Baker, 1999). They also suggest other directions for clinical research aimed at improving cessation outcome in women smokers.

Note that it is almost certainly the case that men and women do not differ on most effects of nicotine, such as its physiological, cognitive, or psychomotor effects (Benowitz & Hatsukami, 1998). Rather, the research literature indicates that men and women differ in sensitivity to a relatively specific but very important area of responses to nicotine, that of nicotine's reinforcing and rewarding effects. Reinforcement pertains to self-administration of the drug as assessed by several procedures (ad libitum, or ad lib, consumption, fixed or variable ratio schedule of

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reinforcement, progressive ratio, choice of active versus placebo substance, etc.). Reward is less precisely defined but refers to the hedonic value of the substance, typically assessed in humans via self-reported "liking," "satisfying," "good drug effects," etc. (Everitt & Robbins, 2005). (Animal studies necessarily employ behavioral indices such as conditioned place preference or perhaps intracranial self-stimulation; see Lerman, Perkins & Gould, in press).

By reinforcement and reward, we are *not* referring to craving, withdrawal, mood, or other characteristics of the drug user's subjective or behavioral state. The latter responses can be distinguished from the former in that the latter can be assessed in the absence of drug availability or indeed any history of drug use at all, while assessment of the former can only be done in the context of substance use. While craving, withdrawal, and mood may, or may not, relate to drug reinforcement and reward, they are certainly not the same thing as reinforcement or reward and should be kept distinct. Thus, while reliable sex differences in these various smoking-related subjective states may exist, such potential differences do not directly bear on the central thesis of this chapter, that men and women differ in the degree to which nicotine versus non-nicotine factors influence smoking reinforcement and reward.

Clinical Implications of Sex Differences in Factors Promoting Smoking Persistence

Identification of consistent sex differences in the factors that maintain smoking persistence or in responses to particular treatments has potentially important implications for clinical practice. First, if women have greater overall difficulty quitting smoking, this sex difference indicates the presence of a very large subpopulation of smokers (nearly half) requiring greater help to quit. Most controlled studies on a variety of treatments do tend to show poorer clinical outcome in women versus men attempting to quit (e.g., Borrelli et al., 2004; Fortmann & Killen, 1994; Scharf & Shiffman, 2004; Wetter et al., 1999). Examining population-based data on current versus former smokers over the age of 34, we observe that the "quit ratio," the ratio of former smokers to ever smokers, is lower in women versus men (55.2% versus 59.2%, respectively, based on 2002 national data presented in Rodu & Cole, 2007). This difference translates to about a million fewer women who have quit smoking, compared to the number one would expect if women quit at the same rate as men. Second, poorer response to certain treatments in women versus men would highlight the inadequacy of these treatments, further indicating a need for improved therapies. Moreover, sex differences in response to particular treatments may reveal important differences between men and women in basic mechanisms that maintain smoking and suggest new directions for research on the etiology of dependence as well as on treatment development.

Even if there were no sex differences in smoking persistence and treatment response, increases in quitting success among women due to improved treatments would arguably have greater public health benefit than the same degree of increase in quitting success among men. Smoking consistently produces greater risks in the

primary smoking-related illnesses among women than men, including lung cancer (International Early Lung Cancer Action Program Investigators, 2006), myocardial infarction (MI, or heart attack; Prescott, Hippe, Schnohr, Ole Hein, & Vestbo, 1998), and deterioration in lung function due to smoking (Dransfield, Davis, Gerald, & Bailey, 2006), perhaps explaining women's greater risk of chronic obstructive pulmonary disease (COPD). These diseases constitute the three most common causes of premature morbidity and mortality due to smoking, accounting for the vast majority of the 440,000 deaths annually in the US (Centers for Disease Control and Prevention, 2005). Furthermore, smoking in women induces health risks not observed in men, such as risks to fetal development in pregnant women who smoke, including infant mortality from several causes and decreased infant lung function (DiFranza, Aligne, & Weitzman, 2004). Maternal smoking, perhaps more than paternal smoking, is also associated with increased risk of the offspring becoming a smoker (Buka, Shenassa, & Niaura, 2003). Thus, developing treatments that improve the quit rates in women smokers would have a larger impact in reducing the total adverse health toll due to smoking than the same improvement in quit rates among men, although treatments that are more effective with all smokers are sorely needed.

Possible Sources of Sex Differences in Smoking Reinforcement

Before reviewing evidence of sex differences in smoking reinforcement and reward, it is instructive to consider the possible sources of such differences. For the most part, any consistent individual difference in drug response is likely due to pharmacokinetic or pharmacodynamic factors, although other sources of sex differences in drug response are possible.

Pharmacokinetic

A difference between groups in response to nicotine administration could be due to pharmacokinetic differences, such that one group has slower or faster absorption or clearance of the drug compared to others. Thus, a smaller reinforcing effect of nicotine in women versus men could be due to women simply having lower blood levels of the drug following administration of a given dose. Recent research does suggest that women may have faster clearance rates of nicotine than men, by about 10%, especially if they also use oral contraceptives (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006). However, this difference is unlikely to account for sex differences in the acutely reinforcing effects of nicotine intake for at least two reasons. First, the half-life of nicotine clearance is about 2 hours, while the reinforcing effects of nicotine are usually measured over briefer periods of time (e.g., minutes). Second, different nicotine blood levels between men and women following dose administration would result in different magnitudes of response on *all* measures of nicotine effects. So, in addition to lower reinforcing effects of nicotine, women would also demonstrate lower heart rate, psychomotor, mood, and all other responses to

nicotine. Such broad-based sex differences in effects of nicotine have not been seen in studies of controlled nicotine administration (e.g., Benowitz & Hatsukami, 1998; Perkins, Gerlach, Broge et al., 2001).

Pharmacodynamic

Differences in the reinforcing effects of nicotine could also be due to pharmacodynamic factors, or differences in tissue sensitivity to a given blood level of nicotine. Controlling for pharmacokinetic factors, people may differ in how sensitive their brain receptors, or other sites of drug action, are to the drug. Because different drug effects typically result from actions of the drug at different brain or body sites, differential sensitivity to nicotine between sites could explain the selective sex difference in sensitivity to nicotine's reinforcing and rewarding effects in the face of virtually no differences in other effects of nicotine, as noted previously. Differences in pharmacodynamic effects of drug are determined by manipulating the drug dose and keeping all other aspects the same (e.g., method of administration, expectations for drug). Considerable evidence, outlined later in this chapter, suggests that women are less sensitive than men to pharmacodynamic effects of nicotine related to reinforcement and reward.

Non-pharmacological

A third, frequently overlooked, explanation for individual differences in drug reinforcement could stem from differences in sensitivity to *non*-pharmacological factors involved in drug use. Drug use of all kinds involves behavioral rituals and accompanying environmental stimuli that can become conditioned to the pharmacological influences of the drug. In tobacco smoking, for example, pulling out a cigarette and lighting it is followed by the sight of a lit cigarette and the olfactory/taste sensations from inhaling the smoke. Such stimuli are often referred to as "cues", or discriminative stimuli for nicotine via cigarette smoking. Less obvious cues also include environmental contextual factors, such as familiar smoking settings (e.g., favorite bar, being with a smoking friend; see Conklin, 2006). Along with cues, which can be viewed as non-verbal information about drug availability, the non-pharmacological factors can include other aspects of drug use, including verbal information about drug availability (i.e., being told about the drug content of a substance) that elicits expectancies for certain drug effects (Perkins, Sayette, Conklin, & Caggiula, 2003).

Consequently, even if men and women did not differ in pharmacokinetic or pharmacodynamic factors, differential responsivity to the conditioned stimuli accompanying nicotine intake via smoking could result in sex differences in reinforcement and reward. Non-pharmacological aspects could include stimuli other than verbal or non-verbal information about drug availability, such as social modeling influences (e.g., watching someone else smoke) or unconditioned effects of substance use (e.g., smoke effects on peripheral sensations). Non-pharmacological influences are examined by manipulating those influences while keeping constant nicotine

dosing (i.e., pharmacodynamics). Less research has examined sex differences in non-pharmacological factors in tobacco smoking, but some research suggests that women are more sensitive than men to certain non-pharmacological effects of smoking (e.g., Perkins et al., 2001). Those findings will also be discussed.

Gender

Finally, a fourth potential explanation for sex differences in nicotine reinforcement and reward concerns the influence of "gender," or constraints on behavior due to cultural expectations about sex roles. Gender influences are likely responsible for the fact that tobacco use in a given society is almost always adopted first by men, then by women. Such influences are probably important in explaining why smoking prevalence remains much lower among women than men in most developing nations (Lopez, Collishaw, & Piha, 1994). However, virtually no controlled laboratory research has examined "gender" influences on smoking reinforcement and reward, and this chapter will therefore not address this possibility. It is worth noting that such influences may be indirectly examined by assessing cross-species consistency in nicotine's reinforcing effects, as sex differences observed in both humans and non-humans would suggest a lack of culturally-specific influences.

Reduced Sensitivity to Nicotine Reinforcement and Reward in Women Versus Men

Beginning in the mid-1980s, we conducted research on a wide variety of acute effects of nicotine per se, administered via nasal spray in order to mimic rapid uptake of nicotine as with tobacco inhalation but in more controlled fashion. We first examined the effects of nicotine on energy balance (resting metabolism, food intake, etc.) to understand the influence of nicotine on body weight regulation (see Perkins, 1993). We then explored the acute effects of nicotine on physiological, psychomotor, and self-reported mood responses to characterize acute and chronic tolerance to nicotine, believed to be a key feature of dependence (USDHHS, 1988). We routinely compared effects between men and women because of reports suggesting that women were *more* sensitive than men to nicotine (e.g., Silverstein, Feld, & Kozlowski, 1980; Grunberg, Winders, & Wewers, 1991). However, sex differences were almost never apparent in any of this research. Only when we began to study nicotine reinforcement and reward in the early 1990 s did we start to observe consistent and robust sex differences, with women less sensitive than men to manipulations of nicotine dose exposure, indicating reduced pharmacodynamic effects of nicotine. This research on reinforcement and reward generally followed two approaches in assessing sensitivity to nicotine: (1) the direct effects of nicotine on self-administration behavior and reward ratings, and (2) the influence of

nicotine dose pre-treatment on subsequent self-administration of nicotine or smoking behavior.

Direct Effects of Nicotine on Self-administration Behavior and Reward Ratings

Sex differences in nicotine reinforcement are perhaps most directly shown by differences in the degree to which nicotine influences self-administration behavior. Since the 1980s, research has shown that humans will self-administer nicotine via novel forms (i.e., other than tobacco smoking), such as via intravenous infusion (Henningfield & Goldberg, 1983). These findings contributed to the view that nicotine was the key psychoactive ingredient in tobacco that made tobacco dependence-producing (USDHHS, 1988).

Ad Lib Self-administration of Nicotine Nasal Spray

The clearest demonstration from our laboratory that nicotine is reinforcing in humans came from a relatively early quasi-clinical study using our experimental nicotine nasal spray and a placebo spray (Perkins et al., 1996). Smokers wanting to quit right away were recruited and received group-based counseling before their quit day. They were then randomized to receive either the nicotine or the placebo spray to use ad lib during their first week after quitting. Subjects returned to the clinic every day during this first week after quitting to provide biochemical validation of abstinence via expired-air CO and to exchange their spray bottle from the prior day for a new one, which allowed us to measure the amount of spray used in the prior 24 hours. Although participants were smokers wanting to quit, the main goal of the study was not to see if nicotine spray aided abstinence but rather to determine whether nicotine nasal spray would be self-administered by humans; smokers wanting to quit provided an appropriate sample with which to study this question over an extended period (i.e., 4 full days in the natural environment, rather than a few hours in the laboratory). At that time, only a few studies had demonstrated nicotine reinforcement in humans, and no prior study had demonstrated nicotine reinforcement via nasal spray. Only subjects who maintained smoking abstinence throughout the week of spray access were included in analyses because spray use in those who continued smoking would be difficult to interpret. Note also that the active spray provided small, "puff" sized doses of nicotine per spray, just 1.5 μg/kg (or about 0.1 mg, versus 0.5 mg in the commercially available Nicotrol^{R} spray marketed as an NRT for smoking cessation).

As shown in the left-hand side of Fig. 9.1, self-administration behavior was similar between the nicotine and placebo spray groups on day 2 (i.e., the day after their quit day), the first full day of spray access, but was maintained across days only in the nicotine group and not in the placebo group. When we examined spray self-administration as a function of sex, we were very surprised to see that nicotine spray use was twice that of placebo spray use among men, but spray use was similar

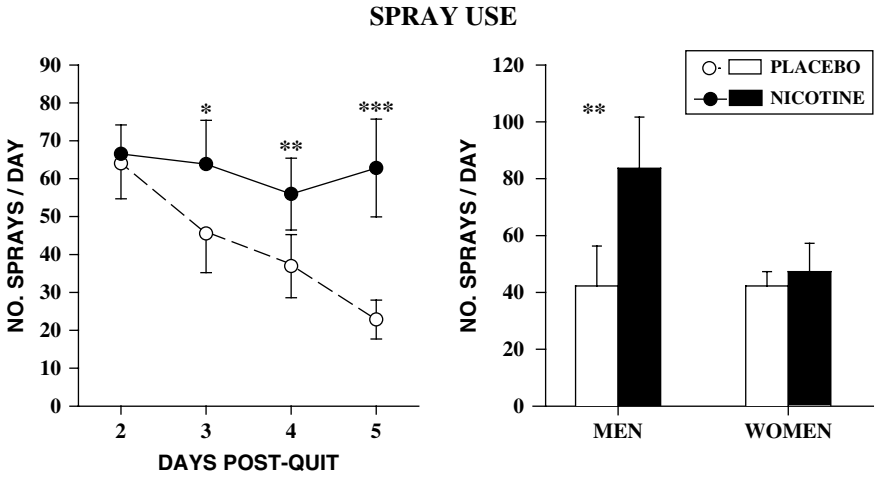

Fig. 9.1 *Left*: Mean ± SEM number of sprays self-administered across each of the 4 days of access by participants randomized to nicotine ($n = 17$) versus placebo ($n = 18$) spray who maintained continuous abstinence during the quit week. *Right*: Mean ± SEM number of sprays self-administered daily by continuously abstinent men versus women randomized to nicotine versus placebo spray. * $p < 0.05$, ** $p < 0.01$, and*** $p < 0.001$ for differences between the groups. Reprinted with permission from Figs. 1 and 2 in Perkins, Grobe, D'Amico, Fonte, Wilson, & Stiller (1996) Low-dose nicotine nasal spray use and effects during initial smoking cessation. *Experimental and Clinical Psychopharmacology, 4*, 157–165, published by the American Psychological Association

between nicotine and placebo among women, as shown in the right-hand side of Fig. 9.1. Because subjects were abstinent smokers, this nicotine self-administration may be an example of negative reinforcement, to relieve the aversive symptoms of tobacco withdrawal, rather than positive reinforcement. Nevertheless, these findings demonstrate that nicotine per se is reinforcing under these conditions, but only in men and not in women.

Nicotine Versus Placebo Spray Choice

We have since used a choice procedure to examine factors that influence nicotine self-administration, including sex differences. In this choice procedure (Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996), subjects are presented in blind fashion with two identically-appearing substances (e.g., nasal sprays, cigarettes) that vary in drug content and are labeled in a way to distinguish them from each other (e.g., "spray A" or "spray B"). They are then instructed to self-administer a set number of substance "uses" (sprays, puffs, etc.) but are free to choose how many will come from the two substances—all from one, all from the other, or a mix of the two. The proportion of choices from the substance with active drug indicates the relative reinforcing value of the drug. In a study of nicotine (2.5 μg/kg per spray) versus placebo nasal spray choice, we found that choice of nicotine spray was greater in smokers versus

nonsmokers, as expected (Perkins, Sanders, D'Amico, & Wilson, 1997). Moreover, nicotine choice tended to be greater in male versus female smokers, as well as nonsignificantly greater in male versus female *non*smokers. This latter, unexpected observation suggested that the sex difference in the relative reinforcing effects of nicotine was apparent from virtually the very first experience with the drug and did not require chronic exposure to it, as in dependent smokers.

These results are a bit difficult to interpret because nicotine spray choice was not above 50% (i.e., above chance levels, to show absolute reinforcement) for most nonsmokers, suggesting that greater nicotine choice in men may reflect less aversiveness rather than greater absolute reinforcement per se. (See Perkins, 2004 for more on how procedural details can influence the specific choice behavior obtained.) Yet, the findings are consistent with the studies of nicotine reinforcement in smokers.

Reinforcing and Rewarding Effects of Nicotine Dose via Cigarettes

To ascertain whether the prior findings with nicotine via spray generalize to the most important form of nicotine use, cigarette smoking, we examined sex differences in the influence of nicotine on the rewarding and reinforcing effects of cigarette smoking (Perkins, Jacobs, Sanders, & Caggiula, 2002). Male and female smokers were given controlled exposure in blind fashion to a "moderate" nicotine cigarette (actually their preferred brand, yield at least 0.7 mg nicotine) and "low" nicotine cigarette (0.1 mg), with each presented on a different day (i.e., only one brand available at a time). They then rated the administered cigarette for its reward value ("liking") and other characteristics, and were given access to additional puffs on a progressive ratio schedule to determine reinforcement. Interactions of sex by dose were observed on most of these measures, as dose effects typically were not significant for women but were for men, as shown in Fig. 9.2. These results indicated that the prior sex differences in nicotine reinforcement, whether by ad lib self-administration in the natural environment or in the choice procedure within the laboratory, were not specific to the nasal spray form of administration but were present with cigarette smoking reinforcement as well.

Influence of Nicotine Pre-treatment on Subsequent Nicotine or Smoking Reinforcement

Other evidence for sex differences in sensitivity to nicotine dose manipulations comes from studies that examined self-administration behavior, of either nasal spray or smoking, following pre-treatment with different doses of nicotine. Theoretically, the greater the dose of nicotine pre-treatment, the less subsequent nicotine self-administration behavior the smokers should engage in, if regulation of nicotine intake is an important factor driving their behavior, as is emphasized in defining dependence (e.g., USDHHS, 1988).

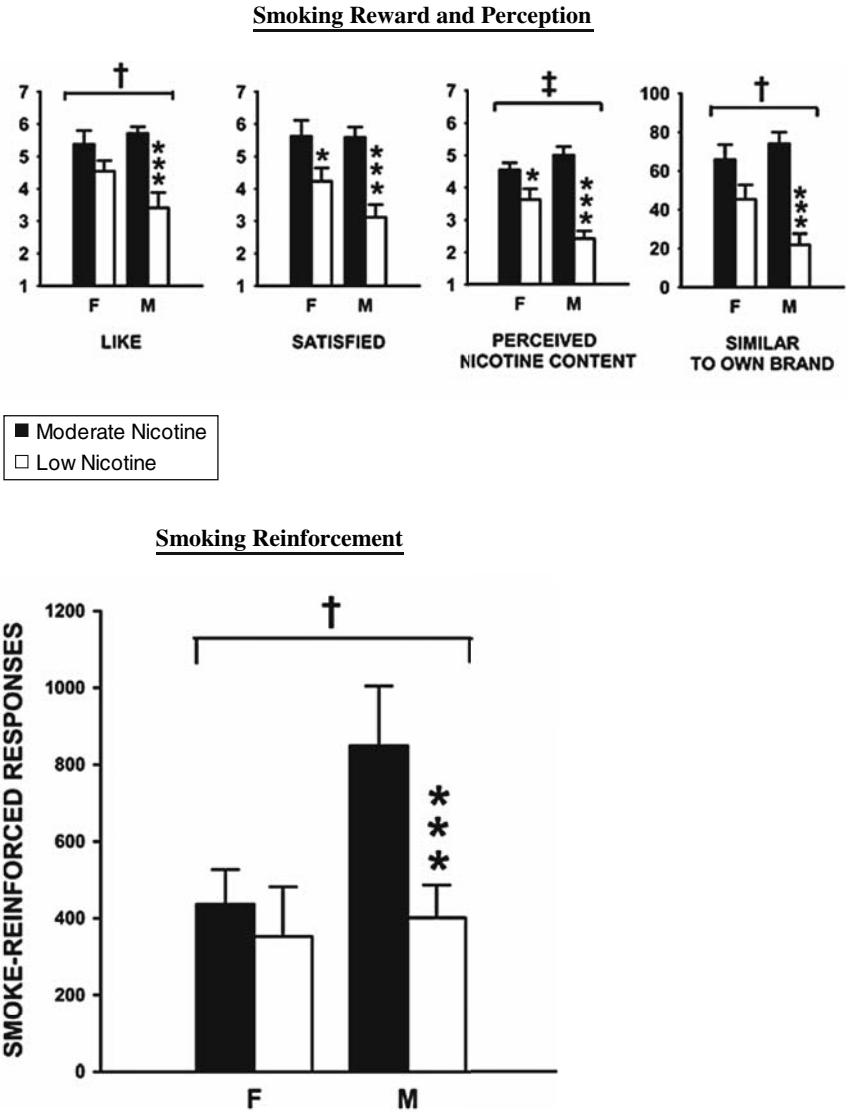

Fig. 9.2 Means ± SEM ratings for smoking reward ("liking," "satisfied") and perception ("perceived nicotine content," "similar to own brand,"; *top*) and responses on a progressive ratio procedure (smoking reinforcement, *bottom*) in men ($n = 17$) and women ($n = 13$) as a function of nicotine dose in cigarettes presented in blind fashion on separate days. ("Moderate" dose was subject's preferred brand, yield $\geq$ 0.7 mg; "low" was 0.1 mg brand.) *Horizontal brackets* indicate a significant dose by sex interaction. + $p < 0.05$, ++ $p < 0.01$. *Asterisks* as in Fig. 9.1. Reprinted from Figs. 1 and 2 in Perkins, Jacobs, Sanders, & Caggiula (2002) Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. *Psychopharmacology, 163*, 194–201. With kind permission from Springer Science and Business Media

Ad lib Smoking Following Nicotine Spray Pre-treatment

In the first such study from our laboratory (Perkins, Grobe, Stiller, Fonte, & Goettler, 1992), smokers abstinent overnight participated in three sessions, in which nicotine by nasal spray (0, 15, or 30 μg/kg, comparable to about 0, 0.5, or 1 cigarette) was administered every 30 minutes for 2.5 hour. In between spray administrations, subjects were free to smoke their preferred brand in unblinded fashion, and the amount of ad lib smoking behavior was assessed. We hypothesized that the greater the pre-treatment dose of nicotine, the lesser is the subsequent smoking in an effort to regulate nicotine intake.

As shown in Fig. 9.3, we found that smoking behavior of men significantly declined as a function of nicotine pre-treatment in dose-dependent fashion, even with the intermediate dose (15 μg/kg), while the smoking behavior of women declined significantly only following the high dose (30 μg/kg) and not the intermediate dose. These results indicated that the smoking behavior of women was less sensitive to nicotine pre-treatment in that a larger pre-treatment dose was required in order to see a significant change in smoking behavior. The fact that nicotine pre-treatment was corrected for body weight ruled out typical body weight differences between men and women as an explanation for the differential sensitivity to the pre-treatment exposure. This study was the first from our laboratory clearly pointing to an important sex difference in nicotine reinforcement.

Nicotines Spray Choice Following Nicotine Patch Pre-treatment

We later examined this question using a different approach, pre-treating abstinent smokers with nicotine patch doses and observing the subsequent self-administration of nicotine spray, using the choice procedure described previously (Perkins, Fonte,

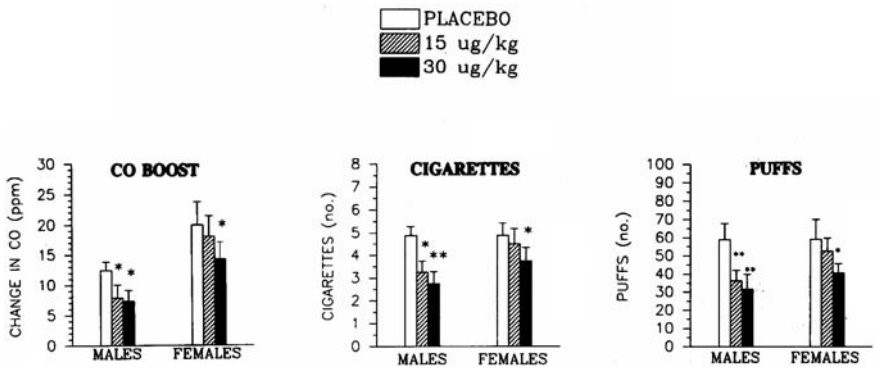

Fig. 9.3 Mean ± SEM carbon monoxide (CO) boost, and total number of cigarettes and puffs in male and female smokers ($n = 8$ each) across the 2.5 hour session as a function of administration of 0, 15, or 30 μg/kg nicotine via nasal spray every 30 minutes. * $p < 0.05$, ** $p < 0.01$ for difference from placebo. Reprinted from Perkins, Grobe, Stiller, Fonte, & Goettler (1992) Nasal spray nicotine replacement suppresses cigarette smoking desire and behavior. *Clinical Pharmacology & Therapeutics, 52*, 627–634, published by Mosby-Year Book, Inc

Meeker, White, & Wilson, 2001). Male and female smokers were pre-treated with 0 (double placebo), 14–21 mg (single active plus single placebo), or 28–42 mg (double active) nicotine via patches. (Whether or not single or double 14 mg patches versus the 21 mg patches were used was determined by subject's body weight in order to equate exposure between heavy and light smokers. As desired, differential dosing by patch based on body weight resulted in equal blood nicotine levels between men and women prior to the choice procedure.) After several hours of rest and other assessments to allow for absorption of nicotine from the patches, subjects chose between active (2.5 μg/kg) and placebo (0) nasal sprays. We hypothesized that nicotine choice would decrease as a function of increasing nicotine patch dose pre-treatment, again indicating nicotine regulation. Nicotine choice tended to decrease in men but was flat in women with increasing nicotine patch pre-treatment, suggesting that nicotine reinforcement was sensitive to the nicotine pre-treatment manipulation in men but not women. This sex difference was not significant, however, perhaps because of the small sample (eight men, eight women).

Other Relevant Findings

We have not conducted extensive research on potential mechanisms for the reduced sensitivity of women to the reinforcing effects of nicotine. However, in a program of research on the discriminative stimulus effects of nicotine by nasal spray, we sometimes, but not always, found that women were less sensitive than men to the influence of dose on these effects of nicotine (Perkins, 1999). Thus, if women are less sensitive to perceiving the interoceptive stimulus effects of nicotine (i.e., its effects in the brain), then it would seem logical that they might alter their self-administration behavior less in response to manipulations of nicotine dose.

On the other hand, little research with non-human species has examined sex differences in nicotine reinforcement, and at least one rat model of intravenous nicotine self-administration suggests that reinforcement may be at least as strong in female versus male rats (e.g., Chaudhri et al., 2005). It is worth noting that animal research indicates greater sensitivity of females to some effects of nicotine, such as anxiolytic effects (Cheeta, Irvine, Tucci, Sandhu, & File, 2001), but less sensitivity to other effects, such as analgesic effects (Damaj, 2001). Such varying patterns of differences may highlight the importance of the dependent measure of interest in considering sex differences in response to nicotine and other drugs, as we stated at the outset.

Sex Differences in Non-Pharmacological Influences of Smoking

All drugs of dependence contain non-pharmacological aspects of use that contribute to the reinforcing effects of the drug, particularly aspects such as the behavioral ritual (e.g., drug seeking and preparation) and sensory stimuli (e.g., sight and smell of cigarette smoke). It is sex differences in these aspects that account for a conundrum raised by the sex difference in nicotine reinforcement and reward described above. That is, if the sole sex difference in factors influencing smoking was that

women were less sensitive than men to the reinforcing effects of nicotine, then it would almost certainly have to be the case that smoking prevalence is substantially lower in women than men. However, although prevalence has typically been lower in women than men, prevalence in the U.S. has declined over the past half century more slowly among women than men, such that it is now similar, about 19% versus 23%, respectively (Centers for Disease Control and Prevention, 2005). We believe that the reduced sensitivity of women to the reinforcing effects of nicotine is essentially countered by their *greater* sensitivity to reinforcement from *non-nicotine* effects of smoking. Such effects include, but probably are not limited to, conditioned reinforcement from environmental stimuli associated with smoking. Such stimuli can be viewed as providing information about drug availability, either in nonverbal form (e.g., drug cues) or verbal form (e.g., oral or written text conveying the drug contents of a substance). Thus, the greater sensitivity of women to non-nicotine effects of smoking balances their lower sensitivity to nicotine effects. Because both pharmacological and non-pharmacological aspects of smoking are intertwined when smokers smoke cigarettes, the sex differences in the relative contributions of these aspects to the behavior are obscured. Only when each aspect is isolated and manipulated is it possible to clearly see sex differences in factors promoting smoking.

Sex Differences in Sensitivity to Nonverbal Drug Information (Cues)

The most obvious cues for smoking are the immediate sensory stimuli of the sight and smell/taste of a lit cigarette. Such an in vivo cue has been widely used in research aimed at assessing self-report and physiological responses to smoking cues (Carter & Tiffany, 2001). Little research has systematically examined sex differences in reinforcement from such cues, but we have found in a few studies that their removal impacts smoking reward and reinforcement more in women than in men.

Smoking Reinforcement due to Lit Cigarette Cue

We tested the influence of a lit cigarette cue on smoking reinforcement in what may have been the first published study to explicitly examine smoking reinforcement (and not just self-report or physiological indices of craving) as a function of smoking-related cues (Perkins, Epstein, Grobe,& Fonte, 1994). Specifically, we compared responding on a simple computer task reinforced by cigarette puffs on four occasions in a 2×2 within-subjects design: in the presence versus absence of a lit cigarette cue, and following overnight smoking abstinence versus no abstinence. Puffs were available on five varying schedules of reinforcement, ranging from "easy" (VR4, or an average of four responses to earn one reinforcer) to "lean" (VR32, or an average of 32 responses to earn one reinforcer), with three intermediate schedules (VR8, VR12, and VR16). A comparison reinforcer of a small amount of money ($.02) was always available on a constant schedule (VR4). The presence of the cue increased smoke-reinforced responding but only under the leanest two schedules

(VR16, VR32), and not under the schedules that provided "easier" reinforcement of smoke puffs. Moreover, in post hoc analyses after publication, we found that this influence of the lit cigarette cue on the abstinent days tended to be greater in women (13.7 versus 50.6 responses for puffs under no cue versus cue, respectively, across the VR16 and VR32 schedules) than in men (45.9 versus 62.1, respectively).

Smoking Reward and Reinforcement after Blocking Smoking Cues

The prior study indicated the importance of an in vivo smoking cue (lit cigarette) to smoking reinforcement, but it was not clear whether this influence was due to the sight or the smell of the lit cigarette. Therefore, we examined further the notion of sex differences in responses to smoking cues in a study that sought to determine whether blocking the sight and/or the taste/smell of cigarette smoke would differentially influence smoking reward and reinforcement in women versus men (Perkins, Gerlach, Vender et al., 2001). Subjects participated in four sessions in a 2×2 within-subjects design involving: the blocking of the sight of a lit cigarette, blocking the taste/smell of a lit cigarette, blocking both, or blocking neither. Subjects, who were not abstinent before the session, smoked one of their preferred brand at baseline and waited one hour. They then took eight puffs via computer instructions on a "test" cigarette (actually another of their preferred brand but with markings covered over) under various blockade conditions. The sight of the cigarette was blocked by opaque goggles (versus the control procedure of clear goggles), while the taste/smell of the cigarette was blocked by nose clips placed so that they closed the nostrils (versus placed higher on the bridge of the nose).

As shown in Fig. 9.4, reward ratings of "liking" and "satisfying" of the puffs were significantly lower in women versus men due to the taste/smell blockade (sex by blockade interaction), regardless of the sight condition. Moreover, blocking of taste/smell, but not sight, significantly reduced subsequent ad lib smoking of the same "test" cigarette type in women but not in men. Thus, smoking reward and reinforcement were more sensitive to manipulations of cigarette smoke taste and smell in women than in men. These results highlighted the importance of olfactory and taste cues, which are often ignored in smoking research, but also showed the relative unimportance of the sight of a lit cigarette, a cue that is often given substantial attention in smoking research.

Sex Differences in Sensitivity to Verbal Drug Information (Expectancies)

In humans, information about the drug content of a substance can also be verbal. Verbal information is displayed in the environment in many different ways, particularly with legal drugs such as nicotine or alcohol. Packaging or advertisements contain text that can convey information about the drug content of the substance, and drug users can be given oral or written information about what is contained in the substance. As with any drug of abuse, information that cigarettes contain

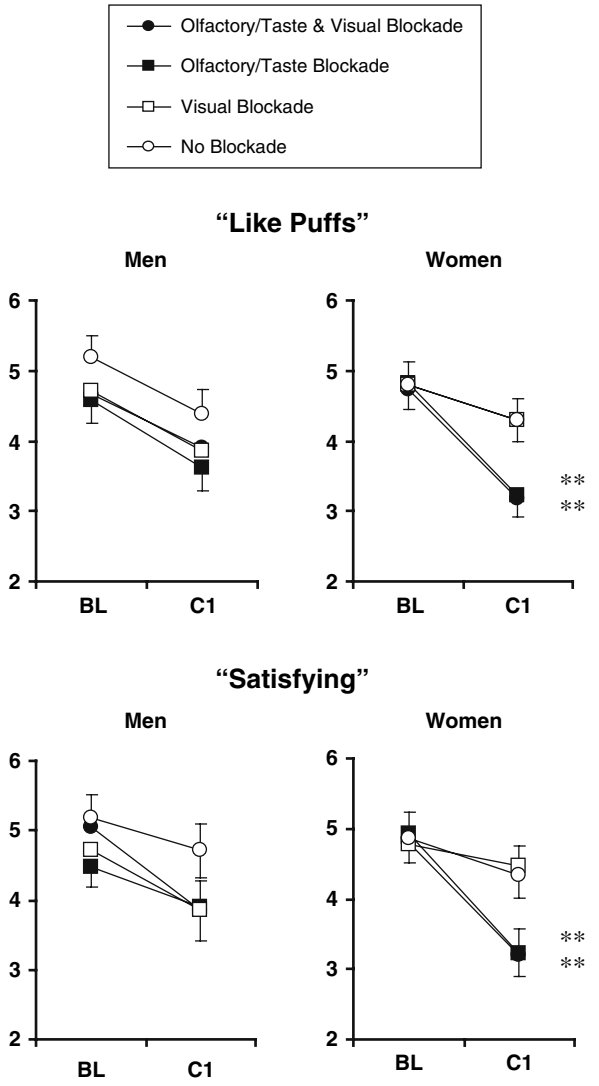

Fig. 9.4 Means ± SEM ratings for smoking reward ("like puffs," "satisfying") in men ($n = 21$) and women ($n = 30$) presented with their preferred brand unblinded at baseline (BL) and then 1 hour later blinded to brand while under olfactory/taste and/or visual blockade conditions (C1). ** $p < 0.01$ for difference from the no blockade condition in change from baseline rating. Reprinted from Perkins, Gerlach, Vender, Grobe, Meeker, & Hutchison (2001) Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine & Tobacco Research, 3,* 141–150, published by the Society for Research on Nicotine and Tobacco (see the journal's website: http://www.informaworld.com)

nicotine creates "stimulus expectancies" for nicotine in the user, which in turn can influence (via "response expectancies") effects the user is likely to experience from nicotine cigarettes (see Perkins et al., 2003).

We first examined sex differences in the influence of verbal information about nicotine on responses to smoking by using the balanced-placebo design (BPD), a procedure used in alcohol research for decades. The BPD involves randomly assigning subjects to receive a substance containing actual drug or no drug, and half of those within each drug condition are told they are receiving actual drug or no drug, in a 2×2 between-subjects design (Perkins et al., 2003). Thus, half the subjects get drug information that is accurate (i.e., they are told and get actual drug, or are told and get a substance with no drug), while the other half get drug information that is inaccurate (i.e., they are told they are getting a substance containing drug but in fact get no drug, or are told they are getting a substance containing no drug but in fact get drug). We employed the BPD to assess the separate and combined effects of actual nicotine dose (via cigarette brands that were moderate or very low in nicotine) and expected nicotine dose (via instructions about the nicotine content of the cigarettes) in men and women (Perkins et al., 2004). Dose instructions had effects larger than actual dose on smoking reward (e.g., "liking") and perception (e.g., "how much nicotine"), but not on craving or withdrawal. Of more interest, women showed greater responses than men to the actual nicotine dose of cigarettes when the dose instructions were accurate, although they did not respond more to inaccurate instructions.

Although this result superficially seemed contrary to the findings noted previously, that women were less sensitive to nicotine dose manipulations, we hypothesized that the greater response of women to dose in this study was due to their greater sensitivity to the accurate dose *instructions* (i.e., the non-pharmacological influence of verbal information about drug). To test this notion, we subsequently repeated the study but with one major change: instead of half the subjects getting inaccurate information about dose, half the subjects got *no* information about dose (i.e., were kept blind to dose). Thus, this study (Perkins et al., 2006) tested the effects of actual nicotine dose in the presence versus the absence of accurate verbal information about dose. Aside from smoking reward ("liking"), we assessed reinforcement by the number of ad lib puffs smoked on that cigarette brand over 30 minutes and by the latency to the first puff. Women showed no effects of actual nicotine dose on smoking reward and reinforcement under blind conditions, consistent with the results of Perkins et al. (2002; Fig. 9.3), described previously, but showed strong dose effects when given accurate dose information. The interaction of dose by instructions (absence/presence) was significant in women for reward and both reinforcement measures. Men showed no dose effects under either instructional condition, except for a dose effect on smoking reward under blind conditions. These findings confirmed that women are more sensitive than men to the non-pharmacological influence of verbal information about nicotine dose.

Sex Differences in the Reinforcing Effects of Control over Smoking

The key to assessing drug reinforcement is that drug administration must be contingent upon a subject's response. Basic research has demonstrated that the effects of the same drug doses can differ when administered non-contingently (i.e., regardless of a subject's behavior) versus contingently (e.g., Dworkin, Mirkis, & Smith, 1995). This effect of the contingency of the drug administration is, by definition, non-pharmacological, as drug dosing (i.e., pharmacology) is kept identical between conditions; the only difference is whether drug is administered contingent or non-contingent on a subject response. To our knowledge, only one published study has examined this notion in humans, finding that cocaine produced greater cardiovascular effects, but similar subjective effects, when presented non-contingently versus contingently (Donny, Bigelow, & Walsh, 2006). No published human research has investigated the influence of contingency in nicotine administration, or individual differences in the influence of contingent versus non-contingent drug administration.

In an unpublished dissertation, Grobe (1999) examined the role of behavioral contingencies surrounding cigarette smoking in moderating acute responses to smoking using a design where smokers were matched in pairs based on smoking characteristics, age, and sex, and then randomly assigned to contingent versus non-contingent smoking groups. Because this study is not published, it will be presented here in detail. Participants were male and female dependent tobacco smokers who abstained from smoking overnight prior to the session. Subjects were 25.4 ± 0.7 (mean, SE) years of age, smoked for 9.1 ± 0.6 years, and had average smoking rates of 18.7 ± 0.8 cigarettes per day. A yoked procedure was developed to equate for dosing, pattern of drug intake, and other stimuli associated with tobacco administration. During the test session, each participant in the contingent group ($n = 31$) had control over tobacco intake. In contrast, each participant in the non-contingent group ($n = 28$) was yoked to the first group in that they smoked according to the pattern established by his or her matched counterpart in the contingent group. (The non-contingent group had three fewer participants than the contingent group, because three in the latter group could not be matched; however, all were included in analyses.)

Self-administration of tobacco smoke was controlled by computerized puffing instructions, to control puff duration. When a person in the contingent group wanted a puff of tobacco smoke, he or she pressed a button to initiate the puffing instructions. The computer recorded the timing of these button presses for puffs by those in the contingent group. This pattern was then presented to the matched subject in the noncontingent group to signal when he or she was to take a puff via the same puffing instructions. Subjects in the noncontingent group could not control the pattern of puffing. With this procedure, the contingent and noncontingent groups were equated on tobacco exposure, pattern of intake, and stimuli associated with drug delivery; control over exposure and pattern was confirmed by the similar CO increases between contingent (13.1 ± 1.1 ppm) versus noncontingent (11.0 ± 0.8 ppm) groups. Thus, the manipulation of controllability was not confounded by substantially different tobacco exposure. After 90 minutes of smoking either contingently or noncontingently, according to the assigned condition, subjects completed 0–100 visual-analog scale measures of subjective

mood (depressed, angry, tense, etc.) and smoking reward ("smoking pleasure"), and a behavioral measure of the relative reinforcing values of the respective smoking contexts (i.e., reinforcement). Reinforcement was determined by responding on an operant task to gain access to continued smoking under their respective smoking context (i.e., contingent versus noncontingent) versus a modest amount of money as an alternative.

Compared to contingent smoking, non-contingent (yoked) smoking resulted in less smoking reward and reinforcement. These effects remained robust after controlling for actual smoke exposure (CO boost). Moreover, compared to contingent smoking, women found noncontingent smoking to be significantly less reinforcing (Fig. 9.5, top) and less effective in alleviating feelings of depressed mood (Fig. 9.5, bottom), perhaps in relief of tobacco withdrawal due to abstaining prior to the

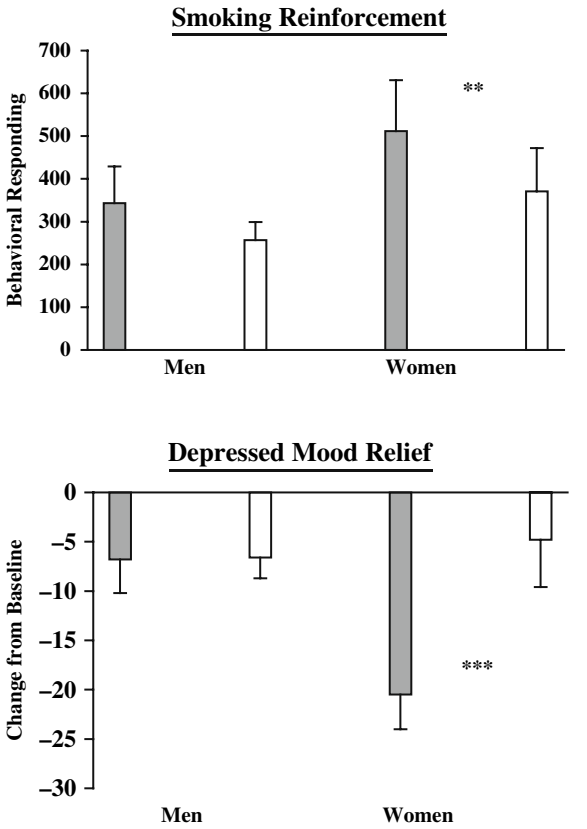

Fig. 9.5 Mean ± SEM responses for continued access to smoking (reinforcement, *top*) and decrease from pre-smoking baseline in 0–100 visual analog scale of "depressed" mood (*bottom*) in men and women who smoked in contingent (*filled bars*, $n = 31$) versus non-contingent (*open bars*, $n = 28$) fashion. ** $p < 0.01$, *** $p < 0.001$ for difference between contingent and non-contingent groups, by sex. From Grobe, J. E. (1999) *The importance of controllability over drug intake in moderating the effects of tobacco smoking*. Unpublished Ph.D. dissertation, University of Pittsburgh

session. In contrast, the men were not significantly affected by the contingency manipulation on these measures. A similar pattern was observed for self-report measures of irritableness and tension (not shown).

These results suggest that the greater influence in women versus men of non-pharmacological factors in cigarette smoking may extend beyond verbal and non-verbal information (cues) about drug content, discussed previously. The results also suggest that studies of acute responses to smoking need to take into consideration the extent to which the smoking is done contingently versus non-contingently (e.g., when done ad lib or when directed to do so by the experimenter) to determine their generalizability to the effects of smoking in the natural environment.

Other Relevant Findings

The studies we discussed in this section indicate that several non-nicotine aspects of smoking influence smoking reward and reinforcement more in women than in men. These factors include the smell or taste, but perhaps not the sight, of cigarette smoke; accurate verbal information about the nicotine content of a cigarette; and controllability over the pattern of ad lib smoking. Many other non-nicotine factors influence smoking reinforcement and reward, and their impact may differ between men and women. For example, one unpublished survey by the American Lung Association (Sept 1998) asked 1,001 smokers who had quit but relapsed why they relapsed. Many responses were given equally between men and women, but women were more likely than men to report that they "missed the comfort of something to hold" (37% versus 28%, respectively) or "missed having something to do with hands" (25% versus 17%, respectively). These observations suggest that the motor effects of smoking (i.e., smoking ritual), in addition to the sensory effects of smoking (e.g., taste and smell of smoke), may differentially influence smoking reinforcement and reward in women versus men. Formal controlled research of this notion is warranted and should be fairly easy to do.

Notably, the sex differences in non-nicotine influences on reinforcement may extend to non-human species, suggesting a difference that is not specific to "gender" (i.e., human sex roles, cultural factors). Chaudhri et al. (2005) assessed nicotine self-administration behavior in the absence or presence of a visual stimulus associated with each nicotine infusion (i.e., cue). In the absence of any cue, male and female rats responded comparably for nicotine (as determined by the difference in responses on the active versus inactive lever). However, when the cue was presented concurrent with nicotine infusion, responding increased and was significantly greater in females versus males. Removal of the cue produced a decrease in responding only among the females, such that responding for nicotine no longer differed between sexes. These findings are generally similar to the sex differences in the influence of non-nicotine factors on smoking reinforcement and reward in humans described previously. Given the limited attention paid to sex differences in nicotine reinforcement in human models, however, a great deal more programmatic research is needed to determine the reliability of such sex differences.

Clinical Implications

Aside from providing directions for the study of possible sex differences in the etiology of tobacco dependence, these results suggest that men and women may differ in their response to smoking cessation treatments. If women's smoking is less responsive to manipulations of nicotine per se, then they should benefit less from the most common medication for smoking cessation, nicotine replacement therapy (NRT), but be at no disadvantage when treated with non-NRT medications. By the same token, if women's smoking is more responsive to non-nicotine factors, then they should benefit more from treatment approaches that address these factors, such as counseling to cope with smoking cues. As will be discussed, considerable evidence supports the first point, that women have less success in quitting with NRT (particularly nicotine patch) and not with other medications. Little research has examined the second point.

Sex Differences in NRT Efficacy

Evidence has accumulated over the past two decades to show that NRT has less influence on long-term quit rates in women versus men (Perkins, 2001; Wetter et al., 1999). In a recent meta-analysis, we found that women have poorer quit rates than men at 6-month follow-up in controlled trials comparing nicotine versus placebo patch (see Perkins & Scott, in press). The odds ratio of abstinence due to nicotine versus placebo patch for men versus women was 1.45 (95% confidence interval of 1.04–2.02, $p = 0.03$). This analysis was a follow-up to a meta-analysis of 11 NRT patch trials concluding that the sex difference in long-term abstinence due to patch was modest and non-significant (Munafo, Bradburn, Bowes, & David, 2004). However, that meta-analysis contained only a fraction of the relevant trials testing patch effects in men and women. Although the authors of the earlier meta-analysis sought outcome data separated by sex from the investigators of some 30 relevant clinical trials, they were successful in obtaining such results for only 10 of them. Results from those 10 trials were added to the lone patch trial in the literature that had reported outcome results by sex, leaving 11 for analysis. (The fact that only one out of 30 relevant NRT patch trials published as of 2004 reported clinical outcome by sex, likely delayed by years a discovery that could lead to improved treatment of women for smoking cessation.) We found results for two additional trials plus another trial published after the Munafo et al., (2004) meta-analysis, and determined that the results from these 14 trials did point to a significant sex difference in NRT patch response (Perkins & Scott, in press).

The full clinical picture may not be so simple, however. Other research indicates that the sex difference in NRT response may vary as functions of: the NRT formulation, interactions of sex by dopamine genotype, or the intensity of the counseling accompanying NRT. First, West and colleagues (West et al., 2001) found small to moderate disadvantages of women versus men in 15-week abstinence rates due to NRT gum, patch, or nasal spray in an open label trial (i.e., no placebo control

condition). However, women tended to do *better* than men on NRT inhaler, which is puffed like a cigarette but delivers nicotine via buccal absorption, similar to gum. The fact that the inhaler mimics some of the sensory-motor effects of smoking cigarettes (i.e., non-nicotine aspects of smoking) could help explain why women may gain better therapeutic response from that formulation. Thus, something about the formulation may moderate the sex difference in outcome due to NRT, and subsequent research could improve quit rates in women by enhancing features of NRT formulations that show better quit rates in women. Notably, women are less compliant than men with nicotine patch (Cooper et al., 2004) and perhaps with nicotine gum (Killen, Fortmann, Newman, & Varady, 1990), which could reflect, or help cause, their poorer clinical outcome with patch and gum. In any case, sex differences in compliance across formulation may be a place to start in examining this issue.

Second, a post hoc analysis of a large placebo-controlled NRT patch trial showed that women with at least one A1 allele of the DRD2 gene had a large therapeutic response (abstinent at 6 months) to active patch, while women homozygous for the A2 allele had no response (Yudkin, Munafo, Hey, Roberts, Welch, Johnstone et al., 2004). Results for men were the reverse (i.e., large therapeutic response in those homozygous for A2). Those of European descent tend to be homozygous for the A2 allele, perhaps helping to account for the poorer outcome of women versus men in many trials of the nicotine patch (Perkins & Scott, in press).

Third, a meta-analysis of 21 studies testing NRT of all types (Cepeda-Benito et al., 2004) found that NRT had no effect at 6 months in women given low-intensity behavioral counseling for cessation (OR = 1.03, CI = 0.62–1.68) but was effective in women given high-intensity counseling (OR = 1.90, CI = 1.58–2.30). The NRT was effective in men regardless of the intensity of counseling (OR's above 2). Note, however, that this observation was not replicated in our meta-analysis focusing on NRT patch trials, as counseling did not moderate the sex difference in patch efficacy (Perkins & Scott, in press). The difference between analyses could be due to the larger number of trials examined by Cepeda-Benito et al. (2004), or to variability in the influence of counseling as a function of NRT formulation. If counseling does in fact moderate the sex difference in NRT efficacy, clinical research could improve cessation rates in women by making use of intense counseling that enhances NRT response. Cepeda-Benito et al. (2004) also found that NRT was not effective in women at all at the one-year follow-up point but was effective in men, supporting the general notion that women are less responsive than men to the therapeutic efficacy of NRT.

Despite some differences in the relative contribution of nicotine versus non-nicotine factors to their smoking reinforcement and reward, most of the causes of smoking persistence in men and women likely are the same. The sex differences in clinical results discussed here are generalizations and do not necessarily apply to every single female or male smoker. Thus, the smoking of many women may be strongly influenced by nicotine dose, and NRT may be very beneficial in helping these women quit, while the smoking of many men may be sensitive to manipulations of non-nicotine factors, and NRT may have little effect in these

men. Furthermore, the safety, low cost, and over-the-counter (OTC) availability of NRT still make it an important medication for all smokers, including women, to use when quitting. In fact, a critical problem with smoking cessation treatment in the general population is that physicians seldom recommend medication, and are only half as likely to recommend medication for women smokers compared to men who smoke (Steinberg, Akincigil, Delnevo, Crystal, & Carson, 2006). Nevertheless, clinical research suggests that women may be more likely than men to need additional help to quit, and NRT alone may have little benefit for most women smokers.

Sex Differences in Response to Other Medications

If women were also less successful than men with cessation medications other than NRT, then one would have to conclude that the sex differences in response to NRT are probably not relevant to the central issue of sex differences in the influence of nicotine on smoking reinforcement and reward. However, clinical evidence indicates that women are equally, or perhaps more, successful than men in studies of non-NRT medications. A meta-analysis of 12 clinical trials with bupropion versus placebo showed similar and highly significant effects of bupropion in women and men (OR's = 2.47 and 2.53, respectively; Scharf & Shiffman, 2004). Yet, women had poorer cessation rates overall (OR = 0.75, CI = 0.59–0.94 for cessation in women versus men), consistent with much other research that women generally have more difficulty quitting (e.g., Perkins, 2001; Wetter et al., 1999). Although less numerous, clinical trials of clonidine and naltrexone tend to show somewhat better outcome in women versus men (Perkins, 2001), although neither drug is clearly efficacious in placebo-controlled trials and thus has not been approved by the FDA for smoking cessation. Notably, clonidine's efficacy in women is more apparent in studies involving intense behavioral counseling, versus minimal counseling (Perkins, 2001), similar to NRT outcome with women in Cepeda-Benito et al., (2004). Thus, women do at least as well as men when trying to quit with non-nicotine medications, and so the specific deficit of women versus men in clinical outcome with NRT supports the idea that nicotine is a less important influence on smoking reinforcement and reward in women versus men.

Sex Differences in Treatments Aimed at Non-Nicotine Influences on Smoking

Standard behavioral counseling for smoking cessation often addresses coping with the influences of smoking cues on craving to smoke. Smokers are usually advised to avoid being in environments where smokers congregate (e.g., smoking areas outside buildings, smoking sections of restaurants) or to engage in cognitive and behavioral strategies to divert attention from the cues, such as by keeping busy with a distracting task or take a walk to escape the cues altogether (Perkins, Conklin,

& Levine, 2008). To our knowledge, no studies have tested sex differences in the effectiveness of these counseling steps. However, relapse risk is very high if quitting smokers are not able to avoid lapsing early in the quit attempt (whatever the cause), and this risk may be much greater in women than men (Borrelli et al., 2004). Thus, improving the ability of quitting smokers to successfully cope with urges to smoke early in a quit attempt, such as by reducing the influence of smoking cues, would greatly increase long-term abstinence, particularly in women.

Another approach in addressing sensory effects of smoking is to provide substitutes that simulate these effects. Standard counseling recommends strategies such as sucking on a straw or consuming carrot sticks or cinnamon sticks as substitutes for the motor effects of smoking. However, the sensory effects of smoking appear more important than the motor effects (Perkins, Gerlach, Vender et al. 2001; Perkins, Ciccocioppo, Conklin, Milanak, Grottenthaler, & Sayette, in press), suggesting that substitutes for the sensory effects may be more effective. Rose and colleagues developed several sensory substitutes that mimicked the throat irritating effects of nicotine-containing smoke, including citric aerosol (Rose & Hickman, 1987). Moreover, denicotinized cigarettes can be viewed as the ultimate in sensory substitutes, since they match almost all the effects of smoking other than nicotine intake (Pickworth et al. 1999). Yet, we are not aware of research that has specifically examined whether men and women differ in clinical response to these substitutes when attempting to quit. Together with the previously noted sex differences in efficacy with the NRT inhaler (West et al., 2001), the formulation whose method of use is most similar to smoking, development of sensory substitutes may be a fruitful area of research into improved cessation methods for women.

The greater influence in women of controllability over smoking may be addressed by behavioral treatments that remove control over smoking in the period prior to the quit date, such as the "scheduled reduction" approach of Cinciripini et al. (Cinciripini, Lapitsky, Seay, Wallfisch, Kitchens, & Van Vunakis, 1995), in which smokers smoke only after a specific amount of time has passed since the prior cigarette. This behavioral procedure has been shown to improve abstinence rates, although the mechanism for its efficacy is unclear. Smokers may learn to cope with urges to smoke that occur before the next "scheduled" cigarette. Alternatively, or in addition, the cues associated with access to smoking may narrow when the availability of each cigarette is determined strictly by time. In any case, such a procedure may aid abstinence more in women than in men.

Conclusions and Future Directions

Because women have greater difficulty quitting smoking and suffer higher risks of smoking-related morbidity and mortality, more effective smoking cessation treatments for women could have profound effects in improving public health. Although men and women smokers are more similar than they are different, we have found that smoking reinforcement and reward in women are influenced less by nicotine and more by non-nicotine factors, compared to reinforcement and reward in men.

Women self-administer nicotine to a lesser degree, and nicotine pre-treatment alters their subsequent smoking or nicotine self-administration to a lesser extent, relative to men. By contrast, smoking reinforcement and reward in women are influenced more by the presence of smoking cues, particularly olfactory/taste of cigarette smoke, and by accurate verbal information about the nicotine content of cigarettes, two factors that are independent of actual nicotine intake (i.e., are non-nicotine in nature). Women may also be more sensitive to the presence of control over the pattern of smoking. These differences may help explain why women benefit less than men from NRT medication, particularly the patch, when trying to quit.

Future research should determine the possible mechanisms for these sex differences. The obvious hormonal differences between women and men have been proposed as a reason women may be less sensitive to the reinforcing and rewarding effects of nicotine (e.g., Sofuoglu, Babb, & Hatsukami, 2001). Craving and withdrawal may vary in women as a function of menstrual cycle phase (Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Perkins et al., 2000), lending some support for this idea. Estradiol in animals and progesterone in humans may blunt responses to nicotine and other drugs (Damaj, 2001; Sofuoglu et al. 2001). However, much of this research is inconsistent or shows only modest effects of cycle phase or hormone manipulations (Terner & de Wit, 2006). Moreover, research indicating that sex differences in response to nicotine may depend on the NRT formulation or interaction involving other genes suggests that simple hormonal levels are unlikely to fully explain reduced nicotine reinforcement in women. Laboratory studies examining more complex interactions may provide a clearer understanding of these mechanisms. For example, Ray and colleagues (Ray et al., 2006) found slightly lower levels of nicotine cigarette choice in women versus men, but the main finding was an interaction of sex by OPRM1 (mu opioid receptor) genotype. Nicotine choice among women was much greater for those homozygous for the A allele compared to those with one or two G alleles, while OPRM1 genotype had no effect on nicotine choice in men.

Other directions for the study of mechanisms for these sex differences include possible differences in neurotransmitter activity in response to nicotine or smoking. For example, in one study, women responded to amphetamine with less striatal dopamine release (via positron emission tomography) and blunted drug reward and other subjective responses, compared to men (Munro et al., 2006). (Menstrual cycle phase had no effect on responses to amphetamine.) Similar neuroimaging research may show comparable sex differences in response to nicotine and/or non-nicotine factors in smoking.

Finally, clinical research should take advantage of these non-nicotine factors that influence smoking reinforcement and reward in women to improve interventions for cessation. The fact that women do at least as well when quitting with non-nicotine medications suggests that further development of such medications is likely to improve cessation rates in women. Development of substitutes that mimic the sensory effects of smoking, such as the taste and olfactory stimuli of tobacco smoke inhalation, may effectively replace cigarette smoking in women early in quitting and help foster smoking abstinence. Use of counseling approaches that reduce control

over the pattern of smoking leading up to the quit day may also aid long-term abstinence in women.

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