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Does Transdermal Nicotine-Induced Withdrawal Suppression Depend on Smokers' Gender?

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by

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List of Abbreviations

ANOVA	analysis of variance
ANCOVA	analysis of covariance
BDI	Beck Depression Inventory
bpm	beats per minute
CBPL	Clinical Behavioral Pharmacology Laboratory
CO	carbon monoxide
CDC	Centers for Disease Control
cpd	Cigarettes per day
DSST	Digit symbol substitution test
e.g.	exempli gratis (for example)
EEG	electroencephalographic
FTC	Federal Trade Commission
FTQ	Fagerström Tolerance Questionnaire
HSD	honestly significant difference (Tukey)
hr	hour(s)
HR	heart rate
IRB	Institutional Review Board
min	minute(s)
mg	milligram
µg	micrograms
NHANES	National Health and Nutrition Examination Survey

NRT	nicotine replacement therapy
ppm	concentration in parts per million
QSU	Questionnaire of Smoking Urges
RVIP	Rapid Visual Information Processing
s	second(s)
TN	transdermal nicotine
USDHHS	United States Department of Health and Human Services
VAS	visual analog scale
VCU	Virginia Commonwealth University
WHO	World Health Organization

Abstract

DOES TRANSDERMAL NICOTINE-INDUCED WITHDRAWAL SUPPRESSION DEPEND ON SMOKERS' GENDER?

By Sarah E. Evans

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Major Director: Dr. Thomas Eissenberg, Associate Professor, Department of Psychology and Institute for Drug and Alcohol Studies

Nicotine replacement therapy (NRT) is a pharmacotherapy used commonly to help tobacco smokers quit smoking. All forms of NRT are demonstrably efficacious for this indication, and several forms, including transdermal nicotine (TN) are available over-the-counter in the United States. NRT is less efficacious in women than in men, although the specific reasons for this gender difference are unknown. NRT generally, and TN specifically, is thought to work, at least in part, by suppressing withdrawal symptoms in abstinent smokers. While TN-induced withdrawal suppression has been demonstrated, the degree to which this withdrawal suppression is influenced by smokers' gender is uncertain. The purpose of this acute laboratory study is to determine if TN-induced withdrawal suppression is influenced by smokers' gender.

One hundred twenty eight overnight-abstinent smokers completed four, double-blind, randomized, 6.5-hour laboratory sessions in which further cigarette abstinence was required. Sessions differed by TN dose (0, 7, 21, or 42 mg). All sessions were double-blind and randomly ordered. Each session included regular assessment of subjective symptoms of nicotine/tobacco withdrawal, subjective effects of transdermal nicotine

dose, psychomotor performance, heart rate and plasma nicotine level. Results from this laboratory study revealed clear nicotine dose-related effects for plasma nicotine and heart rate, symptoms of nicotine intoxication (e.g. Nausea, Lightheaded) and suppression of Urges to smoke and Craving. Many DSM IV nicotine/tobacco withdrawal symptoms did not show dose-related suppression (e.g. Irritability/frustration/anger, Anxious, Difficulty concentrating). Importantly, results from this study indicated that there were very few differences between men and women in nicotine-induced suppression of the nicotine/tobacco withdrawal syndrome. Future research addressing this important issue may benefit from focusing on a potential interaction between gender and other effects of TN (i.e., blunting the effects of a concurrently administered cigarette) and/or on other triggers for relapse (i.e., smoking-related stimuli).

Chapter 1

Introduction

Overview

Tobacco cigarette smoking is the leading avoidable cause of premature death and disease in the United States (Centers for Disease Control [CDC], 2002). Between 1995 and 1999, smoking caused an annual average of 264,087 deaths among men and 178,311 deaths among women in the United States (CDC, 2002). According to the World Health Organization (WHO, 2003), 4.2 million people across the globe die annually from tobacco-related illnesses, a figure expected to rise to more than 10 million annually by 2020. Tobacco smoking causes lung, stomach, kidney, cervix, and a variety of other cancers, as well as cardiovascular disease (Leischow & Djordjevic, 2004; American Cancer Society, 2005). Thus, cigarette smoking is a national and global health crisis, and helping current smokers to quit and preventing non-smokers from starting are vital public health goals. There is an increasing awareness that these goals are particularly relevant to women (WHO, 2003; USDHHS, 2001).

Approximately 1.3 billion people in the world are daily smokers (World Bank, 2003), and an estimated 250 million of these smokers are women (Guindon & Boisclair, 2003). In the United States, approximately 22 million women are cigarette smokers (i.e., 21%; American Heart Association, 2003). Tobacco cigarette smoking puts women at an increased risk for stroke (Lakier, 1992) and a variety of adverse pregnancy outcomes including spontaneous abortion, premature birth, low birth weight and stillbirth (e.g.,

Walsh, Lowe & Hopkins, 2001; Benowitz, 1991.) In addition, the risk of myocardial infarction is greater for women who smoke relative to men who smoke (Prescott, Hippe, Schnohr, Heim & Vestbo, 1998). While lung cancer rates for men have decreased since the 1980's, they have reached epidemic proportions for women, as lung cancer has moved from the seventh to the first most common cause of cancer deaths in the United States (Patel, Bach & Kris, 2004). Overall, despite well-known adverse health and economic consequences, tobacco cigarette smoking among women is still far too common (Thompson, Koplan & Satcher, 2002). Thus, effective cessation strategies, especially for women, are imperative.

Smoking cessation can involve purely behavioral interventions (e.g., clinician advice, Milch, Edmunson, Beshansky, Griffith & Selker, 2004; telephone counseling, Rigotti, 2002) or non-nicotine medications (e.g. bupropion; Scharf & Shiffman, 2004; Jack et al., 2003), but often involves the use of nicotine replacement therapy (NRT). Nicotine is a mild psychomotor stimulant and acetylcholine receptor agonist that is found in tobacco and delivered to the smoker in tobacco smoke. NRT involves the administration of pharmacologically pure nicotine (i.e., not tobacco-delivered nicotine) via transdermal patch, gum, lozenge, inhaler or sublingual tablets (Shiffman, Dresler & Rohay, 2004; Haustein, 2003; Fagerström, Hughes, Rasmussen & Callas, 2000). Relative to placebo, NRT roughly doubles quit rates (Silagy, Mant, Fowler & Lodgy, 1994; Fiore et al., 2000; Hughes, Goldstein, Hurt & Shiffman, 1999), and works, at least in part, by suppressing aversive symptoms that can occur during periods of tobacco abstinence (Henningfield, 1995; Eissenberg, Stitzer & Henningfield, 1999).

In many smokers, periods of tobacco abstinence, such as those that accompany a quit attempt, are associated with an aversive syndrome, including headache, irritability, anxiety, sleep disturbances, an inability to concentrate, and hunger (Hughes, Higgins & Hatsukami, 1990; Hughes & Hatsukami, 1986). This aversive syndrome is known as nicotine/tobacco withdrawal (Shiffman, Khayrallah & Nowak, 2000; Stolerman & Jarvis, 1995; Killen, Fortmann, Kraemer, Varady & Newman, 1992; Shiffman & Jarvik, 1976) and can be observed following abrupt cessation of chronic tobacco administration in humans (nicotine withdrawal is also apparent following abrupt cessation of chronic nicotine administration in non-human animals; Malin et al., 1992). Indeed, nicotine/tobacco withdrawal is often cited by smokers as a reason for failed quit attempts (John, Meyer, Hapke, Rumpf & Schumann, 2004; Piasecki et al., 2000). The suppression of this aversive withdrawal syndrome by continued cigarette use, and its concomitant nicotine self-administration, is thought to perpetuate smoking behavior in humans (Kenny & Markou, 2001; Watkins, Stinus, Koob & Markou, 2000; USDHHS, 1988). This smoking behavior might be eliminated more effectively if the suppression of the negative effects of withdrawal were achieved via another route, such as with the relatively less toxic NRT.

Recognizing cigarette use as a behavior performed to suppress or avoid an aversive withdrawal syndrome suggests the idea that cigarette smoking may be explained in terms of a negative reinforcement model of drug dependence. Negative reinforcement occurs when a behavior is associated with avoidance or termination of an aversive stimulus; future occurrences of that behavior become more likely (Eissenberg, 2004; Sdorow, 1990). With regard to smoking cessation, any behavior associated with a

lessening of the intensity or likelihood of unpleasant withdrawal symptoms may become more likely. Understanding how to use NRT effectively to lessen the intensity or likelihood of aversive withdrawal symptoms in all treatment-seeking smokers may be an important component in maximizing smoking cessation efforts.

One factor that may influence NRT-induced withdrawal suppression is gender. Some studies are consistent with the notion that relative to men, women report less NRT-induced withdrawal suppression using the nicotine patch (Wetter, Fiore, Young, McClure & deMoor, 1999a) or gum (Killen, Fortmann, Newman & Varady, 1990). One such study involved a between-subjects design of 128 smokers (71 women) who were assigned to one of three conditions: 2 mg gum (21 men, 19 women); 4 mg gum (18 men, 23 women) or 4 mg gum to 2 mg gum (18 men, 29 women; Hatsukami, Skoog, Allen & Bliss, 1995). Results indicated that, relative to men who received 2 mg gum, women who received the 2 gum reported subjective ratings of "impatient" and "excessive hunger" that were nearly double that of men. As "impatient" and "excessive hunger" are symptoms of withdrawal, these results indicated a lack of NRT-induced withdrawal suppression for women. Note that the use of a between-subjects design (i.e., across conditions) may have limited sensitivity to gender effects at other gum doses. Future studies aimed at investigating gender differences in NRT-induced withdrawal suppression might be strengthened with an examination of the effects of multiple NRT doses in the men and women who participate (i.e., dose as a within-subject factor, to maximize power). Moreover, assessing the immediate withdrawal suppressing effects of NRT (i.e., rather than after 8 weeks of continuous NRT use; Hatsukami et al., 1995) might be more relevant to understanding relapse to smoking during cessation. Finally, where possible,

future studies might make use of empirically validated assessment instruments rather than symptom checklists used primarily for their face validity (Hatsukami et al., 1995).

Overall, while some studies provide some support for the notion that the magnitude of NRT-induced withdrawal suppression may depend on gender, few have been designed with this issue in mind (i.e., adequate power, multiple NRT doses, validated outcome measures). Given the need to understand and address gender differences apparent in NRT's efficacy, the issue of the influence of gender on NRT-induced nicotine/tobacco withdrawal suppression is an important one to examine in more detail. The primary purpose of this dissertation is to describe a project that examines the extent to which gender influences NRT-induced withdrawal suppression. This introduction begins with a discussion of nicotine/tobacco withdrawal, focusing on preclinical and clinical effects of nicotine abstinence. Next, the introduction presents a discussion of cessation and nicotine replacement therapy, highlighting the efficacy of NRT and its ability to suppress the aversive effects of nicotine/tobacco withdrawal. Finally, the introduction ends with a discussion of gender differences in response to NRT and the potential influence of gender on NRT-induced nicotine/tobacco withdrawal suppression.

Preclinical Evidence for Withdrawal

This section provides evidence for a withdrawal syndrome that occurs in non-human animals after abrupt cessation of chronically delivered nicotine. Following a brief explanation of nicotine as a reinforcer, this section summarizes several studies that demonstrate the withdrawal syndrome under a variety of conditions.

Nicotine is a Reinforcer in Non-human Animals

In animals, nicotine is a reinforcer: the probability of behaviors that are associated with nicotine administration is increased (Perkins, Donny & Caggiula, 1999; Rose & Corrigall, 1997; Goldberg & Henningfield, 1988). For example, in one fixed ratio study, nicotine maintained robust self-administration in rats (Corrigall & Coen, 1989). Fixed-ratio refers to the delivery of a potential reinforcer (e.g., i.v. nicotine administration) after performance of some predetermined number of responses (e.g., lever presses). In this case, male Long-Evans rats were required to perform five lever presses prior to receiving an infusion of 0.01 or 0.03 mg/kg nicotine. The fact that the animals reliably pressed the lever that elicited nicotine administration, and did not press a lever that delivered saline, demonstrates that nicotine can act as a reinforcer under these conditions. Moreover, the fact that the nicotinic antagonist mecamylamine blocked nicotine-reinforced lever pressing in a dose dependent manner highlights the pharmacologic specificity of nicotine reinforcement (Corrigall & Coen, 1989).

Another animal model that has been used to measure the reinforcing properties of nicotine (as well as other drugs) is the intracranial self-stimulation (ICSS) model. In the ICSS model, animals press a lever in order to have electrical stimulation delivered via an electrode implanted into the medial forebrain bundle (thought to be the brain's "pleasure/reward" system). Sessions of ICSS-reinforced lever pressing are repeated until a voltage dose-response curve is determined and a threshold—the lowest voltage at which the animal responds reliably—is established. ICSS can be used to determine if a drug is a reinforcer when the ICSS threshold is determined in the absence and then in the presence of the drug. A drug that acts as a reinforcer should reduce the ICSS threshold, relative to

when no drug is present, because the drug and the ICSS work together on the "pleasure/reward" system. Using this model, nicotine has been demonstrated to be a reinforcer: a continuous infusion of nicotine by osmotic pump lowers ICSS threshold levels (Markou & Koob, 1992). Taken together, studies using self-administration and ICSS techniques support the idea that nicotine acts as a reinforcer. Interestingly, chronic nicotine administration can lead to dependence, as revealed by a withdrawal syndrome that can be observed upon abrupt termination of nicotine administration.

Signs of Nicotine Withdrawal in Non-human Animals. Nicotine withdrawal consists of signs that can be observed directly in non-human animals; it also produces observable changes in behavior. A nicotine withdrawal syndrome has been observed in rats (Hildebrand, Nomikos, Bondjers, Nisell & Svensson, 1997; Malin et al., 1992) and includes shakes, hyperphagia, increases in body weight and decreases in spontaneous activity that occur when chronic nicotine administration is terminated. For example, 11 male Wistar rats were observed for withdrawal signs following seven continuous days of nicotine dosing with an osmotic mini-pump (11.25 mg/kg/day nicotine; Hildebrand, Nomikos, Bondjers, Nisell & Svensson, 1997). Signs of withdrawal, including shakes, teeth chattering, yawning and reduction in locomotor activity, were observed at 16 and 40 hours after nicotine abstinence. Animals in which a pump was not implanted did not show these signs. Withdrawal has also been observed in other studies where 3 mg/kg/day nicotine (N = 8) or 9 mg/kg/day (N = 8) was administered subcutaneously for seven days (Malin et al., 1992). Withdrawal signs were evident at 16 hours after the end of nicotine administration and continued to a lesser degree by 40 hours. These signs included teeth chattering, tremors/shakes and yawns.

A similar nicotine withdrawal syndrome has also been observed in mice. For example, in a study where mice received four daily 2 mg/kg nicotine injections for fourteen days (Isola, Vogelsberg, Wemlinger, Neff & Hadjiconstantinou, 1999), mild somatic withdrawal signs (shakes, scratching, facial tremor and abdominal constrictions) were reported between 24 and 48 hours after the final administration, and some signs persisted for 3 - 4 days. These signs were not observed in the mice who did not receive nicotine injections. Thus, in rodents, somatic signs of nicotine withdrawal are apparent after abrupt discontinuation of chronically administered drug (Stolerman, 1989). When withdrawal appears after abrupt termination of chronically administered drug, it is called *spontaneous* withdrawal; *precipitated* withdrawal refers to a withdrawal syndrome that occurs when an antagonist is administered to an animal that has a history of chronic drug administration.

Antagonist-precipitated nicotine withdrawal has been observed in several animal models (e.g., Malin, 2001). For example, nicotine withdrawal has been evaluated after nicotine maintained rats receive the competitive nicotinic antagonist dihydro-β-erythroidine (Malin et al, 1998). Twenty-four Sprague-Dawley rats were implanted with osmotic mini-pumps that delivered 9 mg/kg/day nicotine into the third ventricle. Six rats each were challenged with an injection of 10, 18 or 35 mg dihydro-β-erythroidine or 20 ml saline. After injection, rats were observed for 20 minutes and behavioral signs (teeth chews/chatter, wet shakes/tremors, gasps/abdominal writhes) were recorded. Significantly fewer abstinence signs were observed in animals that received saline, relative to those who received any dose of the nicotine antagonist. In addition, rats injected with the lowest dose (10 mg) of dihydro-β-erythroidine had significantly fewer

abstinence signs than those receiving the higher doses. Both the 18 mg and 25 mg dose differed significantly from other doses on shakes/tremors, gasps/writhes and chews/teeth chatter, with an increase in observation of those signs. Thus antagonist-precipitated nicotine withdrawal has been characterized in the rat, and antagonist administration produces dose-dependent signs of nicotine withdrawal in nicotine-maintained animals.

A recent study investigated the influence of duration of infusion and nicotine dose on spontaneous and precipitated nicotine withdrawal in the mouse (Damaj, Kao & Martin, 2003). In the spontaneous withdrawal study, mice were infused daily for 14 days with 6, 24, or 48 mg/kg of nicotine via subcutaneous mini-pumps. Pumps were removed on Day 15 and mice were assessed every 24 hours for the next seven days for somatic signs (shakes, tremors, teeth chatters and abdominal constrictions), sensitivity to heat stimuli (using hot-plate and tail flick models; e.g., Damaj et al., 1997) and performance (exploratory behavior) on an elevated plus-maze. The elevated-plus maze consists of two open arms and two arms that are enclosed by high walls. The closed arms are thought to provide security, whereas the open arms are thought to offer exploratory value. All withdrawal effects were nicotine dose-dependent in all measures and were prominent shortly after pump removal, and could be observed through Days 3 and 4. Furthermore, spontaneous withdrawal induced hyperalgesia and decreased exploratory behavior, as measured by time spent in the open arms of the plus-maze.

To study the influence of duration of nicotine exposure, mice were given either a saline solution or 24 mg/kg/day nicotine daily for 7, 14, 30 or 60 days. At Days 7, 14, 30 and 60, different groups of mice were injected with 2 mg/kg of mecamylamine and assessed for withdrawal. As early as Day 7 of nicotine exposure, and continuing to the

same degree after 60 days of nicotine infusion, significant increases in somatic signs of withdrawal were observed, following mecamylamine injection. For example, withdrawal signs of hyperalgesia were maintained at 14 days of nicotine exposure with the hot-plate test, were maintained at 30 and 60 days with the tail-flick test, and were evident at 60 days as indicated by a significant decrease in the time in the open arms of the plus-maze test. In addition, the severity of nicotine withdrawal signs was greater after 60 days of nicotine exposure, relative to seven days' exposure.

To study precipitated withdrawal in more detail, mice received one of four antagonists: mecamylamine (a noncompetitive antagonist; 1 or 3 mg/kg) hexamethonium (a competitive nicotine antagonist; 1.5 or 3 mg/kg), MLA (an α7 antagonist; 7.5 mg/kg) and dihydro-β-erythroidine (a competitive nicotine antagonist; 1.5 or 3 mg/kg) after 15 days of nicotine administration (24 mg/kg/day). Withdrawal signs were measured for 20 minutes immediately after antagonist administration. Similar to other studies (Malien et al., 1994), mecamylamine administration produced increases in the somatic signs of withdrawal, such as increased paw tremors and head shakes, with signs increasing as dose increased. Hexamethonium and MLA produced significant elevation only in paw tremors. The only significant withdrawal sign with dihydro-β-erythroidine was decreased time in open arms of a plus-maze test. Taken together, all antagonists produced signs of withdrawal in animals maintained on chronic nicotine. Results of this comprehensive study of nicotine dependence in the mouse clearly demonstrate that chronic nicotine administration can produce dependence, as indicated by spontaneous and antagonist-precipitated nicotine withdrawal.

Behavioral Signs of Withdrawal in Non-human Animals. Nicotine withdrawal in non-human animals can also be measured using the ICSS model (Markou & Koob, 1991). Once the continuous nicotine infusion to a non-human animal is terminated (e.g., Epping-Jordan, Watkins, Koob & Markou, 1998) or once an antagonist such as mecamylamine is administered (e.g., Watkins, Stinus, Koob & Markou, 2000), an elevation in ICSS thresholds is revealed. Effectively, then, under conditions that have previously been shown to produce spontaneous or precipitated withdrawal, higher voltage stimulation is required to maintain ICSS-reinforced lever pressing than when those conditions are not present. These ICSS results are considered an index of the negative motivational state, or dysphoria, produced by withdrawal (Markou & Koob, 1992; Mathieu-Kia, Kellogg, Butelman & Kreek, 2002). Thus, ICSS results are consistent with the idea that abrupt discontinuation of chronically administered nicotine can produce an aversive withdrawal syndrome in non-human animals.

The influence of nicotine dose, duration of nicotine exposure, and withdrawal history on the severity of nicotine withdrawal in rats also has been characterized using the ICSS model (Skjei & Markou, 2003). Somatic signs of withdrawal and ICSS brain stimulation reward thresholds were assessed in three experiments using male Wistar rats. In the first experiment, ICSS threshold levels and the somatic effects of spontaneous withdrawal were assessed for four days after the removal of an osmotic pump that had delivered nicotine (3.16 mg/kg/day) for six days. This nicotine delivery and withdrawal assessment was repeated an additional three times, for a total of four assessments. Results replicated previous work, and revealed that spontaneous nicotine withdrawal significantly elevated threshold levels and increased the number of somatic signs (e.g.

body shakes, cheek tremors, and teeth chattering) during first two days of withdrawal. The number of withdrawal signs was stable over the four withdrawal periods.

In the second experiment, the effects of repeated precipitated nicotine withdrawal were assessed using two series of five daily injections of the competitive nicotine receptor antagonist dihydro-β-erythroidine hydrobromide (1.0 mg/kg) during chronic nicotine (3.16 mg/kg/day) or saline exposure. In the third experiment the effects of duration (6 or 27 days) and dose (3.26 mg/kg/day or 6.32 mg/kg/day) of nicotine exposure on the nicotine withdrawal syndrome were investigated using osmotic pumps for varying time durations and containing different nicotine doses. Results of these experiments revealed that conditions that produce precipitated and spontaneous nicotine withdrawal elevated ICSS thresholds. Increases in duration of nicotine exposure (from six to 27 days) and in total nicotine exposure (in increasing both nicotine dose and duration of exposure) prolonged the duration of threshold elevations associated with nicotine withdrawal and augmented the overall severity of withdrawal. These results suggest that nicotine dose and duration of exposure can both influence the duration and/or overall severity of subsequent nicotine withdrawal syndrome.

Spontaneous nicotine withdrawal in non-human animals is also notable for its disruption of operant behaviors not directly linked to drug-seeking behavior. For example, when chronic nicotine access in animals is terminated, the reinforcement potential of food or sweetened solution is suppressed, and this interference is immediately reversed when nicotine is again available (Carroll, Lac, Ascenio & Kennan, 1989; Corrigall & Coen, 1989). These behavioral alterations are seen as acute signs of withdrawal and could be compared to the loss of the "psychological benefits" of smoking

commonly described by smokers during abstinence (Mathieu-Kia, Kellogg, Butelman & Kreek, 2002). As antagonist administration can precipitate somatic withdrawal signs (Malin et al., 1998; Hildebrand, Nomikos, Bondjers, Nisell & Svensson, 1997), it can also disrupt operant behavior (Malin et al., 2001), and a subsequent nicotine injection attenuates their intensity (Malin et al., 1992).

Nicotine withdrawal can also disrupt non-food related reward functioning in animals. Previous work has found that animal's access to novel objects is rewarding (Besheer, Jensen & Bevins 1999). Specifically, when using a place conditioning procedure, a model in which animals are tested for their preference for different environmental cues that are present during testing, rats display an increase in preference for an environment repeatedly paired with novel objects (Bevins et al 2002). Using a 1-day place conditioning procedure, researchers (Besheer & Bevins; 2003) performed an experiment where, after one week of chronic nicotine delivery, rats had their access to nicotine terminated and then were observed for four days. For three days after pump removal, conditioning to an environment reliably paired with access to novel objects was blocked. This disruption in non-food related responding may indicate a state of anhedonia, and replicates previous nicotine withdrawal studies (Harrison, Liem & Markou, 2001) in which the impact of rewarding stimuli was reduced.

Overall, the preclinical research reviewed here demonstrates that chronic nicotine administration can produce a well-defined, quantifiable withdrawal syndrome in rats and mice. This withdrawal syndrome includes a variety of somatic signs (e.g., teeth chatter, abdominal constriction, wet dog shakes) and behavioral effects (e.g., disruption of operant responding; blockade of place conditioning). There is a large body of literature

that supports the idea that humans can also experience nicotine withdrawal after abrupt termination of chronic nicotine administration.

Clinical Evidence for Withdrawal

This section describes the effects that humans can experience after abrupt cessation of chronically administered, tobacco-delivered nicotine (i.e., nicotine/tobacco withdrawal). Following a brief description of nicotine as a positive reinforcer in humans, this section summarizes several clinical studies that demonstrate the signs, symptoms, and behavioral manifestations of nicotine/tobacco withdrawal in humans who have terminated their exposure to tobacco-delivered nicotine abruptly (withdrawal can also be demonstrated in humans who have terminated their chronic exposure to pharmaceutically pure nicotine abruptly, though these data are beyond the scope of this work; West & Russell, 1986; Hatsukami, Skoog, Allen & Bliss, 1985).

Nicotine is a Reinforcer in Humans. In humans, as in non-human animals, nicotine can produce positive reinforcing effects (Pomerleau & Pomerleau, 1992; Jarvik & Henningfield, 1988). In fact, nicotine can serve as an effective reinforcer of intravenous drug-taking behavior in humans who smoke tobacco cigarettes regularly (Harvey et al., 2004). Eight male smokers who had smoked 7 – 45 cigarettes per day for the past 13.4 years participated in a study where nicotine or saline was administered intravenously (i.v.) in three hour sessions under a fixed-ratio schedule. By pulling a lever, participants received saline or a nicotine dose of either 0.75, 1.5, or 3.0 mg/injection which varied, as did fixed-ratio response requirement (10-1600 responses), over consecutive sessions. One minute after each injection, participants were presented with a visual analog scale that assessed subjective effects. The visual analog scale consisted of

a horizontal line anchored by "strong positive (good effects)" on the right, "strong negative (bad effects)" on the left and "neutral (no effect)" in the middle. Participants were instructed to place a vertical mark along the horizontal line to indicate their response to each injection.

Results from the study reveal that the number of nicotine injections per session was significantly greater than the number of saline injections per session. In fact, as the work requirement increased, responding for nicotine also increased. Interestingly, the results also revealed that participants adjusted their response rate in a way that maintained a relatively constant nicotine intake. Subjective responses indicated that nicotine produced positive effects, which were significantly greater in magnitude than those produced by saline. The findings indicate that, as with animals (Goldberg, Spealman & Goldberg, 1981), nicotine is an effective reinforcer of drug-taking behavior in humans.

Self-administration is likely supported because nicotine produces positive subjective effects (Perkins, Gerlach, Broge, Fonte & Wilson, 2001). For example, dependent smokers (N = 45; 27 women; mean cpd = 21.3 and mean years smoking = 20.3), nondependent smokers (N = 12; 9 women; mean cpd = 3.4 and mean years smoking = 13.7), ex-smokers (N = 17; 10 women; mean cpd = 25.4 and mean years smoking = 18.5 before they quit smoking), and nonsmokers (N = 19; 9 women) participated in a study where nicotine (12 μg/kg) or a placebo was self-administered via nasal spray (Perkins et al., 2001). The intranasal route of administration was chosen, in part, because the amount of ad-lib nicotine spray self-administration is correlated with the

amount of ad-lib cigarette smoking in an acute lab session (Perkins, Grobe, Caggiula, Wilson & Stiller, 1997; Perkins et al., 1994).

During one 3-hour laboratory session, participants were instructed to choose one of two bottles (one containing placebo; one containing 12 μg/kg nicotine; participants had sampled both bottles at the beginning of the session) and self-administer 8 sprays every 20 minutes. Subjective effects were measured after each nasal administration via the Profile of Mood States (POMS; McNair, Loor & Droppelman, 1971) and various visual analog scale items. The number of times (out of 48) that participants selected the nicotine spray across the six sessions was related to subjective responses to initial nicotine spray exposure. Positive subjective responses were associated with those participants who chose nicotine at least 50% of the time. Thus 23 (out of 45) dependent smokers who self-administered nicotine reported the pleasurable subjective effect of "Head Rush". While no subjective effects were correlated with nicotine self-administration in nondependent smokers, "Vigor" was positively correlated with self-administration of nicotine in ex-smokers (4 out of 17) and "Pleasant", "Vigor", and "Arousal" were associated with self-administration of nicotine in non-smokers (3 out of 19).

These findings that suggest that nicotine can produce pleasurable subjective effects are consistent with experimental results using i.v. nicotine (Harvey et al., 2004). Perhaps more importantly, they are also consistent with a recent review of the subjective effects of nicotine, which indicated that, across various delivery forms, nicotine increased ratings of positive effects in smokers, such as high, liking, and euphoria (Kalman, 2002). Nicotine also appears to reduce stress and anxiety (Parrott, 1994), and suppress appetite

(Jorenby et al., 1996). These nicotine-induced effects may help to explain initiation of tobacco use (Eissenberg & Balster, 2000), and may also be related to maintenance of use (Glautier, 2004). Importantly, in long-time, frequent tobacco users, tobacco abstinence produces aversive effects (Ward, Swan & Jack, 2001; Foulds et al., 1997; Hughes, Gust, Skoog, Keenan & Fenwick, 1991), and the ability of renewed smoking to provide relief from those aversive effects is a factor in the failure of cessation attempts (Droungas, Ehrman, Childress & O'Brien, 1995). Thus, understanding the nature of withdrawal from tobacco-delivered nicotine, and identifying safe and effective ways to suppress it effectively, is critical.

Signs of Nicotine/Tobacco Withdrawal in Humans. As with preclinical research, studies in which chronic nicotine administration (usually tobacco-delivered nicotine) is terminated abruptly in humans demonstrate that these conditions produce several specific signs, including bradycardia, increased caloric intake and weight, and changes in brain activity (as assessed using electroencephalographic methods). These apparent nicotine/tobacco withdrawal signs, some of which are used clinically to diagnose nicotine dependence (American Psychiatric Association, 1994), can be observed after days of tobacco abstinence, but can also be seen under more acute conditions (i.e. after 8-16 hours of abstinence).

For example, in one study of male heavy smokers (N = 26; participants smoked at least two packs of cigarettes a day for five or more years) abstinence effects were assessed for 10 hours a day during a continuous 5-day period of observation (Knapp, Bliss & Wells, 1963). Some participants (N = 11) smoked *ad libitum* and some (N = 15) abstained from smoking during the last three days of observation. Heart rate was

monitored six times daily and blood pressure was assessed three times daily during the 10-hour sessions. The most pronounced findings included a significant decrease in heart rate ($P < .001$; as much as 20 bpm difference) in abstaining smokers when compared to *ad libitum* smokers during the 3-days of observed abstinence. In addition, diastolic and systolic blood pressure dropped markedly in the abstaining smokers. These findings are consistent with other studies that have shown that, in frequent cigarette smokers, nicotine/tobacco abstinence is associated with decreased heart rate (Gilbert et al., 2004; Teneggi et al., 2002; Corrigall, Zack, Eissenberg, Belsito & Scher, 2001; Foulds et al., 1997; Persico, 1992; Kos, Hasenfratz & Battig, 1997; Hughes & Hatsukami, 1986; Hatsukami, Hughes & Pickens, 1985; Hatsukami, Hughes, Pickens & Svikis, 1984; Gilbert & Pope, 1982; Myrsten, Elgerot & Edgren, 1977) and, sometimes, blood pressure (Krivokapich, Schneider, Child & Jarvik, 1985).

Results from another study are also consistent with the notion that bradycardia is a common result of nicotine/tobacco abstinence. During this study of 32 smokers (13 women; mean cpd = 20.7 cigarettes and mean years smoking = 6 years) heart rate was assessed over a 5-day period of tobacco abstinence (Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005). On Day 1 (*ad libitum* smoking baseline) and on Days 2 -5 of tobacco abstinence, heart rate was measured in a clinical laboratory. Heart rate reached a nadir after one day of smoking abstinence, with Day 2 heart rate (mean = 71.2 bpm; SD = 11.2) decreasing by an average of 8.9 beats per minute (SD = 7.2) from Day 1 (see Figure 1). Because similar results were observed during days when participants smoked denicotinized cigarettes, this study supports the notion that heart rate decreases observed in abstaining smokers are a sign of nicotine withdrawal.

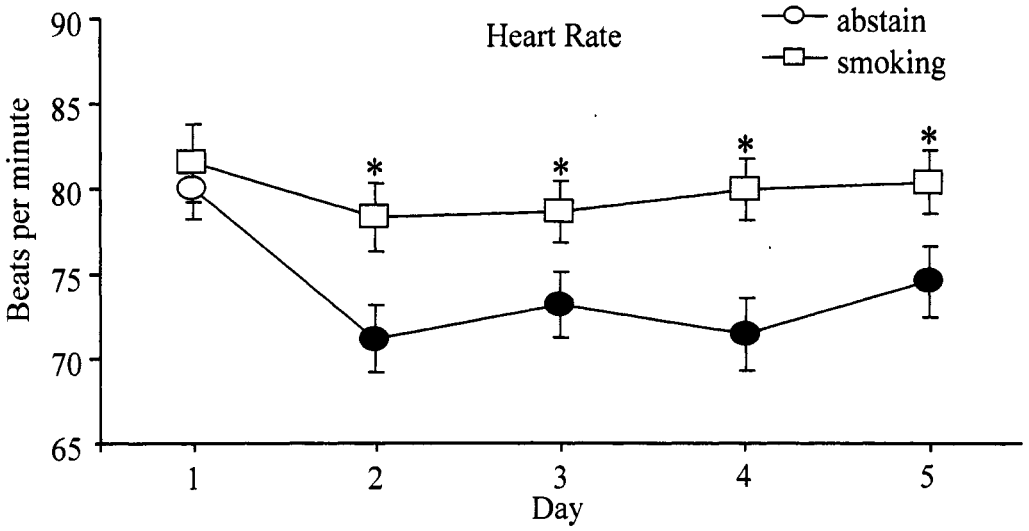

Figure 1. Mean data (+/-one SEM) for heart rate for smokers (N=32) during two, 5-day conditions in which they smoked cigarettes or abstained from smoking. Filled symbols indicate a within-condition significant difference from baseline (Day 1), asterisks (*) indicate a between-condition significant difference on that day (All Ps < .05; adapted from Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005).

Physiological tobacco abstinence signs are also evident in acute settings. For example, in one study heart rate was measured in 27 smokers (19 female; mean cpd = 23.9 and mean years smoking not reported) after 24 hours of tobacco abstinence (West & Russell, 1987). Participants reported to a laboratory setting and their heart rate and skin temperature was monitored for 10 minutes. They then smoked a cigarette and had their heart rate measured for another five minutes. Twenty-one of the participants were instructed to remain tobacco abstinent for the next 24 hours and to then return to the lab the following afternoon for a repeat of the laboratory procedures (the remaining 6 participants were not asked to abstain from smoking before the next visit). After 24 hours of abstinence, the heart rate for the 21 abstainers had dropped a mean of 14.8 beats per minute (Session 1 pre-cigarette 79.4 bpm, SD = 9.6 vs. Session 2 pre-cigarette 64.6 bpm, SD = 7.5). The heart rate for the non-abstainers remained virtually the same (Session 1 pre-cigarette 79.1 bpm, SD = 7.3 vs. Session 2 pre-cigarette 79.8 bmp, SD = 7.9). Thus

bradycardia was observed, consistent with the notion that decreased heart rate is a sign of nicotine/tobacco withdrawal.

While tobacco abstinence causes a decrease in heart rate, nicotine administration reverses that abstinence-induced bradycardia. For example, in one study of male cigarette smokers (N = 14; mean cigarettes per day = 26 and mean years smoking = 8.8), heart rate was assessed during 2-hour sessions in a four-condition study (Krivokapich, Schneider, Child & Jarvik, 1985). Conditions were random-ordered and varied by the cigarettes smoked and gum chewed: in one condition participants smoked high nicotine (2.0 mg) cigarettes, in another they smoked low nicotine (0.2 mg) cigarettes, in the third they chewed high nicotine (4.0 mg) gum and in the fourth they chewed low nicotine (2.0 mg) gum. Heart rates were significantly lower during the baseline/abstinence assessment and nicotine administration reversed that trend in a dose-dependent fashion. That is, higher doses of nicotine caused a greater increase in heart rate than lower doses of nicotine, such that peak heart rate increases (expressed as a percentage of baseline), were 7% (0.2 mg nicotine cigarette), 28% (2.0 mg nicotine cigarette), 6% (2 mg nicotine gum) and 12% (4 mg nicotine gum). In addition, blood pressure also rose after nicotine administration with the highest doses causing the greatest percent increase (e.g. 2 mg nicotine cigarette caused a 9% systolic and 12% diastolic increase over baseline). The observation that smokers who undergoing tobacco abstinence experience a drop in heart rate that is reversed by the administration of nicotine (but not when smoking denicotinized cigarettes) has been supported by a number of studies (e.g., Breland, Evans, Buchhalter & Eissenberg, 2002; Buchhalter, Schrinel & Eissenberg, 2000; Foulds et al., 1997). Clearly, decreased heart rate is associated with tobacco abstinence in regular

smokers; this apparent nicotine/tobacco withdrawal sign is reversible with the administration of nicotine.

Another study which assessed the effects of short-term tobacco abstinence examined whether the nicotine antagonist mecamylamine precipitated withdrawal in heavy cigarette smokers (average 37.5 cigarettes per day; Eissenberg, Griffiths & Stitzer, 1996). Cigarette smokers (N = 10; 3 women) and non-smokers (N = 10; 3 women) participated in three, 6 hour sessions where they received 0, 10 or 20 mg of mecamylamine. Smokers smoked a total of four own brand cigarettes during the first two hours of the session—one every 30 minutes. Mecamylamine was then administered and participants did not smoke for the remainder of the session. Physiological data were collected while participants were seated and resting for the 2 hours prior to drug administration and for 4 hours after drug administration. While smokers' heart rate decreased after receiving placebo mecamylamine, heart rate increased after both the 10 mg and 20 mg doses of mecamylamine (tachycardia is a known side effect of this medication; Nemeth-Coslett, Henningfield, O'Keefe & Griffiths, 1986). Thus, at the doses tested, antagonist administration did not precipitate heart rate reductions normally associated with tobacco abstinence.

In summary, bradycardia is one physiological measure that is a sign of spontaneous nicotine/tobacco withdrawal in humans, and can be measured after only a few hours of nicotine/tobacco abstinence. This withdrawal-related bradycardia can be reversed by nicotine administration. As heart rate can be assessed conveniently, quickly, and non-invasively, it is a reliable measure for assessing withdrawal and withdrawal suppression in men and women.

Weight gain is another reliable measure of withdrawal that is present after periods of tobacco abstinence (e.g., Williamson et al., 1991; Doherty, Militelio, Kinnunen & Garvey, 1996; Nordstrom, Kinnunen, Utman & Garvey, 1999; Hughes, Hatsukami, Pickens & Svikis, 1984). For example, using data from two national probability surveys, the First National Health and Nutrition Examination Survey I (NHANES) conducted from 1971 to 1975, and then the NHANES I Epidemiologic Follow-up Study, conducted with the same cohort from 1982 to 1984, researchers examined the relation between smoking cessation and severity of weight gain (Williamson et al., 1991). The cohort included 1,885 current smokers (1,137 women) and 768 former smokers (359 women) who had quit smoking for one year or longer. In both surveys, researchers weighed participants and administered questionnaires to elicit information about cessation. Compared to the current smokers, the former smokers gained 2.8 kg (men) and 3.8 kg (women) on average after smoking cessation. In fact, 9.8% of men and 13.4% of women who quit gained more than 13 kg. Thus this long-term study demonstrated that weight gain was strongly related to tobacco abstinence.

Another long-term study examined weight gain in smokers (N = 79) who used nicotine gum to help remain tobacco abstinent over a 90 day period (Doherty, Militelio, Kinnunen & Garvey, 1996). Three study conditions were ordered randomly and varied by the dose of nicotine in the gum: in one condition, participants (N=14; 6 women; mean cpd = 15.2 and mean years smoked not reported) chewed placebo gum; in another, participants (N = 31; 17 women; mean cpd = 20.7) chewed 2 mg nicotine gum; in the third condition, participants (N = 34; 12 women; mean cpd = 22.6) chewed 4 mg nicotine gum. Participants were instructed to chew 9 – 15 pieces of gum *ad libitum* per day.

Weight assessments were made at two baseline visits (one the week prior to cessation and one on quit day) and at six follow-up visits (on Days 1, 7, 14 30, 60 and 90 post-cessation). After cessation, participants in all three groups gained weight. Weight gain decreased in a linear fashion as nicotine dose increased, with placebo gum users gaining the most weight (3.7 kg), 2 mg nicotine gum users gaining an intermediate amount of weight (2.1 kg) and 4 mg nicotine gum users gaining the least amount of weight (1.7 kg) by Day 90. Participants in the placebo group gained significantly more weight ($p = .05$) than those in the 4 mg group. This finding is consistent with other studies that showed a linear increase between nicotine dose and cessation-related weight gain (Nordstrom, Kinnunen, Utman & Garvey, 1999; Leischow, Sachs, Bostrom & Hansen, 1992; Gross, Stitzer & Maldonado, 1989).

Yet another short-term study examined weight gain in smokers (N = 89) who used nicotine gum to help remain tobacco abstinent over a four-week period (Leischow, Sachs, Bostrom & Hansen, 1992). Three study conditions were ordered randomly and varied by the dose of nicotine in the gum: in one condition, participants (N=10; 8 women; mean cpd = 26.55 and mean years smoked not reported) chewed placebo gum; in another, participants (N = 11; 3 women; mean cpd = 26.15) chewed 2 mg nicotine gum; in the third condition, participants (N = 14; 5 women; mean cpd = 25.65) chewed 4 mg nicotine gum. Participants were instructed to chew 1 piece of gum per awake hour per day. Weight assessments were made at two baseline visits (one initial visit and one two days before quit day) and at four weekly follow-up visits. After cessation, participants in all three groups gained weight. For men, weight gain decreased in a linear fashion as nicotine dose increased, with placebo gum users gaining the most weight (1.60 kg), 2 mg

nicotine gum users gaining an intermediate amount of weight (1.45 kg) and 4 mg nicotine gum users gaining the least amount of weight (1.18 kg) by Week 4. For women, placebo gum users gained the most weight (1.69 kg), 2 mg nicotine gum users gained a small amount of weight (.33 kg) and 4 mg nicotine gum users lost weight (.26 kg) by Week 4. As this study demonstrated, weight gain is strongly related to nicotine abstinence and nicotine gum helps reduce the increased weight that is associated with abstinence.

Increased caloric intake, as well as post-cessation weight gain, has been shown in short-term studies (Hatsukami, Hughes, Pickens & Svikis, 1984). In one study, smokers (N = 27) were housed for seven days in a general clinical research center and were divided into two groups: control (N = 7; 3 women, mean cpd = 30.4 and mean years smoked = 14.7 years) and experimental (N = 20, 9 women; mean cpd = 36.9 and mean years of smoking = 13; Hatsukami et al., 1984). Both groups smoked their own brand of cigarette *ad libitum* for Days 1 – 3. The control group continued to smoke *ad libitum* on Days 4-7 while the experimental group abstained from smoking for that same period. Body weight and caloric intake were measured twice daily and revealed that there were no significant changes in the control group over the seven days. However, weight in the experimental (abstinent) group increased significantly from mean baseline assessment (67.8 kg) to mean abstinence assessment (68.0 kg; a .79 kg or 1.76 pound increase). In addition, caloric intake in the experimental group increased significantly from mean baseline assessment (1,397 calories) to mean abstinence assessment (1,651 calories). Thus, in smokers, short-term cigarette abstinence can produce reliable increases in weight and caloric intake.

In addition to reduced heart rate and increased caloric intake and weight, changes in electroencephalogram (EEG) activity are also associated with tobacco abstinence, and thus may be a sign of nicotine/tobacco withdrawal (Gilbert et al., 2004; Knott, 2001; Pickworth, Herning & Henningfield, 1989). EEG is a noninvasive measure often used to assess central nervous system "arousal" alterations (Knott, 2001; Knott & Venables, 1977; Lindsley, 1952). Long-term spontaneous EEG activity was measured in 67 women who smoked cigarettes regularly (mean cpd = 20.6 and participants had smoked for at least two years) before and during 31 days of tobacco abstinence. During the study, participants were administered EEGs for five sessions before quitting smoking and again on Days 3, 10, 17 and 31 after cessation. Results showed a slowing of EEG frequency, characteristic of decreased alertness and arousal. These effects did not resolve across the 31 days of abstinence, consistent with a similar work that involved 56 men only (Gilbert et al., 1999). This pattern of results may suggest an extended impact of tobacco abstinence on the brain wave activity of daily smokers.

Short-term smoking abstinence also results in a slowing of EEG frequency (Pickworth, Herning & Henningfield, 1989). In a study of spontaneous withdrawal, seven male smokers who had smoked at least 20 cigarettes per day (mean years smoking = 16) participated in three conditions: first, participants smoked their own brand of cigarettes *ad libitum* for five days; second, they were tobacco abstinent for ten days; last, they resumed *ad libitum* smoking for three days. EEG sessions were held throughout the study and revealed that EEG alpha and beta frequencies that are associated with arousal decreased during abstinence. Thus, there is some support for the notion that decreased EEG activity is a sign of tobacco withdrawal.

Behavioral/Performance Effects of NicotineTobacco Withdrawal in Humans.

Studies in which chronic tobacco administration is terminated abruptly in humans demonstrate that these conditions produce several behavioral effects, such as a decreased ability to concentrate. For example, in one study that examined the effects of tobacco abstinence, cognitive performance was also measured (Gilbert et al., 2004) by use of the rapid visual information-processing task (RVIP). The RVIP is a task that requires sustained attention and working memory (Lawrence, Ross & Stein, 2002) and is a reliable measure of nicotine's effects on concentration (Warburton & Mancuso, 1998). The RVIP task in this study lasted for 17 minutes and consisted of a series of single digits presented on a computer screen at the rate of 116 per minute. When three consecutive odd or even digits are presented then the participant was asked to press a response key. The results indicated that the number of correct detections on the RVIP task decreased significantly ($P < .001$) in the nicotine-abstinent group, indicating decrease in concentration. Cognitive decrements that are associated with tobacco abstinence are often reported using a variety of tasks (Parrott & Kaye, 1999; Foulds et al., 1996; Heishman, Taylor & Henningfield, 1994; Sherwood, Kerr & Hindmarch, 1992; Hatsukami, Fletcher, Morgan, Keenan & Amble, 1989).

Similar results were reported in a study that examined the effects of the transdermal nicotine patch on information processing (Warburton & Mancuso, 1998). Twenty male participants (who smoked at least 15 cpd; smoking history not reported) were asked to perform the RVIP task in a laboratory setting. After a period of 12 hours smoking abstinence, smokers participated in two sessions—one in which they were given a placebo patch and one in which they were given a 21 mg nicotine patch. Six hours after

application of the patch the RVIP was administered. Relative to detections by the placebo group (5.15), the active patch group had a 10.8% increase in correct detections made minute-by-minute (5.71; $P < .005$). After tobacco abstinence, the mean reaction time for the placebo group (444 ms) was significantly longer than for the active patch group (427 mg; $P < .01$). These results suggest that, at least in a controlled laboratory setting, smoking abstinence has a negative impact on attention and reaction time, which may contribute to the performance decrements and discomfort that smokers report during an attempt to quit.

Another study demonstrated performance decrements in abstinent smokers using a general cognitive task – the digit symbol substitution task (DSST; Eissenberg, Griffiths & Stitzer, 1996). The DSST involves participants reproducing randomly selected geometric patterns as accurately as possible during a 90 second period, and was administered every 30 minutes during 6-hour sessions in which nonsmokers (N = 20; 3 women) and smokers (N = 20; 3 women; mean cpd = 37.5 for the past 2 years, on average) participated. Results indicated that, starting at 90 minutes from the onset of nicotine/tobacco abstinence and continuing throughout the rest of the session, abstinent smokers performed significantly worse than non-smokers on the DSST (however, another study failed to observe these abstinence-induced decrements in DSST performance; Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005). These results that suggest that short-term smoking deprivation results in performance decrements are consistent with other studies (Sherwood, Kerr & Hindmarch, 1992; Knott, Bosman, Mahoney, Ilivitsky & Quirt, 1999) and support the finding that withdrawal can be measured on an acute basis.

Symptoms of Nicotine/tobacco Withdrawal in Humans. In addition to signs and behavioral changes, the use of humans as research participants allows measurement of the subjective effects associated with the abrupt termination of chronically tobacco-administered nicotine. These effects have been assessed using a variety of non-standardized (Ward, Swan & Jack, 2001; West & Russell. 1987; Abelin, Buehler, Müller, Vesanen & Imhof, 1989) and standardized (Tiffany & Drobes, 1991; McNair, Lorr & Droppleman, 1971; Shiffman & Jarvik, 1976) questionnaires. These symptoms have been observed over weeks, though they become apparent in hours, as described below.

In cigarette smokers, tobacco abstinence is associated by a variety of symptoms such as anxiety, difficulty concentrating, irritability, insomnia, and increased appetite (American Psychiatric Association, 1994; Hughes, Higgins & Bickel, 1994; Hughes, Gust, Skoog, Keenan & Fenwick, 1991; Hatsukami, Dahlgren, Zimmerman & Hughes, 1988). For instance, in one double-blind study (Hughes et al., 1991), 315 smokers (177 women; mean cpd = 29.5; mean years smoking not reported) who were trying to quit (37.5% had tried to quit more than three times) were assigned to either a placebo or nicotine gum (2 mg) condition; gum was provided for daily use (*ad libitum* for no more than three months) and participants responded to self-report items assessing tobacco withdrawal symptoms immediately prior to cessation, and at 1, 2, 4, 24 -26, and 48-52 weeks after cessation. The items were: angry/irritable, impatient, restless, anxious, drowsy, craving, difficulty concentrating, hunger, insomnia, physical symptoms, stomachache and headache. Participants rated each item on a 4-point scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe). A significant difference between mean scores for participants who receive active and placebo gum was observed on items

assessing anxiety (mean active gum score = 1.6; mean placebo gum = 2.0; P <.001), anger (1.4 active gum vs. 1.8 placebo gum; P <.001), difficulty concentrating (1.2 active gum vs. 1.4 placebo gum; P <.001) and hunger (1.3 active gum vs. 1.6 placebo gum; P <.001) and were reported during the first week of abstinence. While many withdrawal effects returned to pre-cessation levels by 1 month, hunger continued for six months in the smokers who remained abstinent. Thus, this study revealed some symptoms of tobacco abstinence, and demonstrated, similar to other studies (Gross & Stitzer, 1989; Hughes & Hatsukami, 1985) that these symptoms could be suppressed by the active nicotine gum. Note, however, that gum that does not contain nicotine can also suppress tobacco abstinence effects to some degree (Davies, Willner, James & Morgan, 2004; Shiffman et al., 2003).

Symptoms associated with the first month of tobacco abstinence have been reported in several studies (Hughes, 1992; Shiffman, Khayrallah & Nowak, 2000, Gritz, Carr & Marcus, 1991). For example, in a study of, 46 smokers (28 women; mean cpd = 24.6 and mean years smoked = 23.1) were evaluated on Days 1, 7, 14, 21 and 28 after smoking cessation and compared to 29 non-smokers (19 women) who were matched for age and gender (Ward, Swan & Jack, 2001). Symptom evaluation was conducted using an "Abstinence Effect Rating Scale" which was created for the study based on American Psychiatric Association criteria for nicotine withdrawal (e.g., "irritability", "difficulty concentrating"), items listed in two comprehensive reviews of abstinence (Hughes, Higgins & Hatsukami , 1990; USDHHS, 1988; e.g., "fatigue", "drowsiness") and other reported abstinence effects (Hughes, 1992; e.g. "headache", "nausea"). Other measures included the Shiffman-Jarvik Withdrawal Symptom Scale (Shiffman & Jarvik, 1976), the

Perceived Stress scale, the Profile of Mood States (POMS) and a sleep scale. During the first day of withdrawal, abstinent smokers reported depression, anger, difficulty concentrating, anxiety, irritability and restlessness. In addition, they reported other effects in significantly greater percentages than non-smokers, including dizziness (34% smokers vs. 5% nonsmokers), headache (38% smokers vs. 15% non-smokers), and nausea (16% smokers vs. 4% non-smokers). Though the symptoms persisted throughout the 28-day time period, they decreased over time, with the most severe symptoms being reported in the first twenty-four hours after abstinence (Ward, Swan & Jack, 2001).

Many of these same symptoms have been noted studies with shorter-term assessment periods (e.g., Hughes & Hatsukami, 1986). For instance, in one study of 50 smokers (27 women; mean cpd = 29 and mean years of smoking = 21), participants responded to a battery of measures, including a subject-rated symptom rating list and a mood questionnaire, during two days of initial screening (where the participants could smoke their own brand of cigarettes *ad libitum*) and again during four days of cigarette abstinence. While the participants were tobacco abstinent, they were instructed to use placebo gum *ad libitum* whenever they had a craving. Results of this study indicated increases in self-reported craving for tobacco (mean = 2.3, SE = 0.1; $P < .001$), irritability (mean = 1.4, SE = 0.1, $P < .001$) and anxiety (mean = 1.7, SE = 0.1, $P < .001$) during cigarette abstinence. Significant effects of similar magnitude were observed on measures of difficulty concentrating, restlessness, impatience and hunger. These results demonstrate that subject-rated measures are sensitive to changes in nicotine/tobacco withdrawal symptomatology during a 4-day abstinence period.

Another study involved validation of a questionnaire that was designed to assess the effects of tobacco abstinence on smoking urges (Tiffany & Drobes, 1991). The 32-item, 7-point Likert scale (1 "Strongly disagree" to 7 "Strongly agree") Questionnaire of Smoking Urges (QSU) was administered to 230 participants (women = 89; mean cpd = 22.3 and mean years smoking = 4.81) either 0 (N = 80), 1 (N = 75) or 6 (N = 75) hours after onset of tobacco abstinence. Items related to smoking included, "All I want right now is a cigarette," "I would be less irritable now if I could smoke," "Smoking would not help me calm down now," "I will smoke as soon as I get the chance," etc. The data from the 32 items were then analyzed using factor analysis. Results yielded two distinct factors: Factor 1 was a 15-item subscale related to intention to smoke (e.g., "If I were offered a cigarette, I would smoke it immediately") and Factor 2 was an 11-item subscale related to anticipation of relief from withdrawal (e.g., "If I were smoking now I could think more clearly"). For the entire sample across the three different abstinence conditions (0-hour: Factor 1 mean = 4.17, SE = .16 and Factor 2 mean = 2.99, SE = .14; 1-hour: Factor 1 mean = 5.37, SE = .14 and Factor 2 mean = 3.40, SE = .14; 6-hour: Factor 1 mean = 5.88, SE = .12 and Factor 2 mean = 3.96, SE = .17), Factor 1 and Factor 2 scales were reliable ($P < .0001$) with scores that were directly related to abstinence duration. This study demonstrates that empirically-validated subject-rated measures are sensitive to changes in nicotine/tobacco withdrawal symptomatology during abstinence periods of 0, 1, or 6 hours. Both the Hughes & Hatsukami (1986) questionnaire, which measures potential direct effects of withdrawal, and the Tiffany & Drobes (1991) questionnaire, which is an empirically-validated measure of smoking urges, have become commonly used subject-rated measures of nicotine and tobacco withdrawal and have

been used often in clinical studies of nicotine/tobacco withdrawal (Breland, Evans, Buchhalter & Eissenberg, 2002; Eissenberg, Adams, Riggins & Likeness, 1999; Eissenberg, Griffiths & Stitzer, 1996).

Symptoms of tobacco abstinence have been measured using the QSU and items from the Hughes & Hatsukami (1986) questionnaire (in visual analog scale format, see Eissenberg, Griffiths & Stitzer, 1996) in a placebo control study of nicotine/tobacco withdrawal (Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005). In this laboratory-based, within-subject study, 32 smokers (13 women; mean cpd = 20.7 cigarettes and mean years smoking = 6 years) completed 5-day conditions in which they smoked nicotine-containing cigarettes or no cigarettes (see Figure 2). Relative to Day 1 of smoking abstinence, mean scores for "intention to smoke" increased 33.5% after 4 days of no smoking ($P < .05$). Ratings of "Urges to smoke" also increased significantly from Day 1 of smoking abstinence (mean = 57.4, SD = 20.9) to Day 2 (mean = 73.9, SD = 20.0), and remained significantly elevated across Days 3 (mean = 72.4, SD = 23.9), 4 (mean = 70.6 SD = 25.5), and 5 (mean = 67.0, SD = 29.6; $Ps < .05$).

Overall, tobacco abstinence symptoms can include irritability, anxiety, difficulty concentrating and craving for tobacco (Hughes, Hatsukami, Pickens, Krahn, Malin & Luknic 1984; West & Hajek 1997, Shiffman, Khayrallah & Nowak, 2000), and may also include depressed mood and dysphoria. For example, in one study (Foulds et al., 1997), 18 smokers (mean cpd = 21 for at least the prior two years) and 18 non-smokers participated in a double-blind, placebo-controlled cross-over design with three nicotine dose conditions (0, 0.3, and 0.6 mg nicotine s.c.). Each participant arrived at the laboratory for one familiarization session and three experimental sessions, at which

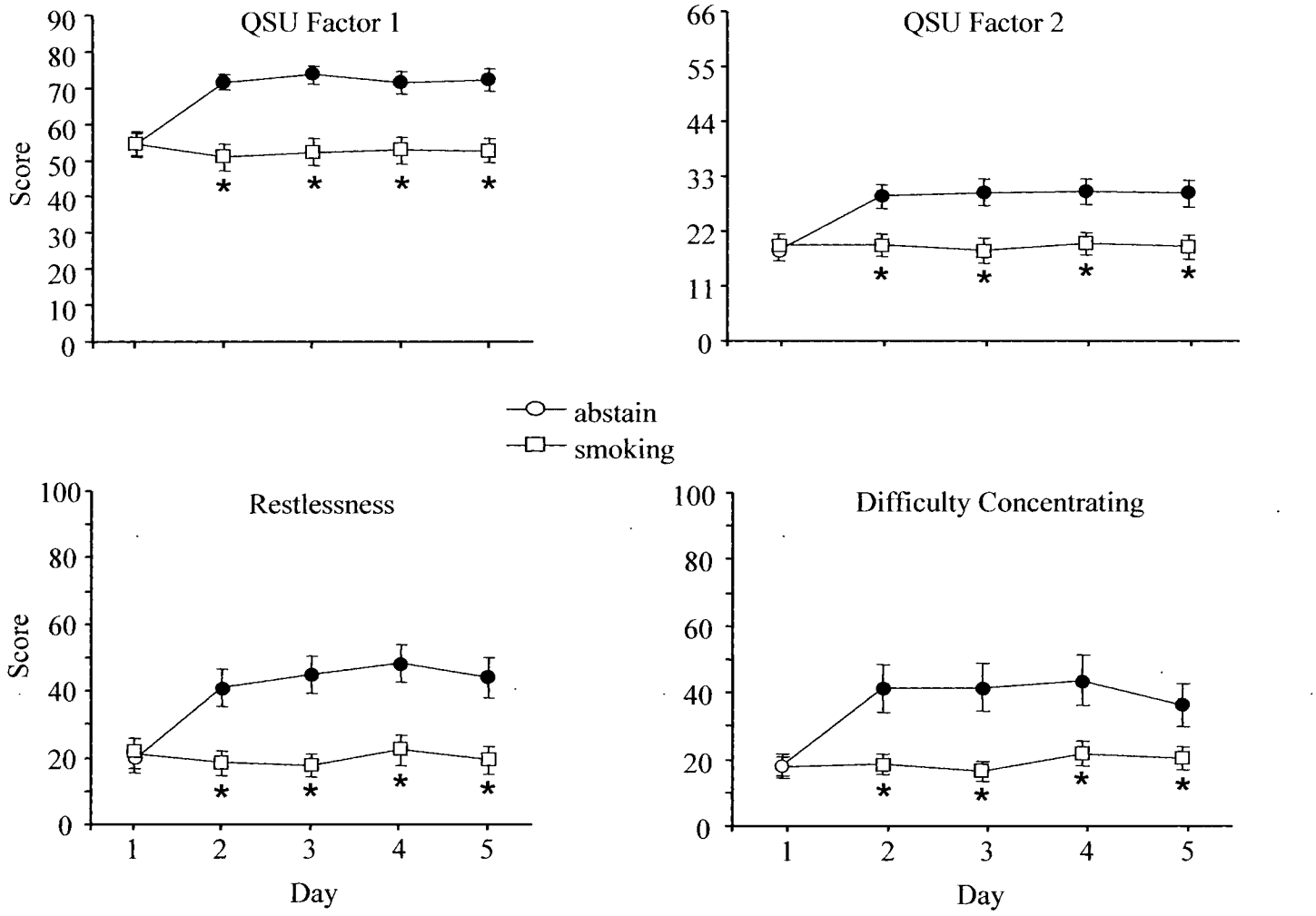

Figure 2. Comparison of withdrawal responses to nicotine/tobacco withdrawal. The figure shows averaged data (+/-one SEM) from 32 smokers. In all other respects the figure is identical to Figure 1.

participants had to be nicotine abstinent for the past 24 hours. Participants responded to a tobacco withdrawal symptom questionnaire at the beginning of each session and a mood questionnaire before and after the nicotine injection. Results revealed that mood deteriorated significantly more for abstinent smokers than for non-smokers on measures of contentedness ($P < .01$), calmness ($P < .046$) and dysphoria ($P < .048$) when they were assessed after 24 hours of withdrawal and neither the 0.3 or 0.6 mg nicotine reversed the mood deficit. In non-smokers, mean changes of pre-post first injection scores in mood decreased when 0.6 mg nicotine was administered for alertness (mean = -9.4, SD = 12) and contentedness (mean = -7.2; SD = 14). The worsening of mood response to 0.6 mg nicotine in non-smokers was though to be related to symptoms of nicotine toxicity whereas the significant decrease in mood following abstinence in smokers was characteristic of tobacco withdrawal (APA, 1994).

In summary, this section demonstrates that, in humans who self-administer tobacco-delivered nicotine chronically (i.e., regular, frequent tobacco users), tobacco abstinence results in a well-defined, quantifiable syndrome that includes observable signs (decreased heart rate, increased caloric intake and weight, EEG changes), behavioral decrements, and, most reliably, aversive subjective effects (irritability, restlessness, impatience). This syndrome, often referred to as "nicotine/tobacco withdrawal" (Jarvis, 2004; Buchhalter, Schrinel & Eissenberg, 2001; Jorenby et al., 1996; Hatsukami, LaBounty, Hughes & Laine, 1993) likely contributes to the difficulty in quitting smoking reported by treatment-seeking smokers (Fagerström, Schneider & Lunell, 1993; Killen, Fortmann, Kraemer, Varady & Newman, 1992; Hughes & Hatsukami, 1996) and also the fact that while 46% of U.S. smokers try to quit smoking each year, only 7% achieve one-

year abstinence (Fiore et al., 2000). The signs, performance decrements, and symptoms, associated with nicotine/tobacco abstinence are thought to arise, at least in part, from nicotine deprivation (O'Dell, Bruijnzeel, Ghozland, Markou & Koob, 2004; Heishman, Taylor & Henningfield, 1994; Hughes, Gust, Skoog, Keenan & Fenwick, 1991). Thus, the administration of pharmacologically pure nicotine may reduce these symptoms, and be an efficacious smoking cessation pharmacotherapy, as reviewed below.

Pharmacologically Pure Nicotine is Efficacious and Suppresses Withdrawal. Pharmacologically pure nicotine used as "nicotine replacement therapy" (or NRT), has been a mainstay for the treatment of nicotine dependence for several years (Fant, Owen & Henningfield, 1999; Hurt, 1999). Use of NRT can approximately double a person's chance of quitting smoking (Silagy, Lancaster, Stead, Man & Fowler, 2002). The first preparations of pharmacologically pure nicotine that were used for smoking cessation were the polacrilex gum and transdermal patch. Originally, both were available only by prescription but are now available over the counter (Fiore, Smith, Jorenby & Baker, 1994). Other nicotine preparations available over the counter include a lozenge (Shiffman, Dresler & Rohay, 2004) and sublingual tablet (in Europe; Glover et al., 2002). Nicotine inhaler (Leischow, Ranger-Moore, Muramoto & Matthews, 2004) and nasal spray (Lerman et al., 2004; Sutherland et al., 1992) are available by prescription only (Schneider et al., 2004). This section begins with a brief statement of the general characteristics of nicotine replacement therapy, with a focus on transdermal nicotine (TN). It then summarizes studies that support the efficacy of NRT, specifically TN. Finally, this section summarizes studies that show the ability of TN to suppress

nicotine/tobacco withdrawal in smokers, including the signs, performance decrements and, especially, the oft-reported and aversive withdrawal symptoms.

Pharmacologically Pure Nicotine is Efficacious. Nicotine replacement therapy is recommended as a first-line treatment for tobacco dependence (Fiore, 2000; Watts, Noble, Smith & Disco, 2002). This recommendation is based on numerous randomized clinical trials that demonstrate that, relative to placebo, cessation rates are higher when treatment seeking smokers receive active nicotine gum (Silagy, Mant, Fowler & Lancaster, 2000; Hajek et al., 1999), inhaler (Bollinger et al., 2000; Hughes, Grass & Pillitteri, 2000), nasal spray (Schneider et al., 2003; Croghan et al., 2003), lozenge (Shiffman, Dresler & Rohay, 2004; Shiffman et al., 2002), or patch (Kalman et al., 2004; Hughes, Shiffman, Callas & Zhang, 2003; Kotlyar & Hatsukami, 2002; Sachs, Sawe & Leischow, 1993). In addition, randomized clinical trials have shown that, relative to advice and support alone, NRT produces better cessation rates when used in specialized cessation clinics (Okuyemi, Ahluwahlia & Harris, 2000; Tonnesen et al., 1999, Transdermal Nicotine Study Group, 1991) or in primary care settings (Coleman, Wynn, Barrett & Wilson, 2003; Russell et al., 1993). A meta-analysis of over 100 randomized trials concluded that NRT approximately doubles the rates of long term cessation (Fiore et al., 2000; Silagy et al., 2000). In addition, meta-analysis of the efficacy of solely over-the-counter NRT also revealed that NRT is efficacious (Hughes, Shiffman, Calla & Zhang, 2003).

NRT's efficacy was highlighted in a study that examined individual preferences for and response to four types of nicotine replacement products (West et al, 2001). Five-

hundred and four participants (328 women; mean cpd = 25 and mean years of smoking not reported) in a cessation study were shown a brief video explaining four NRT products: transdermal patch, gum, nasal spray and nicotine inhaler. After viewing this video at a hospital clinic on their quit date, participants were asked to provide ratings on opinions on the four products. Men and women differed in their preference for different products—the patch was the most preferred for both sexes and the difference was more robust for women (48% women vs. 37% men). After rating the products, participants were assigned randomly to use one of the four products for the following 15 weeks. Abstinence was assessed at Weeks 1, 4, 12 and 15; continuous abstinence rates were: patch (23.4%), spray (23.0%), gum (22.8%) and inhaler (27.6%), with no significant differences between the groups—thus NRT was efficacious for cessation. However, male and female participants differed in their 15 week success rates, with men more successful in every condition except the inhaler, and abstinence rates using the patch greater for men (24%) than for women (17%; n.s.).

Indeed, transdermal nicotine, the first NRT preparation on the market, is the easiest form of NRT for patients to use (Shiffman, Khayrallah & Nowak, 2000) and one of the most commonly used NRTs in the United States (Johnson & Hill; 2004). Transdermal nicotine patches produce steady blood nicotine levels, which are dose-dependent and plateau within four to six hours (Henningfield & Kennan, 1993). Plateau levels are sustained for 16-24 hours depending on the transdermal delivery system (Hurt, 1999). Transdermal nicotine offers the opportunity to deliver a variety of nicotine doses and, in general, higher doses are applied at the start of treatment, and doses can be tapered as desired (Waring, 2003). A recent meta-analysis confirmed the efficacy of

various transdermal patch preparations in improving the success of smoking cessation attempts (Silagy, Lancaster, Stead, Mant & Fowler, 2004). Because TN is efficacious, readily available, provides several dose options, and allows precise control of peak nicotine levels, efficacy data for this form of NRT are reviewed briefly, below.

One of the earliest clinical trials of the transdermal nicotine (TN) patch was a randomized, placebo-controlled, double-blind study (Daughton et al., 1991). Participants (N=158; mean cpd = 32.9 and mean years smoking = 23.9) were randomly assigned to one of three study conditions where 21 mg of nicotine or placebo patches were applied daily for four weeks. In one condition participants received 24-hour nicotine delivery, in another they received nicotine only during waking hours (approximately 16 hours) and in the final condition they received placebo. Participants were monitored for abstinence weekly for four weeks and also at six months post-quit. During the last two weeks of the weekly monitoring period, 13.5% of the placebo group were tobacco abstinent, as compared to 39% of the 24-hour nicotine delivery group (p=.002) and 35% of the 16-hour nicotine delivery group (p=.003). At the six month follow-up visit, 8% of the placebo group were tobacco abstinent, as compared to 22% of 24-hour nicotine delivery group quitters (p=.046) and 31% wakeful group quitters (p=.003). As compared to placebo, active TN was more effective at successful cessation rates.

Because smokers who are motivated to stop smoking in the near future are more likely to have tried TN than other smokers (Pierce, Gilpin & Farkas, 1995), a substantial portion of smokers who use transdermal nicotine are probably trying it for a second or subsequent time. Thus, evaluating the efficacy and safety of TN in smokers who have relapsed to moderate to heavy smoking after an initial attempt to stop smoking by using

active TN may be important (Gourlay, Forbes, Marriner, Pethica & McNeil, 1995). In a double-blind, placebo controlled trial evaluating this issue, 629 smokers (362 women; mean cpd = 32.6 and mean years of smoking = 23.2) received active TN patches (randomized treatment of four weeks each of 21 mg/day, 14 mg/day, 7 mg/day, or placebo) and brief counseling (e.g. 5 – 10 minutes of counseling and a booklet containing advice on smoking cessation) for twelve weeks (Gourley et al., 1995). At weeks 4, 8, 12 and 26 after quit day, participants were interviewed and assessed for adverse events. Most adverse experiences were mild and consisted mostly of reactions at the site of application of the patch, whether active or placebo, though there were a few reports of headache (4.5% active vs. 9.1% placebo) and nausea (5.6% active vs. 4.9 % placebo). TN improved the success rate of cessation to (6.7% active vs. 1.9% placebo) at Week 12 and (6.4% active vs. 2.6% placebo) at Week 26. Repeated treatment with TN with brief counseling has demonstrated improved cessation rates in recently relapsed, moderate to heavy smokers.

Not only is TN effective as a cessation tool, but at least one study (Tonnesen et al., 1999) found that higher doses of TN patches increased cessation rates. In that particular study, a total of 3,575 smokers (1,716 women, mean cpd = 26.8 and participants had smoked for a least 3 years) were enrolled in a double-blind, placebo-controlled study and given placebo, 15 mg/day or 25 mg/day TN patches for either 8 or 22 weeks. Smokers visited clinics at Weeks 1, 2, 4, 8, 12, 22, 26 and 52 to assess cessation. After one year, success rates for cessation were: placebo (9.9%); 15 mg TN patch for 8 weeks (11.7%), 15 mg TN patch for 22 weeks (13.7%); 25 mg TN patch for 8 weeks (15.9%), and 25 mg TN patch for 22 weeks (15.4%). At all time points the

success rate was significantly higher for the 15 mg TN patch vs. the placebo group and for the 25 mg TN patch group vs. the 15 mg TN patch group. Therefore, the TN patch facilitated cessation, with higher TN patch doses yielding higher cessation rates (see also Dale et al., 1995; Transdermal Nicotine Study Group, 1991; Tonnesen et al., 1991, Daughton et al., 1999) though a dose effect on cessation is not always observed (e.g. Daughton et al., 1991; Jorenby et al., 1996).

In summary, numerous clinical trials in a variety of settings support the efficacy of several NRT preparations as smoking cessation pharmacotherapies. TN is one such preparation that is easy to use, available in several doses, yields precise steady-state plasma levels, and, some evidence suggests, provides increased efficacy with higher doses. The efficacy of TN (and all NRT preparations) is thought to be based, at least in part, on its ability to suppress withdrawal in abstinent smokers. The following section explores the data that support the notion that TN suppresses withdrawal, and is followed by a discussion of the potential role that gender may play in modulating this withdrawal suppressing effect.

Pharmacologically Pure Nicotine Suppresses Withdrawal

Pharmacologically pure nicotine has been proven to suppress signs of withdrawal (West & Shiffman, 2001; Molander, Lunell & Fagerström, 2000; Hurt et al., 1998; Leischow et al., 1997; Foulds et al., 1992; Killen, Fortmann, Newman & Varady, 1990; Hughes, Gust, Keenan & Fenwick, 1989; Hughes et al., 1984; West, Jarvis, Russell, Carruthers & Feyerabend, 1984). For example, in one smoking cessation study, 1,218 smokers (630 female; mean cpd = 24.8 and mean years smoking = 24.5) were assigned to one of four study conditions: 2 mg gum (used *ad libitum)*, 2 mg nicotine gum (chewing

according to a fixed schedule), placebo gum, and no gum (Killen, Fortmann, Newman & Varady, 1990). At 48 hours, and 2, 6, and 12 months after stopping smoking, participants were assessed for craving based on their responses to two questions: "Have you felt craving for a cigarette?" and "Have you felt a strong urge to smoke?". While there was no significant difference in craving scores between conditions for women, there was a significant difference in craving scores for Weeks 1, 2 3 and 4 (p=.02, p=.05, p=.05 and p=.03) in men who received active nicotine gum under a fixed chewing regimen then for men who did not receive nicotine gum. That is, men who chewed active nicotine gum under a fixed chewing regimen (mean craving scores for Weeks 1 -4 = 2.6, 2.2, 2.0 and 1.8) reported lower craving scores across testing times compared to men who received placebo gum (mean craving scores = 2.8, 2.5, 2.2, 2.2) or no gum (mean craving scores = 3.1, 2.7, 2.5, 2.4). Thus, at least for men, nicotine gum suppresses the withdrawal symptoms that appear after cessation of tobacco smoking.

NRT-induced withdrawal suppression is evidenced not only with nicotine gum but also with the nicotine inhaler (Hurt et al., 1998). In a randomized, single-blind study, 91 participants (41 female, mean cpd = 24.5 and mean years smoking = 19.9) were assigned to received either 1 mg nicotine nasal spray (N=29; 14 women), placebo nasal spray (N=16; 8 women), 4 mg nicotine gum (N=31; 15 women) or placebo gum (N=15; 7 women). After verified overnight abstinence, participants were assessed for withdrawal repeatedly via visual analog scales during a 30 minute baseline period and then for 120 minutes after drug administration. This assessment was repeated for a total of three times during a study day. For all time points, the active nasal spray reduced withdrawal (P <

.05) and craving ($P < .05$) significantly more than placebo nasal spray. Thus the nicotine inhaler was proven effective tobacco withdrawal suppression.

The nicotine sublingual tablet has also been proven to reduce tobacco withdrawal symptoms (Molander, Lunell & Fagerström, 2000). In a double-blind, placebo-controlled study, 20 participants (12 women, mean cpd = 19.5; participants had smoked for at least the past year) were given either a 2 mg sublingual nicotine tablet or placebo to use for two consecutive days, with each condition being separated by one week (Molander, Lunell & Fagerström, 2000). Over each 2-day period withdrawal symptoms of "irritability"," impatience", "difficulty concentrating", "dizziness" and a total withdrawal score, as well as craving items of "urges to smoke," "missing cigarettes" and a total craving score, were assessed in the laboratory nine times using visual analog scales. At all time points, active nicotine total withdrawal symptom (mean = 23, SD = 27) and total craving (mean = 45, SD = 28) scores were significantly lower as compared to placebo total withdrawal symptom (mean = 71, SD = 59) and total craving scores (mean =87, SD = 32; $P < .005$). This study clearly demonstrates that withdrawal symptoms of smoking abstinence are reduced by the nicotine sublingual tablet.

In addition to gum, inhaler, and sublingual tablet, the nicotine lozenge also suppresses the symptoms associated with tobacco abstinence (Muramoto, Ranger-Moore & Leischow, 2003). In one open-label, within-participant study, 11 smokers (6 women, mean cpd = 25 and mean years of smoking = 23). used three different flavors (peppermint, cinnamon and unflavored) of a 4 mg nicotine lozenge during eight days of tobacco abstinence. On Days 1 and 8, participants spent 8 hours in a laboratory environment using between 12 – 18 lozenges *ad libitum* per day and on Days 2 through 7

participants used the lozenges in their natural environment. During laboratory sessions, participants were assessed for eight withdrawal symptoms via a questionnaire (Hughes & Hatsukami, 1986), including: "craving", "irritability/frustration/anger", "anxiety", "difficulty concentrating", "restlessness", "increased appetite", "depressed mood" and "impatience". Mean withdrawal scores pre- and post-lozenge decreased significantly ($P < .05$) for anxiety (1.96, SD 1.15= vs. 1.32, SD = .67), craving (2.80, SD = 1.39 vs. 1.37, SD = .81), difficulty concentrating (1.80, SD = 1.27 vs. 1.40, SD = .75, impatience (1.80, SD = 1.11 vs. 1.30, SD = .61) and restlessness (1.88, SD = 1.16 vs. 1.29, SD = .58). Therefore, suppression of withdrawal symptoms was clearly demonstrated with the nicotine lozenge.

In summary, NRT-induced withdrawal suppression has been demonstrated with gum (Hughes, Gust, Keenan & Fenwick, 1990; Hughes, Gust, Skoog, Keenan & Fenwick, 1991), the inhaler (Schneider et al., 1996; Lunell, Molander, Leischow & Fagerström, 1995) the sublingual tablet (Molander, Lunell & Fagerström, 2000) and the lozenge (Muramoto, Ranger-Moore & Leischow, 2003). The next section will highlight TN's ability to suppress tobacco withdrawal.

Transdermal Nicotine Suppresses Signs of Withdrawal

TN suppresses several withdrawal signs, including decreased heart rate, changes in brain activity and weight gain (Hughes, 1993). For example, decreases in heart rate and brain activity that accompany tobacco withdrawal can be reversed by the administration of TN (Pickworth, Fant, Butschky & Henningfield, 1996). In one study, ten participants (1 woman; mean cpd = 29 and mean years smoking = 14.3 years) were administered four doses of TN patch (either 0, 10, 20 or 30 mg nicotine) daily for three

consecutive days, with participants randomly receiving each dose condition, a different one every week, for four consecutive weeks (Pickworth, Fant, Butschky, & Henningfield, 1996). Heart rate and brain activity were assessed six hours after the application of the TN. Heart rates in the 20 mg TN patch and 30 mg TN patch conditions were significantly higher ($P < .05$) than the placebo condition, where heart rate decreased by up to 10 bpm by Day 3. In addition, during the placebo condition, EEG frequency was significantly lower ($P < .001$) which is characteristic of decreased alertness and arousal, and this effect was reversed during the 20 mg TN patch and 30 mg TN patch nicotine condition.

TN can reduce withdrawal deficits of decreased EEG activity after just one dose (Knott, Bosman, Mahoney, Ilivitsky & Quirt, 1999). Sixteen men (mean cpd = 23.0 and mean years smoking = 12.8) who abstained from smoking overnight were administered either a placebo or a 21 mg TN patch on two separate test days in double-blind, placebo-controlled laboratory study (Knott, Bosman, Mahoney, Ilivitsky & Quirt, 1999). EEGs were administered immediately prior and 4 hours after patch application. Relative to placebo, where a decrease in brain arousal was seen, transdermal nicotine increased alpha ($p=.001$) and beta ($p=.02$) EEG frequency waves significantly, thus reversing nicotine withdrawal.

TN reduces weight gain in participants who have quit smoking successfully (Jorenby et al., 1996; Tonnesen et al., 1991; Transdermal Nicotine Study Group, 1991). Hispanic women ($N = 55$; mean cpd = 18.6 and mean years of smoking = 21.3) and men ($N = 53$; mean cpd = 21.0 and mean years smoking = 23.6) were assigned randomly to receive either placebo or TN for 10 weeks (21 mg TN for six weeks, 14 mg TN for two

weeks and 7 mg TN for two weeks; Hill, Roe, Taren, Muramoto & Leischow, 2000). Participants were weighed at the beginning of the study and at follow-up visits at Weeks 2, 6 and 10. By Week 6, significant differences in weight gain between quitters and non-quitters were significant for men (2.3 kg vs. 1.2 kg; p=.045) and women (2.0kg vs. 0.86 kg; p=.014). By Week 10, only women showed a significant difference in weight gain between quitters (N = 39; 2.8 kg) and non-quitters (N = 69; 1.1 kg; p = .007). With the women who had quit successfully, the nicotine-treated group gained weight (mean = 2.3 kg) at a significantly lower rate than the placebo treated group (mean = 4.1 kg; p = .047). This study and others (Jorenby et al., 1996) demonstrate the effectiveness of the TN to aid cessation, and suggests that this preparation suppresses the weight gain that is associated with tobacco abstinence.

TN also reduced weight gain and other symptoms of withdrawal in an additional study (Jorenby et al., 1996) where 211 participants (114 women) participated in a 5-week, randomized, double-blind study in which they were given either 21 mg dose TN patch (mean cpd = 29.4; participants had smoked for at least the past year) or a placebo (mean cpd =30.9) to use daily for four weeks of treatment. Twice a day, participants completed two different smoking withdrawal symptom questionnaires. At the end of the treatment period, 75% of the TN patch users were tobacco abstinent. Nicotine replacement via TN significantly attenuated the tobacco withdrawal symptoms of craving for cigarettes, anxiety, and irritability over the four week treatment period. In addition, for the first month of cessation, lower appetite ratings and significantly less weight-gain were reported with the use of TN, a finding consistent with other acute studies (i.e. Hughes & Hatsukami, 1997).

Effects of Transdermal Nicotine on Behavioral/Performance Outcome Measures

Performance decrements in abstinent smokers have been demonstrated (Gilbert et al., 2004; Eissenberg, Griffiths & Stitzer, 1996) and TN suppresses these cognitive effects of withdrawal (Pickworth, Fant, Butschky & Henningfield, 1996). For example, ten participants (1 woman; mean cpd = 29 and mean years smoking = 14.3) participated in a study where general cognitive task decrements were reversed using TN. Four doses of TN (0, 10, 20 or 30 mg nicotine) were administered daily for three consecutive days, with participants randomly receiving each dose condition, a different one every week, for four consecutive weeks. Six hours after the application of the TN, cognitive measurements of withdrawal were assessed using the DSST and a six-letter task search. In that task, six letters appear at the top and a string of 20 letters appear at the bottom of a computer monitor. If the six letters at the top appeared in the string at the bottom then participants responded with a key stroke. During the nicotine-free condition, mean response time was significantly longer (10.4 seconds) than during the 20 mg TN (8.8 seconds) or 30 mg TN (8.6 seconds) weeks. In addition, during the nicotine-free condition the mean number of DSST symbol attempts (50.5) decreased significantly ($P < .05$) from the 30 mg TN (53.8) condition. Thus these results support other study findings that the effects of tobacco abstinence reveal decreased performance outcomes (Heishman, Taylor & Henningfield, 1994; Snyder, Davis & Henningfield, 1989) which are reversed with nicotine administration (Snyder & Henningfield, 1989).

Transdermal Nicotine Suppresses Symptoms of Withdrawal

As many as two-thirds of regular smokers experience withdrawal symptoms, which are especially common among those who smoke every day or regularly smoke

more than 10-15 cigarettes per day (Colby, Tiffany, Shiffman & Niaura, 2000). TN relieves the somatic and affective symptoms of withdrawal, including craving (Levin et al., 1994). Craving for cigarettes is the most reported reason for relapse (Nørregaard, Tonnesen & Petersen, 1993), can increase in intensity after one hour of cigarette deprivation, and may reach peak levels within 6-24 hours of abstinence (Maude-Griffin & Tiffany, 1996; Gupta, Okerholm, Coen, Prather & Gorsline, 1993).

TN's ability to suppress withdrawal has been demonstrated in large-scale clinical trials (Wetter et al., 1999b) as well as smaller, more acute laboratory studies (i.e., Pickworth, Fant, Butschky & Henningfield, 1996). For example, one long-term, double-blind, placebo-controlled study examined the effects of TN on craving and withdrawal symptom relief in 199 participants (Abelin, Buehler, Müller, Vesanen & Imhof, 1989). Ninety-nine participants (38 women; mean cpd = 27.3 and mean years smoking =23.7) were given placebo patches and 100 participants (42 women; mean cpd = 27.7 and mean years smoking = 20.7 years) were given active TN patches to use daily for 12 weeks. Participants in the active TN group who smoked more than 20 cpd were given 21 mg TN patches; otherwise, participants in the active group received 14 mg TN patches. At the end of every week, participants noted their withdrawal symptoms in a questionnaire that rated nine subjective symptoms: craving for cigarettes, thinking about cigarettes, irritability/aggressiveness, bad temper/moodiness, restlessness/nervousness, tenseness, difficulties of concentration, feeling of hunger, and constipation. Craving and withdrawal symptoms decreased more with TN than with placebo. That is to say, the difference in craving between the TN group and the placebo group was significant during Week 4 ($p=.01$) and Week 10 ($p=.02$). In addition, there was significant difference between

groups in "thinking about a cigarette" during Weeks 4 (p=.03), 5 (p=.04), 6 (p=.05) and Week 8 (p=.03). Thus this study demonstrated that craving and withdrawal symptoms are significantly reduced when TN is used over a long-term period.

Another study that highlighted the efficacy of over-the-counter NRT also examined TN and its ability to relieve craving and withdrawal over a long-term period (Shiffman, Khayrallah & Nowak, 2000). After six weeks of cessation using 21 mg/day TN, 421 participants (258 women; mean cpd = 30.8 and mean years smoking = 25.2) were then randomized to receive active TN (N = 212) or placebo (N = 209) patches for another four weeks. Participants in the active dose condition received 14 mg/day TN for the first two weeks and 7 mg/day TN for the subsequent two weeks. All participants were assessed daily, via self-report, on fourteen items that were divided into four content areas: craving, withdrawal symptoms, negative mood and self-efficacy. During each of the two week assessment periods, active patch users reported significantly lower craving and withdrawal scores and rated their moods more positively than the placebo users. Specifically, for Weeks 7-8 ($P < .001$) and Weeks 9-10 ($P < .02$) the TN group reported significantly lower craving than the placebo group. Withdrawal scores were also significantly lower for the TN group during both assessment periods (Weeks 7-8: $P < .001$ and Weeks 9-10: $P < .01$). Participants receiving TN also rated their mood as better during Weeks 7-8 ($P < .02$) and Weeks 9-10 ($P < .02$). Consistent with similar studies (Transdermal Nicotine Study Group, 1991) this study demonstrated the efficacy of TN in suppressing craving and withdrawal in smokers after 6 -10 weeks of treatment.

Still another study has shown the short-term effects of TN on craving and withdrawal in smokers (Teneggi et al., 2002). As withdrawal symptoms appear within 6

– 12 hours after cessation (Hughes, 1992), researchers were interested in assessing relief of withdrawal symptoms in smokers deprived of cigarettes for 72 hours. Twenty-four individuals (4 women; mean cpd = 20 and participants smoked for at least the past year) participated in this randomized, double-blind, three-session study. One session consisted of participants smoking *ad libitum*, one consisted of verified abstinence with 21 mg TN patches, and the other consisted of enforced abstinence with placebo patches. Self-report questionnaires, including a brief form of the QSU (Cox, Tiffany & Christen, 2001), were administered at 11 time-points throughout each 72-hour session. Results indicated that withdrawal was significantly higher in the placebo condition (average score = 61) versus the free-smoke (average score = 44) or TN (average score = 56) condition. In addition, overall craving in the placebo condition (average score = 4.5) was significantly higher than in the other two conditions, with no overall differences found between free-smoke (3.6) and TN (3.8). Thus, this study demonstrated that TN was effective at reducing reports of withdrawal and craving.

Another study highlighted the efficacy of TN at relieving craving and withdrawal over a short-term period (Shiffman, Khayrallah & Nowak, 2000). As most nicotine is cleared from the body overnight, smokers wake in a state of nicotine deprivation, this is thought to produce craving and withdrawal. Morning craving in particular is thought to be a uniquely robust predictor of relapse to smoking, and thus control of morning craving may be an important clinical objective (Shiffman et al, 1997). Accordingly, the comparative efficacy of two TN doses for relief of morning craving was examined. Participants (N = 244; 168 women, mean cpd = 24.0 and mean years smoking = 20) were assigned randomly to receive either a 24 hour/day TN patch (21 mg) or a 16 hour/day TN

patch (15 mg) and used a palm-top computer to report their craving and withdrawal symptoms several times a day. The participants assessed their symptoms (e.g. Urges to smoke, Craving a cigarette, Difficulty concentrating) for one week of baseline data and for two weeks after cessation. While both patch doses provided craving relief, the 21 mg/day TN provided better control of morning craving and also craving throughout the day, in addition to the greater reduction in anxiety, irritability and restlessness. These findings were in agreement with previous findings of morning craving relief from two doses of TN (Leischow et al., 1997). These findings demonstrate that 21 mg/day TN affords relief for craving and withdrawal symptoms during the first two weeks of abstinence from smoking.

TN also relieves craving in acute laboratory settings (Tiffany, Cox & Elash, 2000). In particular, the effect of TN on abstinence-induced and cue-elicited craving in smokers was examined in sixty-one smokers (31 women; mean cpd = 29 and mean years smoked = 7.2). Participants were assigned randomly to receive either a 21mg TN patch or a placebo patch to wear during a six hour interval between two 90 minute sessions. During each session, participants were presented with 12 exposure trials which consisted of different cue content (cigarette vs. neutral) and mode of stimulus presentation (imagery and in vivo). After each presentation participants completed the QSU brief, an empirically validated 11-item craving measure. Participants assigned to placebo TN had a significantly greater increase in craving ($P < .05$) across sessions than those receiving active TN, indicating that active TN reduced craving to smoke. This result is consistent with other laboratory studies that demonstrated that TN significantly reduced the craving that resulted from tobacco abstinence (Rose, Herskovic, Trilling & Jarvik, 1985).

In summary, this section demonstrates that nicotine replacement therapy is safe, efficacious and suppresses withdrawal. In particular, TN is an effective cessation product and is a popular, over-the-counter treatment. TN is especially effective in curbing short-term and long-term craving and withdrawal symptoms.

Gender Differences In Response to Nicotine Replacement Treatment

As reviewed above, cigarette smokers are often nicotine dependent and experience aversive withdrawal symptoms during periods of tobacco abstinence. Nicotine replacement is an efficacious pharmacotherapy for smoking cessation that works, in part, due to its ability to suppress nicotine/tobacco withdrawal in abstinent smokers. Interestingly, some clinical trials suggest that NRT may be less efficacious for women (Gourlay, Forbes, Marriner, Pethica & McNeil, 1994; Bjornson et al., 1995; Swan, Jack & Ward, 1997; Dale et al., 2001), perhaps because it does not suppress withdrawal as well (Wetter, Fiore, Young, McClure & deMoor, 1999a). The sections below begin with a brief review of preclinical work relevant to gender differences in response to nicotine, and then present evidence for an apparent gender difference in nicotine's effects and in NRT's efficacy and ability to suppress withdrawal. They conclude with some hypotheses regarding why women may respond differently to NRT.

Preclinical Evidence for Sex Differences in Response to Nicotine. Preclinical studies cannot address directly the issue of gender differences in the efficacy of NRT as a smoking cessation pharmacotherapy. However, studies using non-human animals as subjects are relevant, as they can reveal sex differences in nicotine sensitivity. If these studies generalize to humans, and if women are less sensitive to nicotine's effects, than gender differences in NRT-assisted cessation may be linked to this reduced sensitivity.

In fact, several preclinical studies suggest that there are sex differences in response to nicotine in non-human animals (e.g., Damaj, 2001; Faraday, O'Donoghue & Grunberg, 2003; Faraday, Elliott, Phillips & Grunberg, 2003; Cheeta, Irvine, Tucci, Sandhu & File, 2001; Grunberg, Winders & Popp, 1987). For example, in a comprehensive examination of the sex differences in the potency of nicotine between male and female Institute of Cancer Research mice (Damaj, 2001) female mice were less sensitive to the acute affects of subcutaneously administered nicotine. Mice were infused with nicotine subcutaneously and evaluated for sensitivity to pain. Antinociception was measured five minutes after nicotine injection (using hot-plate and tail flick models; e.g., Damaj et al., 1997) as nicotine has antinociceptive effects in rodents (Apatov, 1998). After establishing dose-response relationships for nicotine in the female and male mice by measuring antinociception at the time of maximal effect (5 minutes), female mice were found to be less sensitive to the effect of nicotine with both models. Nicotine was three times less potent in females as compared with males in the tail-flick test as measured with the ED_{50} (the Effective Dose 50; the amount of nicotine dose required to produce a specified effect in 50% of the animal population) and confidence level (CL). While nicotine produced tail flick latencies in both female and male rats, a higher ED_{50} was measured for female mice--ED_{50} (±CL) 2.9 (1.4 - 5.8) mg/kg--than for male mice--ED_{50} (±CL) 1.0 (0.6 - 1.3) mg/kg, meaning that female mice needed more nicotine to produce antinociceptive effects. Results were similar for the hot plate test with an ED_{50} (±CL) 0.9 (0.8 - 1.2) mg/kg for female mice and ED_{50} (±CL) 0.5 (0.4 - 0.6) mg/kg for male mice. Results from both tests demonstrate a lesser sensitivity to nicotine's acute antinociceptive effects for female mice.

Sex differences in antinociception were also evident after intrathecal injection of nicotine, as evaluated by the tail-flick test. Again, while nicotine produced a dose-responsive increase in tail flick latencies in all rats, a higher ED_{50} was measured for female mice--ED_{50} (±CL) 23 (15.1 - 34.2) μg/animal -- than for male mice -- ED_{50} (±CL) 11.4 (9.5 - 13.7) μg/animal, replicating the effects observed with subcutaneous nicotine that female mice needed more nicotine to produce antinociceptive effects. These reports of sex differences in nicotine-induced antinociception are inconsistent with other studies (e.g., Chiari, Tobin, Pan, Hood & Eisenach, 1999; Lavand'homme & Eisenach, 1999) but are consistent with human studies that show women to be less sensitive to nicotine than men (Jamner, Girdler, Shapiro & Jarvik, 1998; Perkins, 1999). However, because the relationship between antinociception and NRT efficacy is uncertain, the relevance of these results to understanding gender differences in NRT efficacy is unclear

While sex differences were apparent with antinociception, subcutaneous nicotine administration did not produce sex differences on a plus-maze activity or on body temperature, seizure activity or locomotor activity. One proposed mechanism underlying the sex differences could have been the influence of gonadal hormones. Thus, after the subcutaneous administration of nicotine and the tail-flick test, the interaction of nicotine and different sex hormones (progesterone, 17β-estradiol and testosterone) was examined.

Progesterone, which was evaluated for its likelihood to antagonize the nicotine dose of 3.0 mg/kg, blocked nicotine-induced antinociception in female mice when given subcutaneously four hours before nicotine. Specifically, the AD_{50} (the Antagonist Dose 50; the amount of antagonist dose required to produce a specified effect in 50% of the animal population) was (±CL) 4.8 (2.8 – 8.4) mg/kg. Antagonism of nicotine-induced

antinociception was both time-dependent (peak blockade at 3-4 hours after injection) and dose dependent (10 mg/kg and 20 mg/kg doses of progesterone significantly blocked nicotine-induced antinociception; $P < .05$).

Similar to progesterone, 17β-estradiol produced significant time and dose-dependent antagonism of nicotine-induced antinociception ($P < .05$). Specifically, the peak blockade was 3 hours after injection, the AD_{50} was (±CL) 5.5 (4.0 – 6.6) μg/k when was 17β-estradiol was given four hours before nicotine and 10 μg/kg and 20 μg/kg doses of 17β-estradiol significantly blocked nicotine-induced antinociception. Testosterone did not produce significant time and dose-dependent antagonism at the doses tested. Results of this comprehensive study of gender and sex hormones on the pharmacological effects of nicotine in the mouse demonstrate clearly that female mice were less sensitive to the acute effects of nicotine and that progesterone and 17β-estradiol nicotine produced antagonist effects on nicotine-induced antinociception.

Sex differences in the effects of nicotine in mice are evident in adolescence (Klein, Stine, Vandenbergh, Whetzel & Kamens, 2004). In a dose-response experiment which examined sex differences in nicotine consumption,150 periadolescent mice (125 female) were given access to a choice of either saccharine or nicotine solution to drink. The nicotine was provided to the mice in one of six dose solutions: 10 µg/ml (20 males, 23 females); 25 µg/ml (20 males, 21 females); 50 µg/ml (20 males, 20 females);75 µg/ml (20 males; 20 females); 100 µg/ml (21 males, 20 females) and 200 µg/ml (20 males, 21 females). The mice were given 24-hour access to the solutions while housed in single cages for a seven day period. Saccharine was available in one bottle while the nicotine solution was available in the other; bottle locations were switched daily to prevent

conditioned place preference to either side of the cage. Mice in the four lowest nicotine concentration groups (10, 25, 50 and 75 μg/ml) drank significantly more nicotine solution than did mice in the highest nicotine concentration groups (100, 200 μg/ml; $P < .001$). Even though both female and male mice drank similar volumes (ml) of nicotine, when adjustments were made to account for body weight differences, in every nicotine concentration group female mice consumed more nicotine (mean mg/kg = 14.7, SD = 0.5) than male mice (mean mg/kg = 12.2, SD = 0.5; $P < .0001$).

Sex differences in response to nicotine are also apparent in rats (Booze et al., 1999; Harrod et al., 2004, Donny et al., 2000). One such study used 106 Sprague-Dawley rats (55 female) to determine if female rats would self-administer nicotine, and to explore if self-administration patterns differed by sex (Donny et al., 2000). Rats were divided into four dose groups of nicotine (0.02, 0.03, 0.06 and 0.09 mg/kg) and allowed to self-administer the nicotine for at least two full estrous cycles (9-12 days) on fixed and progressive ratio reinforcement schedules. Acquisition of self-administration was faster ($P < .01$) and more stable ($P < .05$) for females for the 0.02 mg/kg dose. In addition, latency to the first infusion was shorter ($P < .05$) and break points, or the point at which the animal stopped responding for infusions, were higher ($P < .001$) for females than for males on both reinforcement schedules. As a higher break point is considered to be a measure of increased motivation (Markou et al., 1993), and there was a significant relationship between latencies and break points with shorter latencies predicting higher break points ($P < .001$), these results could indicated that females have higher motivation to self-administer nicotine than males.

Sex differences in rats have also been found in behavioral sensitization (the progressive increase of behavioral responses to psychomotor stimulants after repeated administration) after repeated intravenous nicotine administration (Booze et al., 1999). Ninety-six Sprague-Dawley rats (48 female) were implanted with osmotic mini-pumps that delivered 50 μg/kg nicotine once a day for 14 days (Booze et al., 1999). During daily 60-minute sessions in an activity chamber, behaviors such as grooming, biting, rearing and licking were observed six times, once every 10 minutes. Specific locomotor activity in response to nicotine was measured immediately after the first nicotine injection and after the Day 14 nicotine injection, thus controlling for confounds of pairing of nicotine injection and testing environment. Results of the observation revealed that female rats were more active than male rats as a function of nicotine injection ($P < .009$). In addition, female rats demonstrated an increased sensitivity to repeated nicotine as evidenced in more rapid responses (e.g., grooming; $P < .002$). Specific locomotor activity (peripherally directed activity) was significantly greater for female rats after the first injection ($P < .002$) and after the Day 14 nicotine injection, as well ($P < .001$). Thus, as compared to male rats, female rats demonstrated greater behavioral sensitization to repeated intravenous nicotine administration.

These findings were supported by a similar study that examined sex differences and behavioral sensitization to repeated intravenous nicotine (Harrod et al., 2004). In this study, 96 Sprague-Dawley rats (48 female) were implanted with osmotic mini-pumps that delivered 50 μg/kg/day nicotine for 21 days and specific locomotor activity in response to nicotine was measured immediately after the Day 1 and Day 21 nicotine injection. Activity behaviors (e.g., rearing, grooming) were also observed during daily 60-minute

sessions in an activity chamber. Results of the observation revealed an increased sensitivity to repeated nicotine administration (e.g. rearing) in female rats (Day 1 vs. Day 21 = 230% increase; $P < .0001$) as compared to male rats (Day 1 vs. Day 21 = 70% increase; $P < .04$). Specific locomotor activity (entry into the centermost region of the activity chamber) was significantly greater for female rats after the Day 1 and Day 14 nicotine injections ($P < .05$). As compared to male rats, female rats demonstrated increased behavioral sensitization to acute and repeated intravenous nicotine administration.

Sex differences are also evident with the effects of nicotine administration and cessation on body weight and food consumption in rats (Grunberg, Bowen & Winders, 1986; Bowen, Eury & Grunberg, 1986; Grunberg & Bowen, 1985). Specifically, one study found greater sensitivity to nicotine in female rats as indicated by an increase in feeding behaviors and body weight as compared to male rats (Grunberg, Winders & Popp, 1987). Thirty-six Sprague-Dawley rats (18 female) had body weight and food consumption measured for 22 days before nicotine administration, 16 days of drug administration (saline, 6 mg or 12 mg nicotine via osmotic pump) and 18 days after nicotine cessation. Data were reduced to 6-day periods of before, during and after drug infusion and when analyzed revealed that female rats had an increase in body weight and feeding behaviors as compared to male rats. Specifically, both groups of rats gained more weight than the control rats, but after a four month follow-up period the average body weights for the 12 mg nicotine treated females were 99.5% that of control vs. 93.4% for males (indicate significance and variability). While male rats showed similar changes in food consumption from before to during drug administration and from during to after

drug administration, female rats showed complex food consumption. From before to during drug administration, food consumption increased for the 6 mg nicotine group but decreased for the 12 mg nicotine group. However, from drug administration to cessation, the 12 mg nicotine group increased significantly compared to the control and 6mg group. Thus, different sensitivity to different doses of nicotine in female rats was shown in this study. Because hunger is a nicotine/tobacco withdrawal symptom, and because concern regarding post-cessation weight gain may influence cessation rates in women more than men (Borrelli, Spring, Niaura, Hitsman & Papandonatos, 2001; Borrelli & Mermelstein, 1998) these results may be relevant to gender differences in NRT efficacy.

While female mice show a decrease to nicotine sensitivity in antinociception studies and rats show gender differences in nicotine sensitivity in feeding behavior and weight studies, nicotine sensitivity has been identified in other effects in rodents. For example, female rats appear to be more sensitive than male rats to nicotine-induced increases in locomotor activity (Kanyt, Stolerman, Chandler, Saigusa & Pogun, 1999; Faraday, O'Donoghue & Grunberg, 2001, Battig, 1981). Yet other studies have not supported a sex difference in locomotor activity (Faraday, Elliott, Phillips & Grunberg, 2003). Still other studies have found that female rats are more sensitive to nicotine-induced increases in anxiolytic effects (Cheeta, Irvine, Tucci, Sandhu & File, 2001). Regardless of greater or lesser sensitivity to nicotine in female non-human animals, sex differences in the effects of nicotine clearly exist; however, for many outcome measures, the relationship of these sex differences to NRT effectiveness is uncertain.

Clinical Evidence for Gender Differences in Response to Nicotine

This section describes several laboratory evaluations and clinical trials which are presented as clinical evidence for gender differences in response to nicotine. This section begins by detailing gender differences in pain sensitivity, subjective and reinforcing effects to nicotine and differences in self-administration of nicotine. The next section summarizes several clinical studies that support the assertion that women experience lower rates of smoking cessation than men. All of these studies support the idea that gender plays a role in response to nicotine, and this role may be relevant to understanding gender differences in NRT-assisted cessation.

Gender Differences in Response to Nicotine: Laboratory Evaluations. Laboratory evaluations have demonstrated gender differences in response to nicotine (Perkins, Jacobs, Sander & Caggiula, 2002; Jamner, Girdler, Shapiro & Jarvik, 1998; Girdler, Jamner, Jarvik, Soles & Shapiro; Perkins, 1996; Perkins et al., 1996). Specifically, gender differences in response to nicotine have been reported in response to the analgesic properties of nicotine (Grobe & Perkins, 1997; Jamner, Girdler, Shapiro & Jarvik, 1998). One such study examined whether TN would reduce the pain sensitivity of men and women and whether the reduction would be greater in men as compared to women (Jamner, Girdler, Shapiro & Jarvik, 1998). Thirty men (17 smokers; mean cpd = 18.0 for at least the prior two years; 13 nonsmokers; neversmokers or smokers who had quit for a minimum of five years) and 44 women (21 smokers; mean cpd = 21.1 cpd for at least the two prior years; 23 nonsmokers; neversmokers or smokers who had quit for a minimum of five years) participated in the two-session, double-blind study. Women were tested during the midluteal (days 7 – 10) phase of their menstrual cycle to control for hormonal

variations in sensitivity to pain, and nonsmokers were tested to determine if reduced sensitivity to pain was to due relief of withdrawal symptoms.

During two sessions, participants reported their perceptions of a painful stimulus 2.5 hours after administration of either a placebo or a 21 mg nicotine patch. The pain procedure consisted of an electrical current (milliampers; mA) through an electrode being delivered twice in each session and participants making four subjective judgments: 1) sensation – when the stimulus was first detected; 2) discomfort – when the stimulus first became uncomfortable; 3) pain threshold – when the stimulus reached a painful level; and 4) tolerance – when the stimulus could no longer be accepted. A significant gender difference was demonstrated with men showing an increase in electrical pain threshold and tolerance after TN application but women showing no effect in response to TN. Specifically, as compared with placebo, after application of TN men showed an increase in electrical pain threshold (mean 4.88 mA vs. 5.87 mA, $P < .033$) and tolerance (mean 6.36 mA vs. 7.66 mA, $P < .023$) whereas nicotine did not significantly effect the threshold and tolerance judgments for women (n.s.). In addition, mean pain thresholds were significantly greater for male smokers (6.47 mA) than male nonsmokers (4.28 mA, $P < .032$) but there were no differences between female smokers and nonsmokers (2.93 mA vs. 3.11 mA, p=n.s.). Finally, smokers had a greater level of tolerance (mean 6.25 mA) than nonsmokers (mean 4.95 mA; p=.049). This particular study demonstrated that TN reduced pain sensitivity in men and not women.

Gender differences have also been reported in a laboratory study which examined the sex differences in the subjective and reinforcing effects of cigarette nicotine dose (Perkins, Jacobs, Sanders & Caggiula, 2002). Thirty men (N=17; mean cpd = 18.3 and

mean years smoking = 6.6) and women (N=13; mean cpd = 14.2 and mean years smoking = 6.6) smokers participated in three laboratory sessions where they smoked either a medium nicotine yield (own brand, ≥ 7 mg nicotine) or low yield (Carlton ultralight, 0.1 mg nicotine) cigarette. Participants were blinded to the type of cigarette that they smoked and were overnight abstinent before each session. In two of the sessions the participants received only one type of cigarette (independent assessment condition) and in the other session both of the cigarettes were available (concurrent assessment condition). Subjective ratings of the cigarettes were obtained via questionnaires and reinforcement was determined by responses on a computer task designed to earned single puffs on the designated cigarette. Results show the difference in ratings between doses for the subjective assessments were of lesser magnitude for women than for men in both the concurrent and independent ($P < .05$) assessments. Men showed a significant ($P < .05$) decrease in the number of smoke-reinforced responses for the low vs. moderate nicotine dose. Thus in women, cigarette nicotine dose influences subjective and reinforcing effects of smoking to a lesser degree than men.

There are not only gender differences in subjective and reinforcing effects of nicotine but also discrimination and self-administration of nicotine (Perkins et al., 1996). For example, in one study smokers (N =11; 5 women; mean cpd = 20.1 and mean years smoking = 5.7) and neversmokers (N = 10; 5 women) participated in a study where nicotine (20 μg/kg; about 2.5 μg/kg per spray) or a placebo was self-administered via nasal spray (Perkins, Sanders, D'Amico & Wilson, 1997). During a 3-day laboratory session, participants were trained to discriminate 20 μg/kg nicotine via nasal spray from a placebo spray on Day 1. On Day 2, participants discriminated between varying doses of

nicotine nasal spray (0, 3, 6, 12 and 20 μg/kg). On Day 3 participants were instructed to choose one of two bottles (one containing placebo; one containing 20 μg/kg nicotine) and allowed to self-administer 8 sprays every 25 minutes for 2.5 hours (for a total of six choice trials). Results indicated that placebo engendered more nicotine-appropriate responding in female smokers as compared with neversmokers and male smokers ($P < .05$) and thus women's discrimination of nicotine was less sensitive with increasing nicotine doses. In addition, women self-administered less nicotine than males. Specifically, for neversmokers, women self-administered fewer sprays of nicotine than men (1.6 vs. 7.6 sprays, n.s.) and for smokers women self-administered fewer sprays of nicotine than men (10.8 vs. 23 sprays; $P < .10$). Thus, gender differences in response to nicotine may be due to reduced intensity of nicotine's discriminative effects in women and greater use of nicotine spray by men suggests a gender difference in reinforcement from nicotine via this method.

In conclusion, the laboratory studies summarized above note gender differences in pain sensitivity, subjective and reinforcing effects to nicotine and differences in self-administration of nicotine. Thus these studies support the idea that gender plays a role in response to nicotine, and this role that may be relevant to understanding gender differences in NRT-assisted cessation.

Gender Differences in Response to Nicotine: Clinical Trials. Poorer abstinence rates for women vs. men have been demonstrated in several smoking cessation trials and studies (Swan et al., 2003; Killen, Fortmann, Varady & Kraemer, 2002; Borrelli, Papanonatos, Spring, Hitsman & Niaura, 2001; Dale et al., 2001; Osler, Prescott, Godtfredsen, Hein & Schnohr, 1999; Royce, Corbett, Sorensen & Ockene, 1997; Ward,

Klesges, Zbikowski, Bliss & Garvey, 1997) especially those using nicotine replacement products (Perkins, 2001; Perkins et al., 1996; Nides et al., 1995; Bjornson et al., 1995) including the nicotine patch (Bohadana, Nilsson, Rasmussen & Martinet, 2003; Swan, Jack & Ward, 1997; Wetter, Fiore, Young, McClure & deMoor, 1999a; Nørregaard, Tonnesen & Petersen, 1993; Gourlay, Forbes, Marriner, Pethica & McNeil, 1994; Transdermal Nicotine Study Group, 1991). Thus, while nicotine replacement treatment is not necessary to demonstrate poorer treatment outcome for women, many trials using NRT demonstrate this effect. For example, in the Lung Health Study, which was designed to investigate the relationship of gender to smoking cessation at 12 and 36 months after quitting, women were less likely than men to quit initially (Nides et al., 1995) and were significantly less likely to maintain abstinence at both follow-up points (Bjornson et al., 1995). In this multi-site trial of 3,923 participants (1,475 women; mean cpd = 30.9 and mean years smoking = 30.9) all participants received as much 2 mg nicotine gum (up to 30 pieces per day) as they wanted for the duration of the study along with a 12-week group smoking cessation intervention. After 12 months, 25% of women vs. 29% of men were considered nonsmokers ($P < .009$). This finding of cessation rates that were significantly lower for women was also evident after 36 months when 19% of the women vs. 22% of the men had remained abstinent ($p=.001$). In addition, women in the trial were also more likely than men to have tried and failed to stay quit using nicotine gum (42% vs. 34%, respectively).

Gender differences in smoking cessation rates with NRT have been highlighted in a review paper that examined the relationship between gender and abstinence among smokers (N = 632; mean cpd = 30.0 and mean years smoking = 24.4) who participated in

three clinical trials using TN (Wetter, Fiore, Young, McClure & deMoor, 1999a). Participants received either eight weeks of 22 mg TN with group counseling or four weeks of 22 mg followed by two weeks of 11 mg TN with brief individual counseling. The three studies were analyzed for potential mediator and moderator variables and revealed that women had lower cessation rates than men at every follow-up visit. Specifically, women were less likely than men to be abstinent at Week 1 (32% vs. 42%), at end of treatment (29% vs. 45%) and at six months (12% vs. 25%). Thus, women were more likely to relapse immediately after cessation, during treatment and after quitting smoking, again highlighting gender differences with NRT-aided cessation.

Other studies also report that women show lower smoking cessation rates after use of TN (Swan, Jack & Ward, 1997). Reanalyzing results from a previously run multi-center parallel group clinical trial (Transdermal Nicotine Study Group, 1991) researchers found that women experienced significantly shorter time to relapse than did males. The original study consisted of 935 participants (564 women; mean cpd = 30.7 and mean years smoking = 24.1 years). The participants in Group 1 (N = 513) were randomly assigned to received either a placebo or a 7, 14 or 21 mg/day dose of transdermal nicotine for six weeks. Participants in Group 2 (N = 422) were randomized to the same treatments with just the 14 or 21 mg/day doses. Using TSSR analysis to predict subgroups of participants who were likely to relapse, the sample was classified according to six variables: gender, motivation to quit, FTQ scores (a measure of dependence), BMI, age and number of cigarettes smoked. In the 21 mg nicotine group, there were significant gender differences, with women's success being predicted by motivation to quit and men's success being predicted by FTQ scores. That is to say, the mean time in days to

relapse for women with high (75.5; SD = 63.0) and low (57.1; SD = 52.6) motivation to quit was much shorter than the mean to relapse for men with low (106.6; SD = 64.7) and high (82.5; SD = 59.6) scores.

Yet another study shows gender differences in a smoking cessation clinical trial that used TN (Nørregaard, Tonnesen & Petersen, 1993). Over a one year period, 289 participants (205 women; mean cpd = 21and mean years smoking = 26) received either active 14 mg TN (N=145) or placebo (N=144) patches from a cessation clinic to use daily. Participants visited the clinic on Weeks 1, 3, 6, 12, 26 and 52 after their cessation date and were asked if they had smoked since their last clinic visit. Results after one year revealed that there were no significant gender differences in participants (N=30) who successfully remained tobacco abstinent. However, a trend toward poorer cessation outcome for women (p=.13) was evident after the Week 6 follow-up. Specifically there was a trend for women (N=51) to have relapsed more than men in the nicotine group (N=24; p=*ns)* and women (N=90; P < .05) significantly relapsed more than men (N=30) in the placebo group.

Still another clinical trial that used TN shows gender differences in smoking cessation (Gourlay, Forbes, Marriner, Pethica & McNeil, 1994). Over a twelve week period, 1,481 participants (823 women; mean cpd = 32.3 and mean years smoking = 23.2) received active TN: 21 mg TN for the first four weeks, 14 mg TN for the next four weeks and 7 mg TN for the remaining four weeks. Participants were then assessed for tobacco abstinence after 26 weeks post-cessation. Of the 316 successful abstainers (21.3%) only 18% of women were abstinent versus 25% of men (p=.023). In fact, men were significantly more likely to be abstinent from smoking than women (adjusted odds

ratio 2.0, 95% confidence level 1.5 to 2.7). Thus another clinical trial that used NRT, and specifically TN, demonstrated poorer cessation rates for women.

Women show lower smoking cessation rates after combination use of TN and the nicotine inhaler (Bohadana, Nilsson, Rasmussen & Martinet, 2003). Four hundred participants (204 women) were enrolled in a double-blind, placebo-controlled trial and evaluated for abstinence at 6 and 12 weeks and 6 and 12 months after cessation. Group 1 included 200 smokers (101 women; mean cpd = 26.1 and mean years smoking = 20.7) who received the nicotine inhaler (4 mg) and TN (15mg) for six weeks, then the inhaler and placebo patch for six weeks, then the inhaler alone for 14 weeks. Group 2 included 200 smokers (103 women; mean cpd = 23.5 and mean years smoking = 20.4) who received the inhaler plus placebo patch for 12 weeks, then the inhaler alone for 14 weeks. At all follow-up visits, men had statistically higher rates of abstinence. Specifically, for men vs. women, cessation was significant at Week 6 (61.7% vs. 46.65; p=.0022); at Week 12 (42.3% vs. 30.9%; p=.017), at 6 months (30.1% vs. 17.6%; p=.003) and at 12 months (23.0% s. 10.8%, p=.001).

In summary, many clinical trials support the contention that woman experience lower rates of smoking cessation than men (but see Killen, Fortmann, Varady & Kraemer, 2002; Gritz et al, 1998). Importantly, this effect is apparent in trials where participants use NRT products, including transdermal nicotine. In their comprehensive review of this literature, Perkins, Donny and Caggiula (1999) noted the many observations that treatment outcome is worse for women and also concluded that ". . . no clinical outcome study examining nicotine replacement had reported superior outcome in women vs. men" (p. 303). Thus, there is a substantial body of literature that supports the

notion that NRT is less effective for women, though an explanation for this difference remains uncertain.

Why Might Gender Influence NRT Efficacy?

Several explanations for gender differences in cessation outcome have been suggested, including women's fear of weight gain (Borrelli, Spring, Niaura, Hitsman & Papandonatos, 2001; Pinto et al, 1999; Gritz, Nielsen & Brooks, 1996; Klesges et al., 1988), greater need for social support to quit smoking (Westmaas, Wild & Ferrance, 2002; Jensvold, Hamilton & Halbreich, 1996), greater anticipation of difficulty in quitting smoking (Schmitz, 2003; Pomerleau, Brouwer & Pomerleau, 2001) and possible gender differences in nicotine pharmacokinetics (Prather, Tu, Rolf & Gorsline, 1993). Gender differences in cessation outcome could also be the result of negative mood related to premenstrual discomfort in female smokers. Several studies have reported increased menstrual and tobacco withdrawal symptoms in women during quit attempts, especially in the luteal, rather than the follicular, phase of the cycle (Perkins et al 2000; Pomerleau, Garcia, Pomerleau & Cameron, 1992; O'Hara, Portser & Anderson, 1989). Nevertheless, in a short-term laboratory study that involved cigarette abstinence, neither tobacco withdrawal symptoms nor smoking behavior were influenced by menstrual cycle phase (Allen, Hatsukami, Christianson & Nelson, 1999). In addition, a recent study performed in women during acute abstinence showed that the nicotine patch was efficient in reducing withdrawal symptoms (Allen, Hatsukami, Christianson & Brown, 2000).

Gender differences in smoking cessation outcome may also be related to withdrawal and withdrawal suppression. With regard to withdrawal itself, some studies report gender differences in withdrawal symptomatology (e.g., Wetter, Fiore, Young,

McClure & deMoor, 1999a; Hatsukami, Skoog, Allen & Bliss, 1995; Hughes, 1992; Killen, Fortmann, Newman & Varady, 1990; Shiffman, 1979) though others do not (e.g., Perkins, Jacobs, Sanders & Caggiula, 2002; Gritz, Nielsen & Brooks, 1996; Pomerleau, Tate, Lumley & Pomerleau, 1994; Svikis, Hatsukami, Hughes, Carroll & Pickens, 1986; Gunn, 1986). With regard to withdrawal suppression, there is evidence that women experience the withdrawal suppressing effects of cigarettes differently from men (Eissenberg, Adams, Riggins & Likness, 1999) and that women might be reinforced less by nicotine and more by non-nicotine factors (e.g. smoking cues; Perkins, Donny & Caggiula, 1999; Niaura et al., 1998; Perkins, 1996). If men and women differ in the withdrawal suppressing effects of nicotine, including NRT, this difference may underlie the oft-reported gender difference in NRT-assisted smoking cessation.

While not a DSM-IV withdrawal symptom, craving for cigarettes may be related to withdrawal, and thus gender differences in craving suppression have been examined in some studies of NRT effect. In one cessation study that measured craving, 1,218 smokers (630 women) were assigned to one of four conditions: 2 mg nicotine gum on a fixed regimen, 2 mg nicotine gum *ad libitum*, placebo gum and no gum (Killen, Fortmann, Newman & Varady, 1990). Participants (mean cpd = 24.8 and mean years smoking = 24.5) in the fixed regimen group were told to chew 1 – 2 pieces of gum per hour for at least 12 hours a days and had their gum use tapered starting in Week 4 (with elimination by Week 8). Participants in the *ad libitum* and placebo group were given up to 30 pieces per day of gum to chew whenever they had an urge to smoke and were told to cut back on their gum use by Week 4 (with gum elimination by Week 9). Participants were assessed for craving 48 hours after cessation, as well as at follow-up visits at 2, 6

and 12 months. Results indicated that no treatment was significantly better among women, whereas men who received active gum were significantly more likely to be abstinent at all follow-up visits. In addition, nicotine gum only reduced craving in men and not women.

Further support that withdrawal is the mechanism behind gender differences in cessation is supported by a study that was designed to assess gender differences and the effects of different doses of nicotine gum on tobacco withdrawal symptoms (Hatsukami, Skoog, Allen & Bliss, 1995). The study involved a between-subjects design of 128 smokers (71 women; mean cpd = 28.1 and mean years smoking = 18) who were assigned in a double-blind manner to one of three conditions: 2 mg gum (21 men, 19 women); 4 mg gum (18 men, 23 women) and 4 mg gum to 2 mg gum (18 men, 29 women). Participants in the 2mg and 4 mg conditions used the gum for two months; participants in the other condition used 4mg of gum for four weeks and then 2 mg of gum for four weeks. All participants were told to chew at least six pieces of nicotine gum per day *ad libitum.* Using a withdrawal checklist questionnaire that consisted of *DSM-III-R* symptoms for nicotine withdrawal (e.g. craving for a cigarette, impatient, difficulty concentrating, etc.), measurement of withdrawal symptoms from nicotine gum were assessed in Days 1, 2 and 4 after gum discontinuation. In the 2 mg nicotine gum condition, subjective ratings of "impatient" and "excessive hunger," as well as total withdrawal scores were nearly doubled in women, relative to men in that condition. In the 4 mg condition men experienced greater reduction in "anxious-tense."

Even more support for withdrawal as a mechanism behind cessation differences is the relation of withdrawal to gender differences in response to NRT (Wetter et al.,

1999b). One study that examined this issue specifically sought to determine if gender interacted with NRT condition (active or placebo) on objective measures of withdrawal (i.e., sleep disturbances; Wetter et al., 1999b). Thirty-four participants (17 women; mean cpd = 30.5 for the last year) were enrolled in the study. Because tobacco withdrawal increases sleep fragmentation, including awakenings per hour of sleep time (Wetter, Fiore, Baker & Young, 1995; Prosise, Bonnet, Berry & Dickel, 1994), participants were administered a series of overnight polysomnography sessions to measure sleep disturbance. The polysomnography sessions were conducted five and seven days before quitting smoking and on Days 1, 3 and 5 after quitting. After their quit date, participants were assigned randomly to receive either an active patch (22 mg nicotine) or a placebo for five days. Women demonstrated significant withdrawal effects on "sleep efficiency" (the total sleep time expressed as a percentage of the time spent in bed with lights out) and "time awake after sleep onset," and NRT heightened these effects. That is to say, female active nicotine patch participants experienced no improvement in "sleep efficiency" or withdrawal relief while female placebo patch participants and all men experienced an increase in sleep efficiency by Day 5. Men in both groups and women in the placebo group also showed an increase in "time awake after sleep onset" that peaked on the first day of quitting and declined thereafter, while women in the active patch group displayed an increase in time awake, and those no withdrawal relief, across the entire study period. In summary, NRT exacerbated withdrawal signs in women and alleviated withdrawal signs in men.

NRT may be less efficacious in women because the direct effects of nicotine may be more positive for men (Wetter et al., 1999b). In addition, relative to men, women may

smoke less for nicotine reinforcement and more for non-nicotine reinforcement (e.g., sensory effects of smoking, secondary social reinforcement; Perkins, 1996). Women exhibit less robust self-administration of nicotine than men (Perkins, Grobe, Stiller, Fonte, & Goettler, 1992). For example, in one study 52 participants (31 women; mean cpd = 23.0 and mean years smoking = 13.9) were assigned to use either a placebo or *ad libitum* nicotine spray (1.5μg/kg, or approximately 0.1 mg, per spray) daily the first week after cessation (Perkins, Grobe, Wiess, Fonte & Caggiula, 1996). Mean daily use of nicotine vs. placebo spray was significantly greater in men (83.7 vs. 42.3 sprays; 7.6 ng/ml nicotine; $P < .01$) but not in women (3.9 ng/ml nicotine) These results suggests a sex difference in reinforcement from nicotine via this method. Nicotine reduced withdrawal significantly, as assessed via daily subjective questionnaires; however, there were no significant differences between sexes in nicotine's influence on withdrawal during this short-term, low dose study.

Overall, some research suggests that NRT's differential effects in men and women are associated with a failure to suppress women's nicotine/tobacco withdrawal adequately. However, there are several limitations associated with this literature. First of all, several studies have not assessed gender differences (Jorenby et al., 1996; Hughes, Gust, Keenan & Fenwick, 1990) or been designed with the issue of gender differences in mind (Leischow et al., 1997; Hurt et al., 1998; Hajek, Jarvis, Belcher, Sutherland & Feyerabend, 1989). Second, the studies have had a small sample size (Pickworth, Fant, Butschky & Henningfield, 1996, Lunell, Molander, Leischow & Fagerström, 1995) and thus limited power, which could have contributed to failure to find a real effect. Finally, most studies have not used multiple doses (Jorenby et al., 1996) and therefore results

could be inadequate as multiple doses could determine if a certain dose was insufficient for withdrawal suppression for women. Thus, one important step in understanding gender's influence on NRT efficacy is to examine withdrawal suppression in a large number of men and women across a wide range of NRT doses.

Statement of the Problem

While nicotine replacement therapy and, in particular, TN, are effective at helping people quit smoking, cessation rates are different for women and men (Toneatto, Sobell & Sobell, 1993). One reason that cessation rates may differ is that NRT-induced withdrawal suppression may be less for women. Most studies examining this issue have not been designed with this issue in mind (i.e., clinical trials with few withdrawal-related outcome measures, small between-subjects sample sizes, and/or single dose comparisons). The study proposed here is designed to address these limitations, and to determine if the dose response function for TN-induced withdrawal suppression differs by smokers' gender.

Statement of Hypothesis

The primary hypothesis is that the dose response function for transdermal nicotine induced withdrawal suppression will differ by smokers' gender, with less withdrawal suppression observed for women at some or all doses.

Chapter 2

Method

Summary

This laboratory study used a within-participant, double-blind, Latin square-ordered design to determine the influence of gender on the withdrawal suppressing effects of four doses of transdermal nicotine (0, 7, 21 and 42 mg) in 128 men and women who smoked tobacco cigarettes. Each volunteer abstained from smoking for at least 10 hours before completing each of four sessions. At the beginning of each of the four sessions, one of the transdermal nicotine doses was administered; no smoking was allowed throughout the session. Each session was separated by a minimum 48-hour washout period to avoid carryover effects, and included periodic blood sampling (for analysis of plasma nicotine level), continuous monitoring of physiological responses, and hourly subjective assessment (symptoms of nicotine/tobacco withdrawal and the direct effects of nicotine), as well as hourly assessment of psychomotor performance.

Volunteers and Setting

Recruitment for this Institutional Review Board (IRB) approved study was from media advertisements, flyers, and word-of-mouth. Individuals were included in this study if they were between the ages of 18 to 55 and were self-reported smokers of $\geq$ 15 cigarettes per day for the past two years. All volunteers provided an afternoon expired air carbon monoxide (CO) sample of $\geq$ 15 parts/million (ppm) at screening and were healthy according to self-reported medical history and physical examination; a 12-lead ECG was

used to determine normal cardiovascular function. This population was appropriate for the proposed studies because their smoking history made them candidates for the highest dose of nicotine transdermal patch approved by the FDA for smoking cessation (i.e., 21 mg), while their medical history and current health status suggested that they would tolerate higher patch doses.

Individuals were excluded if they were pregnant or breast feeding, or had any self-reported history of chronic health problems or psychiatric conditions. Other exclusion criteria were: history of or active cardiovascular disease, low or high blood pressure, seizures, peptic ulcer, and diabetes. Any individual who reported that they were currently trying to quit or reduce their cigarette intake was excluded because the study was not intended to provide therapeutic benefit. In addition, volunteers who scored greater than 17 on the Beck Depression Inventory were excluded. The BDI is a 21-item normed instrument designed to assess the severity of depressive symptoms in adolescents and adults (Hurt et al., 1997). The BDI's design makes it a potentially useful screening instrument for depression. Scores from 0-9 are "minimal," scores of 10-16 are "mild", scores of 17-29 are "moderate", and scores of 30-63 are "severe" (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). Any volunteer who scored greater than 17 on the BDI was excluded from this study, as such a score could be indicative of at least moderate depression, which could influence tobacco withdrawal symptomatology and might be exacerbated by smoking cessation (Covey, 1999). All eligible volunteers provided informed consent and agreed to abstain from cigarettes for at least 10 hours prior to each of the four required sessions.

All experimental sessions took place at the Clinical Behavioral Pharmacology Laboratory (CBPL). The CBPL consists of approximately 1000 square feet of space and was designed for human behavioral pharmacology research. It is divided into four separate laboratory rooms, each equipped with PC-linked physiological monitoring devices, sinks, and individual computer stations for control of experimental procedures, data collection, and statistical analysis. This research suite also contains a refrigerated centrifuge and a -70°C freezer for storage of biological samples. The CBPL is located on the medical campus of Virginia Commonwealth University, across the street from the hospital's emergency department, so that critical care is always available. The CBPL is easily accessible by foot or public transport, so that interested community volunteers could conveniently participate in the study.

One hundred twenty-eight men and women community volunteers, with a mean group size of 64 [i.e., $(N_{men} + N_{women})/2 = 64$], were needed to complete this protocol in order to provide power of at least 0.70, assuming a moderately sized gender effect (i.e., **f** = 0.25; Cohen, 1977). An effect size refers to the size of a relationship between two or more variables and is usually expressed as the proportion of variance in the dependent variable that can be accounted for by the independent variable. Specifically, the effect size is defined as the standard deviation of standardized means and is expressed as

$$\mathbf{f} = [\, \eta^2/(1-\eta^2)\,]^{1/2}$$

where η^2 is equal to multiple R^2, which is an index of the proportion of variability explained by the independent variable (Cohen, 1988). In smoking cessation trials, gender effect sizes have approached the moderate level (e.g. **f** = 0.17, Wetter et al., 1999b). Importantly, cessation trials typically use a relatively insensitive dichotomous outcome

measure of tobacco abstinence (i.e., long-term abstinence equals treatment success; non-abstinence equals treatment failure). A dichotomous outcome measure provides little information regarding reasons for treatment failure and thus may fail to capture subtle gender differences in response to treatment (e.g., Wetter et al., 1999b). The power observed in cessation trials may underestimate that available in laboratory studies that use non-dichotomous, and targeted outcome measures. In fact, where they exist, laboratory studies that support gender differences related to smoking cessation are consistent with effect sizes that are, at the least, moderate. For example, with respect to withdrawal suppression, one study of 19 men and 21 women showed that, relative to women, nicotine replacement therapy of 2 mg gum was approximately twice as effective at suppressing withdrawal in men (Hatsukami, Skoog, Allen & Bliss, 1995; see Figure 2, Panel F, p. 168). Thus, assuming similar effect magnitude, and a sample size of 128 men and women, this laboratory study that used non-dichotomous outcome measures was likely to be very sensitive to gender effects (i.e., power > 0.70).

Screening and Informed Consent Procedures

Individuals who were interested in participating in this study were screened using telephone and in-person interviews (see Appendix A). The telephone interview used questionnaires to assess medical history and level of nicotine dependence (i.e., the Fagerström Tolerance Questionnaire, or FTQ; Fagerström, 1978; CAGE questionnaire for smoking, Lairson et al., 1992), as well as alcoholism (i.e., CAGE questionnaire for alcoholism, Ewing & Rouse, 1970) and marijuana abuse (questions are identical to the CAGE questionnaire for smoking/nicotine dependence).

When individuals arrived at the CBPL for an in person screening interview, they were provided with a copy of an informed consent form (see Appendix B). A study staff member read the form to each individual, who had an opportunity to discuss it and address any issues or concerns to their satisfaction. Each volunteer received a copy of the fully executed informed consent document. After volunteers provided their written, informed consent to participate in the study, they were asked to provide information about their health and smoking history using a variety of questionnaires, including the FTQ (Appendix C) and the BDI. Many of the in-person screening questionnaires were identical or similar to those used in the telephone screen. This redundancy allowed an assessment of individuals' ability to report information reliably: individuals who were unable to report on their health and or smoking history reliably were excluded from participation. Data collected during the in-person screening were used to determine eligibility and to describe volunteers' demographic and other characteristics. The in-person screening interview also included a full physical examination (with a 12-lead ECG) that was performed by the study physician. In addition, volunteers were provided an opportunity to familiarize themselves with study equipment and procedures (i.e., physiological recording instruments; subjective questionnaires, etc.).

Menstrual Cycle Phase

One potential concern for this study was that hormonal fluctuation in women who participated may have influenced study outcome measures. Indeed, steroid hormones can influence nicotinic receptor expression in oocytes (Valera, Ballivet & Bertrand, 1992) and may lead to a decreased antinociceptive effect of nicotine in mice (e.g., Damaj, 2001). However, few clinical studies support the notion that menstrual

cycle phase influences nicotine/tobacco withdrawal symptomatology in humans. For example, several studies report a failure to observe menstrual phase-dependent effects on measures relevant to this project, including tobacco withdrawal symptoms, craving, cigarette intake, and the physiological, subjective, and biochemical responses to pharmacologically pure nicotine (e.g., Marks, Pomerleau & Pomerleau, 1999; Masson & Gilbert, 1999; Pomerleau, Mehringer, Marks, Downey & Pomerleau, 2000; Pomerleau, Tate, Lumley & Pomerleau, 1994). Three studies that have noted menstrual cycle phase effects in women who quit smoking for two days or more indicate that the late luteal phase is a potential factor, perhaps due to premenstrual symptomatology (Allen, Hatuskuami, Christianson & Nelson, 2000; Allen, Hatsukami, Christianson & Nelson, 1996; O'Hara, Porster & Anderson, 1989; Perkins et al., 2000). Importantly, in a short-term laboratory study that involved cigarette abstinence, neither tobacco withdrawal symptoms nor smoking behavior were influenced by menstrual cycle phase (Allen, Hatsukami, Christianson & Nelson, 1999). Thus, available data are consistent with the notion that complex strategies to control for menstrual cycle may not be necessary in research studies like this one, where only short-term abstinence is required (Allen et al., 1999).

Nonetheless, this study minimized potential effects of menstrual cycle phase on outcome measures by scheduling women's participation during the time corresponding to the follicular to early luteal phase of their menstrual cycle. Women volunteers were asked to call the laboratory on or about day 1 of their cycle (onset of bleeding) to schedule their experimental sessions. All women completed all sessions during days 2-16 of their cycle, and were able to participate across two cycles if necessary. Thus,

although extant data suggest no need to control for menstrual cycle phase in short-term studies, careful scheduling of experimental sessions was used to limit any influence of hormonal cycle on study outcomes.

Demographic Summary

A total of 302 community volunteers consented to participate in this protocol. 118 out of these 302 volunteers failed their in-person screening (e.g., provided a screening CO sample < 15 ppm) and were disqualified from further participation. Of the 184 remaining volunteers, 27 voluntarily withdrew before the first scheduled experimental session or repeatedly failed to attend the first scheduled experimental session and were subsequently disqualified from the protocol. Thus, a total of 145 out of 302 volunteers, or 48%, never participated in a single session. The remaining 157 volunteers, having participated in at least one experimental session, constitute those categorized as either completers or non-completers. Of these, 6 withdrew voluntarily while 16 were disqualified due to non-compliance (e.g. failing three times to qualify for participation in a scheduled session). Of the 6 who withdrew, 4 withdrew during the 42 mg condition, 1 withdrew during the 21 mg condition and 1 withdrew during the 7 mg condition; all voluntarily withdrew because they experienced nausea and/or vomiting. In addition, 6 volunteers had their participation stopped by the principal investigator, 3 because their blood pressure was elevated and 3 because of difficulty obtaining blood samples. Finally, due to computer error, one volunteer who completed all sessions did not have a complete data set, and this individual's data were excluded from analysis and the volunteer was categorized as a non-completer. As indicated in Table 1, completers (N=128) and non-completers (N=29) did not differ significantly in terms of general

characteristics (e.g. education level, body mass index [BMI]) save for age. That is to say, completers (mean age = 34.10, SD = 10.36) were significantly older than non-completers (mean age = 27.86, SD = 10.20; $P < .001$). Completers and non-completers did not differ in characteristics related specifically to alcohol or marijuana use. They did, however, differ in three characteristics related to cigarette smoking. With regard to duration of cigarette smoking, completers (mean duration of use = 11.49 years, SD = 9.17) had smoked significantly longer than non-completers (mean duration of use = 6.50 years, SD = 6.57). In addition, with respect to the CAGE questionnaire completers had a higher mean score (mean summed score = 2.46, SD = 1.11) as compared to non-completers (mean summed score = 1.90, SD =.86; $P < .05$). Finally, fewer completers smoked hard pack cigarettes as compared to non-completers (76.56% vs. 96.55%, $P < .05$).

As show in Table 2, 75 men (37 non-white; mean age = 35.39 years, SD = 10.20) and 53 women (27 non-white; mean age = 32.26 years, SD = 2.14) completed the protocol. All completers were smokers, as defined by the following criteria: a) afternoon expired CO levels of 15 ppm or higher (men's mean CO = 24.99, SD = 8.38; women's mean CO = 24.64, SD = 9.52), and b) self-reported daily intake of 15 cigarettes/day or more (men's mean = 24.11 cigarettes/day, SD = 10.04; women's mean = 21.27 cigarettes/day, SD = 5.79) for the past 2 years (mean's mean duration = 12.98 years, SD = 9.34; women's mean duration = 9.13 years, SD = 7.44). Of the 128 smokers who completed the protocol, 62 volunteers (36 men) were smokers of mentholated cigarettes. Based on published nicotine, CO, and tar levels (FTC, 2000). men who completed smoked cigarettes that, on average, yield 1.04 mg nicotine (SD = .26) and 14.50 mg tar (SD = 3.34) whole women who completed smoked cigarettes that, on average, yield .99

mg nicotine (SD = .30) and 13.74 mg tar (SD = 3.94). Published data were not available for all cigarette brands and therefore nicotine, CO and tar data are based on varying sample sizes (i.e., 118, 117 and 117 volunteers, respectively). Smokers who completed this study were moderately dependent, as indicated by a mean score of 5.77 (SD = 2.14, max score = 11) for men and a mean score of 5.13 (SD = 1.97) for women on the Fagerström Tolerance Questionnaire (FTQ; Fagerström, 1978). On average, smokers reported 4.02 (SD = 7.37; men) and 2.58 (SD = 2.52; women) quit attempts. Thirty-five volunteers (18 men) reported previous use of pharmacotherapy for nicotine dependence, including 26 volunteers (13 men) who had used transdermal nicotine.

Men and women did not differ significantly in terms of general characteristics (e.g. educational level, BMI) or those related specifically to cigarettes, alcohol or marijuana use (except for an observed difference in duration of use of cigarettes, with women smoking for about 4 years less than men, on average). The impact on study outcomes of this apparent difference in duration of use is uncertain, given that on many other demographic measures there were no differences between men and women (including measures more sensitive to potential differences in nicotine/tobacco dependence, such as the Fagerström Tolerance Questionnaire). In fact, with 29 demographic variables, one difference may reflect a chance outcome, rather than a true difference between the populations. Because the groups did not differ on other demographic measures, and because of the likelihood of type I error, duration of use was not entered as a covariate into any analysis.

Procedure

After providing informed consent, volunteers who were eligible for the study were asked to complete four, approximately 6.5-hour long experimental conditions in the CBPL, with each condition corresponding to a transdermal patch dose (0, 7, 21, or 42 mg). Conditions were conducted double-blind; that is, neither investigator nor volunteer were aware of which transdermal nicotine dose was administered on a particular day. Conditions were separated by at least 48 hours (to avoid carryover effects) and conducted by trained research staff that monitored volunteers continually.

On each condition day, volunteers reported to the CBPL at approximately 8 AM and left at approximately 3 PM (times varied across subjects, but were constant within-subject). Because withdrawal suppression was the focus of this study, volunteers started each session after at least 10 hours of objectively-verified nicotine/tobacco abstinence, so that withdrawal levels were at least moderate. Thus, immediately after arrival at the CBPL, expired air CO level were measured to verify pre-study cigarette abstinence: CO levels had to be $\leq$ 10 ppm (e.g., Buchhalter & Eissenberg, 2000; Buchhalter, Schrinel, & Eissenberg, 2001; Breland, Evans, Buchhalter, & Eissenberg, 2002). If the CO level did not meet criterion, volunteers waited in the CBPL until it did, or had the option of rescheduling that day's condition.

Once the CO criterion was met, women in the study provided a urine sample to determine if they were pregnant; a positive test lead to exclusion from all further study participation. After the CO and urine pregnancy tests, eligible volunteers were connected to equipment that recorded and monitored heart rate and blood pressure continuously.

Table 1.
Statistical Analysis Results for Completed Subjects' Demographic Data by Completion Status

	Completers (N=128)	Non-Completers (N=29)	F	P
Demographic variables				
General[a]				
% Caucasian	50.00	51.72	0.03	0.87
% Employed	59.38	55.17	0.17	0.68
% Not married	72.66	89.66	3.76	0.05
Age in years				
Mean (SD)	34.10(10.36)	27.86 (10.20)	8.60	0.00
Years education completed				
Mean (SD)	12.94 (1.97)	13.19 (1.53)	0.42	0.52
BMI				
Mean (SD)	26.65 (5.89)	25.72 (5.90)	0.58	0.45
BDI				
Mean (SD)	4.77 (4.38)	3.42 (3.01)	2.52	0.12
Screen CO				
Mean (SD)	24.84 (8.83)	25.17 (11.54)	0.03	0.87

(table continues)

(Table 1 continued)

	Completers (N=128)	Non-Completers (N=29)	F	P
Cigarette smoking related				
Cigs per day[a]				
Mean (SD)	22.93 (8.63)	20.45 (6.49)	2.13	0.15
Duration of use in years[a]				
Mean (SD)	11.49 (9.17)	6.50 (6.57)	7.66	0.01
FTC Tar yield[b]				
Mean (SD)	14.25 (3.60)	12.82 (3.66)	3.55	0.06
FTC Nic. Yield[b]				
Mean (SD)	1.02 (.27)	.92 (.26)	3.06	0.08
FTC CO[c]				
Mean (SD)	14.71 (3.06)	13.64 (3.23)	2.69	0.10
No. quit attempts[a]				
Mean (SD)	3.43 (5.89)	2.14 (3.13)	1.30	0.26
Fagerström[a]				
Mean (SD)	5.51 (2.10)	5.07 (2.45)	0.97	0.33

(Table 1 continued)

	Completers (N=128)	Non-Completers (N=29)	F	P
+ responses CAGE				
Mean (SD)	2.46 (1.11)	1.90 (.86)	6.61	0.01
% Hard pack[a]	76.56	96.55	6.12	0.01
% King size[a]	72.66	75.86	0.12	0.73
% Nicotine medication naïve[a]	72.66	82.76	1.27	0.26
Alcohol related[a]				
% Use	71.88	89.66	4.06	0.05
Use per day				
Mean (SD)	1.16 (1.86)	.97 (1.58)	0.26	0.61
Use past 30 days				
Mean (SD)	5.09 (6.56)	6.78 (7.40)	1.48	0.23
% Treated abuse/dependence	3.13	0.00	0.92	0.34
+ responses CAGE				
Mean (SD)	.40 (.89)	.10 (.41)	3.03	0.08

(Table 1 continued)

	Completers (N=128)	Non-Completers (N=29)	F	P
Marijuana smoking related				
% Use ever[a]	83.44	82.76	0.01	0.91
% Use last month[a]	36.31	41.38	0.10	0.76
Use past 30 days[d]				
Mean (SD)	1.80 (5.38)	1.39 (2.38)	0.20	0.66
Money spent per month[d]				
Mean (SD)	8.77 (48.40)	4.64 (13.47)	0.25	0.62
Other drug related				
% Used other drugs[a]	3.18	0.00	1.16	0.28

[a] df = 1, 154: all participants, N=156

[b] df = 1, 143: data available for only 145 participants

[c] df = 1, 142: data available for only 144 participants

[d] df = 1, 153: data available for only 155 participants

Table 2.
Statistical Analysis Results for Completed Subjects' Demographic Data by Gender

	Men (N=75)	Women (N=53)	F	P
Demographic variables				
General[a]				
% Caucasian	50.67	49.06	0.03	0.86
% Employed	60.00	58.49	0.03	0.87
% Not married	74.67	69.81	0.36	0.55
Age in years				
Mean (SD)	35.39 (10.20)	32.26 (10.40)	2.87	0.09
Years education completed				
Mean (SD)	12.77 (1.83)	13.18 (2.14)	1.37	0.25
BMI				
Mean (SD)	26.26 (4.80)	27.20 (7.16)	0.80	0.37
BDI				
Mean (SD)	4.80 (4.60)	4.74 (4.10)	0.01	0.94
Screen CO				
Mean (SD)	24.99 (8.38)	24.64 (9.52)	0.05	0.83

(table continues)

(Table 2 continued)

	Men (N=75)	Women (N=53)	F	P
Cigarette smoking related				
Cigs per day[a]				
Mean (SD)	24.11 (10.04)	21.27 (5.79)	3.42	0.07
Duration of use in years[a]				
Mean (SD)	12.98 (9.34)	9.13 (7.44)	6.19	0.01
FTC Tar yield[b]				
Mean (SD)	14.59 (3.34)	13.74 (3.94)	1.58	0.21
FTC Nic. Yield[c]				
Mean (SD)	1.04 (.26)	.99 (.30)	0.79	0.38
FTC CO[b]				
Mean (SD)	14.83 (2.77)	14.52 (3.48)	0.28	0.60
No. quit attempts[a]				
Mean (SD)	4.02 (7.37)	2.58 (2.52)	1.86	0.18
Fagerström[a]				
Mean (SD)	5.77 (2.15)	5.13 (1.97)	2.95	0.09

(Table 2 continued)

	Men (N=75)	Women (N=53)	F	P
+ responses CAGE[a]				
Mean (SD)	2.31 (1.12)	2.68 (.98)	3.59	0.06
% Hard pack[a]	78.67	73.58	0.44	0.51
% King size[a]	68.00	79.25	1.98	0.16
% Nicotine medication naïve[a]	76.00	67.92	1.01	0.32
Alcohol related[a]				
% Use	71.00	74.00	0.13	0.72
Use per day				
Mean (SD)	1.33 (2.13)	.91 (1.38)	1.64	0.20
Use past 30 days				
Mean (SD)	4.97 (5.90)	5.26 (7.44)	0.06	0.81
% Treated abuse/dependence	4.00	1.89	0.45	0.50
+ responses CAGE				
Mean (SD)	.43 (.84)	.36 (.96)	0.18	0.67

(Table 2 continued)

	Men (N=75)	Women (N=53)	F	P
Marijuana smoking related[a]				
% Use ever	82.67	84.91	0.11	0.74
% Use last month	26.67	47.17	1.19	0.28
Use past 30 days				
Mean (SD)	2.17 (6.67)	1.49 (4.43)	0.42	0.52
Money spent per month[d]				
Mean (SD)	7.33 (37.39)	12.98 (69.77)	0.35	0.56
Other drug related[a]				
% Used other drugs	1.33	7.55	3.22	0.08

[a] df = 1, 126: all participants, N=128

[b] df = 1, 115: data available for only 117 participants

[c] df = 1, 116: data available for only 118 participants

Then, a nurse placed a catheter in a forearm vein, and 10 ml of blood was sampled, centrifuged, and plasma was frozen for later determination of baseline nicotine levels. Volunteers then responded to a battery of computerized questionnaires and performance tasks to assess baseline responding. After completion of the tasks, a patch dose, pre-determined by Latin square order, was administered.

After the condition's transdermal nicotine dose had been administered, blood samples (10 ml each) were sampled at 30-minute intervals for exactly 6 hours. Thus, including baseline, there were a total of 13, 10-ml blood samples in each condition, leading to a total of 13*4 = 52 10-ml blood samples, or 520 ml sampled for each volunteer who completed the study. The amount of blood taken across the four days of the study (with a 48 hour inter-session interval) was only 60 ml more than the amount that would be donated at a single sitting during a blood drive (473 ml).

Subjective measures were assessed every hour throughout each condition; physiological responses were recorded continuously. At the end of the 6-hour, post-medication period the catheter was removed and volunteers were assessed by a staff member for any residual medication effects (i.e., dizziness, nausea, etc). Once any effects dissipated the volunteer was paid $100 for the time spent in the laboratory and dismissed. Volunteers received $100 for each session completed, plus an additional $100 after completing the entire study. Thus, volunteers who successfully completed the entire study earned $500.

Transdermal Nicotine and Placebo Patches

NicoDerm CQ™ (GlaxoSmithKline Consumer Healthcare, L.P.) transdermal nicotine patches were used for all active nicotine doses. Blood levels of nicotine

delivered from this product peak within approximately 4 hours and then remained at a steady state (Shiffman, Khayrallah & Nowak, 2000; Henningfield & Keenan, 1993), thus making the patches appropriate for a short-term study of transdermal nicotine-induced withdrawal suppression. The 7 and 21 mg transdermal doses were chosen because they covered the range of nicotine doses that are currently approved for cessation. The 42 mg dose was chosen to ensure that dose effect functions cover the highest doses that could be delivered safely in a short-term study (Benowitz, Zevin & Jacob, 1998; Fredrickson et al., 1995; Pickworth, Bunker & Henningfield, 1994).

Transdermal nicotine dose is controlled, in part, by patch size (i.e., the 7 mg patch is 70 mm by 70 mm; the 21 mg patch is 220 mm by 220 mm). Each volunteer always received one 7 mg-sized patch and two 21 mg-sized patches: none, one, or two of these could have been active (thus yielding 0, 7, 21, or 42 mg doses). Placebo patches (1-800-Patches, Salt Lake City, Utah) were of the same size as the active patches but contained no nicotine. In order to strengthen the study blinding procedures further, all patches were placed on each volunteer's upper back by staff with minimal patient contact, and the patches were covered with taped gauze. The same staff member removed and disposed of the patches/gauze at the end of each condition.

Primary Outcome Measures

Primary outcome measures included plasma nicotine levels that demonstrated transdermal nicotine dosing, subjective measures of withdrawal that addressed the study's primary hypothesis, and heart rate, because heart rate is influenced by tobacco abstinence and nicotine administration.

Plasma Nicotine Level. Ten ml of blood was sampled from a forearm vein every 30 minutes and stored briefly in tubes containing sodium heparin. These samples were centrifuged and the plasma was separated and stored at -70° C. The plasma was analyzed for nicotine and cotinine using high performance liquid chromatography (HPLC) and liquid chromatography mass spectrometry (a modified version of that reported by Naidong, Shou, Chen & Jiang, 2001). This assay had a limit of quantitation of 2.0 ng/ml. Plasma nicotine levels are elevated depending on transdermal nicotine dose (Fant, Henningfield, Shiffman, Strahs & Reitberg, 2000).

Heart Rate. During each session, heart rate was measured every 20 seconds by non-invasive computerized equipment (Noninvasive Patient Monitor model 507E, Criticare Systems, Waukesha, WI). Data collection began immediately prior to patch administration and ended immediately after the last blood sample. Heart rate data was grouped into thirty minute bins and averaged so that there was one value for every thirty minutes of the session. Thus, there were twelve heart rate data points for each condition. Heart rate is reduced during tobacco abstinence and elevated upon nicotine administration (Garrett & Griffiths, 2001; Jones, Garrett & Griffiths, 1999).

Hughes and Hatsukami Questionnaire. All subjective measures were computerized (Plowshare Technologies, Baltimore, MD) and volunteers responded to them using a computer mouse. The Hughes & Hatsukami Questionnaire (1986; Appendix F) consisted of 11 items: "Urges to smoke", "Irritability/frustration/anger", "Anxious", "Difficulty concentrating", "Restlessness", "Hunger", "Impatient", "CRAVING a cigarette/nicotine", "Drowsiness", "Depression/feeling blue", and "Desire for sweets." The 11 items were presented in a visual analog scale (VAS) format with a

word or a phrase centered above a horizontal line anchored on the left with "not at all" and on the right with "extremely." Volunteers responded to each item by moving a computer mouse-controlled cursor to any point on the horizontal line and clicking a mouse button, which produced a vertical mark on the line; this mark could be further adjusted with the mouse if necessary. The score was calculated as the distance of the vertical mark from the left anchor, expressed as a percentage of the total length of the horizontal line. This measure has been shown to be sensitive to abstinence-induced withdrawal and tobacco cigarette-induced withdrawal suppression (Breland, Evans, Buchhalter & Eissenberg, 2002; Buchhalter, Schrinel & Eissenberg, 2001).

Tiffany-Drobes Questionnaire of Smoking Urges. The QSU (Tiffany & Drobes, 1991; Appendix G) was made up of 32 smoking-related items (e.g., "Smoking would make me feel very good right now", "I have an urge for a cigarette") and has been validated empirically. Each item was presented as a phrase centered below seven ovals that were anchored on the left with "strongly disagree" and on the right with "strongly agree." Volunteers responded to each item by moving a cursor to highlight one of the ovals. Volunteers could adjust the placement of the cursor prior to advancing to the next item; scores for each of the seven ovals ranged from 0 to 6. Items from the QSU were collapsed into two factors that have been previously defined by factor analysis: Factor 1 was related to intention to smoke and Factor 2 was related to anticipation of relief from withdrawal (Tiffany & Drobes, 1991). This measure has been shown to be sensitive to abstinence-induced withdrawal and tobacco cigarette-induced withdrawal suppression suppression (Breland, Evans, Buchhalter & Eissenberg, 2002; Buchhalter, Schrinel & Eissenberg, 2001).

Secondary Outcome Measures

Secondary outcome measures included direct effects of transdermal nicotine, a performance measure, and several physiological measures, as described below.

Direct Effects Scale (DES). Direct effects of transdermal nicotine were assessed after withdrawal assessment using 10 VAS items that included known nicotine effects (Pullan et al., 1994; Gourlay, Forbes, Marriner, Pethica, McNeil, 1995): "Nauseous", "dizzy", "lightheaded", "nervous", "sweaty", "headache", "excessive salivation", "heart pounding", "confused" and "weak."

Digit Symbol Substitution Test (DSST). Behavioral effects of withdrawal and transdermal nicotine were assessed using the DSST (McLeod, Griffiths, Bigelow & Yingling, 1982), which consisted of randomly selected digits appearing on the center of a computer monitor. Volunteers were instructed to use the numeric keypad to reproduce a geometric pattern associated with a digit according to the digit code presented continuously at the top of the screen. Volunteers were instructed to complete as many patterns as possible while maintaining accuracy during the 90-s task presentation. Volunteers had an opportunity to practice this task during their in-person screening. Data collected from this performance measure included the number of trials attempted and the number of correct trials completed. These data were used to generate a "percent correct" for each DSST administration. The DSST is a performance measure that has been shown to be sensitive to nicotine/tobacco withdrawal (e.g., Eissenberg, Griffiths & Stitzer, 1996; but see also Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005).

Physiological Measures. During each session, blood pressure (systolic and diastolic) was measured every 5 minutes by non-invasive computerized equipment

(Noninvasive Patient Monitor model 507E, Criticare Systems, Waukesha, WI). Blood pressure data were grouped into thirty minute bins and averaged so that there was one value for every thirty minutes of the session. Thus, there were twelve blood pressure data points for each condition. Expired air CO (measured in ppm) was measured at screening (to verify smoking status) and before each condition (to verify abstinence) using a computerized monitor (BreathCO; Vitalograph, Lenexa, KS).

Volunteer Safety and Rights

This study used established methods and procedures and involved only minimal risk. Volunteers were advised that they could experience mild discomfort during abstinence from smoking or the blood sampling procedure. Though uncomfortable, short-term withdrawal was not medically dangerous. Regarding the blood sampling, volunteers were protected by sterile, disposable equipment and aseptic nursing procedures. Volunteers were able to leave the study at any time if they found these effects aversive.

Potential adverse effects associated with transdermal nicotine could include headache, nausea and vomiting (Hurt, 1999). These effects can be dose-related (Hughes et al., 1999) and thus the 42 mg dose was expected to produce noticeable effects in some individuals. Several studies have shown that higher doses of transdermal nicotine are safe for use with study participants (Dale et al., 1995; Frederickson et al., 1995; Jorenby et al., 1996). In one cessation study, seventy-one light (N=23), moderate (N=24) and heavy smokers (N=24) were given either a placebo or 11, 22 or 44 mg/day dose of transdermal nicotine for 6 days of intensive inpatient treatment and then another 7 weeks of outpatient treatment (Dale et al., 1995). Higher patch doses produced better

withdrawal symptom relief and little nicotine toxicity, and the 44 mg/day dose was deemed safe for use in heavy smokers. In another cessation study, 504 participants were given either a 22 mg/day dose or a 44 mg/d dose of nicotine patch during an 8-week clinical trial (Frederickson et al., 1995). The only observable difference in adverse effects between the two doses, which were more common with the 44 mg/day dose of patch, were nausea (28% vs. 10%) and vomiting (10% vs. 2%). Finally, 40 smokers in a cessation study received 4 weeks of 44 mg/day dose nicotine patch followed by 4 weeks of 22 mg/day dose patch and they experienced no significant adverse events (Jorenby et al., 1996). Higher patch doses have been safely administered (e.g. 63 mg) but those doses produced an increase in signs of nicotine toxicity (Zevin, Jacob III & Benowitz, 1998; Benowitz, Zevin & Jacob, 1998).

Highly trained staff ensured protection of volunteers' safety and rights for the entirety of the study. Non-invasive equipment monitored heart rate and blood pressure when volunteers were in the laboratory setting. Medical staff (on-site nurse; on-call physician) were notified if heart rate exceeded 120 beats per minute, if systolic blood pressure exceeded 120 mmHg or if diastolic blood pressure exceeded 100 mmHg. To ensure confidentiality, volunteers were not referred to by name but by a coded identifier. All identifying study information was secured in a locked cabinet within a locked room.

Missing Data

Computerized measurement decreased the likelihood of missing data in this study. Nonetheless, missing data arose from computer malfunction, volunteer discomfort (e.g., bathroom breaks), and human error. In those cases, the missing values were replaced by the average of the single values surrounding the missing points as has been reported

elsewhere (e.g., Eissenberg, Griffiths & Stitzer, 1996). In cases where this interpolation method was not possible (e.g., when several consecutive plasma nicotine values were unavailable, as occurred for 7 volunteers) the analysis was carried out by excluding the volunteers with missing data.

Data Analysis Plan

In order to examine gender differences, each demographic variable was analyzed with a single factor, between subject analysis of variance (ANOVA) with gender as the grouping variable. Results from this analysis were discussed above, and are presented in Table 3, which reveals that men and women differed on only one of 29 variables.

All data except pre-session CO level were entered into a mixed analysis of variance (ANOVA) where gender (two levels, men and women) was a between subject factor and dose (four levels: 0, 7, 21, 42 mg) and time were within-subject factors. The number of levels for the time factor varied depending upon outcome measure. For plasma nicotine and subjective and performance measures there were 7 levels (although plasma nicotine samples were taken every 30 minutes, yielding 13 samples, financial restrictions lead to analyzing only the baseline and hourly post-patch application samples). For heart rate and blood pressure there were 12 levels. Pre-session CO level data were entered into a dose by gender ANOVA.

In order to clarify the effects of TN dose on study outcomes, all data were analyzed using area under the time course curve analysis (AUC; as in Strain, Moody, Stoller, Walsh & Bigelow, 2004). The trapezoidal method is used to approximate the area under the curve. This is done by circumscribing *n* number of trapezoids under a curve. The area of the trapezoids are then summed. In the current study, the AUC data is

collapsed across time and gender. The analysis provides an estimate of the amount of nicotine absorbed and is used a measure of nicotine exposure.

Huynh-Feldt corrections were used to adjust for violations of the sphericity assumption in all within-subject analyses. The sphericity assumption states that the variance of the difference scores in a within-subjects design are equal across the groups. When this assumption is violated, there will be an increase in the probability of Type I error (falsely rejecting the null hypothesis), because the critical values in the F-table are too small (Minium, King & Bear, 1993). The Huynh-Feldt correction is an adjustment factor based on the amount of variance heterogeneity. Once it is computed, both the degrees of freedom in the numerator and the degrees of freedom in the denominator are adjusted by the factor so that the F critical values will be somewhat larger (Keppel, 1991). Tukey's Honestly Significant Difference (HSD) was used to explore differences after a significant ANOVA. Tukey's HSD is a conservative post-hoc test designed to compare all possible pairs of means while correcting for increases in the Type I error rate which occur when making the multiple comparisons. While comparing all means, Tukey's HSD maintains Type I error rate and experiment-wise error rate at alpha (Pagano, 1990). The mean square error terms for the overall interaction were used to conduct Tukey HSD post hoc tests and comparisons for which $P < .05$ were reported as significant.

Chapter 3

Results

This within-participant, double-blind, Latin square-ordered study was designed to determine the extent to which smokers' gender influenced the withdrawal suppression produced by different TN doses. The data of primary interest are men's and women's responses on the physiological, subjective and performance measures collected during each of the four study conditions (0, 7, 21 or 42 mg TN). Results for all statistical analyses for these measures are shown in Tables 3 (main effects of time course data), 4 (interactions of time course data) and 5 (main effects and interactions for AUC data). For the gender comparison, any main effect or interaction involving this between-subjects factor is relevant. For the withdrawal suppression produced by different TN doses, significant interactions involving dose and time are of most interest (or main effect of dose for AUC data), as they indicate that responses may differ depending on TN dose, and/or may help delineate the time course of withdrawal suppression.

The Effects of Gender on Study Outcome Measures

As the purpose of this study was to examine the effects of gender on TN-induced withdrawal suppression, results of the effects of gender on primary and secondary outcome measures will be presented first. Because there were no main effects of gender observed on any outcome measure (See Table 3), the results presented below will focus on interactions that involved the gender factor.

Table 3.
Statistical Analysis Results for Subjective, Performance and Physiological Measures Collected During Four Conditions – Main Effects.

	Gender[a]		Dose[b]		Time[c]	
	F	P	F	P	F	P
Physiological measures						
Heart rate	3.4	*n.s.*	114.3	<.001	108.0	<.001
Plasma nicotine	0.5	*n.s.*	906.7	<.001	466.1	<.001
Subjective effects						
Hughes Hatsukami Questionnaire						
Urges to smoke	0.3	*n.s.*	12.6	<.001	65.0	<.001
Irritability/Frustration/Anger	0.7	*n.s.*	3.3	<.05	22.2	<.001
Anxious	0.0	*n.s.*	2.8	<.05	26.6	<.001
Difficulty concentrating	1.5	*n.s.*	1.6	*n.s.*	5.7	<.001
Restlessness	0.9	*n.s.*	0.5	*n.s.*	3.9	<.05
Hunger	0.0	*n.s.*	1.4	*n.s.*	77.2	<.001
Impatient	0.0	*n.s.*	3.7	<.05	11.7	<.001
Craving a cigarette/Nicotine	0.2	*n.s.*	14.2	<.001	54.5	<.001
Drowsiness	1.8	*n.s.*	1.6	*n.s.*	13.4	<.001
Depression/Feeling blue	0.0	*n.s.*	2.0	*n.s.*	3.2	<.05
Desire for sweets	0.9	*n.s.*	1.8	*n.s.*	3.3	<.05

(table continues)

(Table 3 continued)

	Gender[a]		Dose[b]		Time[c]	
	F	P	F	P	F	P
Tiffany Drobes QSU						
Factor 1	0.1	*n.s.*	19.7	<.001	56.2	<.001
Factor 2	1.2	*n.s.*	11.9	<.001	44.3	<.001
Direct Effects of Nicotine						
Nauseous	2.6	*n.s.*	22.6	<.001	8.2	<.001
Dizzy	1.2	*n.s.*	17.9	<.001	5.3	<.005
Lightheaded	1.5	*n.s.*	16.3	<.001	6.3	<.001
Nervous	0.4	*n.s.*	9.5	<.001	4.7	<.005
Sweaty	0.4	*n.s.*	13.8	<.001	1.2	*n.s.*
Headache	1.0	*n.s.*	3.1	<.05	3.8	<.01
Excessive Salivation	0.6	*n.s.*	4.8	<.005	0.6	*n.s.*
Heart Pounding	0.6	*n.s.*	8.3	<.001	4.8	<.01
Confused	1.4	*n.s.*	3.8	<.05	3.4	<.05
Weak	3.3	*n.s.*	19.2	<.001	9.6	<.001
DSST	3.8	*n.s.*	1.0	*n.s.*	4.8	<.005

[a] df = 1, 126: all participants, N=128

[b] df = 3, 378

[c] df = 6, 756

Table 4.
Statistical Analysis Results for Subjective, Performance and Physiological Measures Collected During Four Conditions - Interactions.

	Dose * Time[a]		Dose * Gender[b]		Time * Gender[c]		Dose * Time * Gender[a]	
	F	P	F	P	F	P	F	P
Physiological measures								
Heart rate	13.6	<.001	3.6	<.05	3.0	<.05	1.3	*n.s.*
Plasma nicotine	235.1	<.001	1.0	*n.s.*	1.6	*n.s.*	1.3	*n.s.*
Subjective effects								
Hughes & Hatsukami Questionnaire								
Urges to smoke	2.6	<.005	0.3	*n.s.*	0.7	*n.s.*	1.4	*n.s.*
Irritability/Frustration/Anger	2.2	<.05	0.5	*n.s.*	1.2	*n.s.*	2.5	<.005
Anxious	0.9	*n.s.*	0.7	*n.s.*	0.4	*n.s.*	1.0	*n.s.*
Difficulty concentrating	1.2	*n.s.*	1.7	*n.s.*	0.8	*n.s.*	0.5	*n.s.*
Restlessness	1.2	*n.s.*	0.7	*n.s.*	1.2	*n.s.*	1.2	*n.s.*
Hunger	1.7	*n.s.*	2.5	*n.s.*	3.6	<.05	1.4	*n.s.*
Impatient	1.5	*n.s.*	1.1	*n.s.*	1.0	*n.s.*	1.0	*n.s.*
Craving a cigarette/Nicotine	4.0	<.001	1.1	*n.s.*	0.7	*n.s.*	1.6	*n.s.*
Drowsiness	1.4	*n.s.*	1.8	*n.s.*	0.5	*n.s.*	0.8	*n.s.*
Depression/Feeling blue	0.9	*n.s.*	0.3	*n.s.*	1.0	*n.s.*	0.9	*n.s.*
Desire for sweets	0.7	*n.s.*	4.9	<.005	1.5	*n.s.*	1.1	*n.s.*

(table continues)

(Table 4 continued)

	Dose * Time[a]		Dose * Gender[b]		Time * Gender[c]		Dose * Time * Gender[a]	
	F	P	F	P	F	P	F	P
Tiffany Drobes QSU								
QSU Factor 1	6.0	<.001	3.2	<.05	1.3	*n.s.*	1.7	*n.s.*
QSU Factor 2	6.0	<.001	1.2	*n.s.*	1.3	*n.s.*	1.7	*n.s.*
Direct Effects of Nicotine								
Nauseous	5.8	<.001	1.2	*n.s.*	2.2	*n.s.*	1.0	*n.s.*
Dizzy	4.6	<.001	1.2	*n.s.*	1.8	*n.s.*	2.1	<.05
Lightheaded	3.6	<.001	2.6	*n.s.*	0.9	*n.s.*	1.3	*n.s.*
Nervous	1.8	*n.s.*	2.0	*n.s.*	1.2	*n.s.*	0.8	*n.s.*
Sweaty	3.9	<.001	3.2	<.05	0.4	*n.s.*	0.4	*n.s.*
Headache	1.6	*n.s.*	0.7	*n.s.*	0.9	*n.s.*	0.7	*n.s.*
Excessive Salivation	1.2	*n.s.*	1.2	*n.s.*	0.4	*n.s.*	0.5	*n.s.*
Heart Pounding	1.4	*n.s.*	0.1	*n.s.*	1.3	*n.s.*	0.8	*n.s.*
Confused	1.7	*n.s.*	1.5	*n.s.*	2.1	*n.s.*	1.7	*n.s.*
Weak	4.6	<.001	1.5	*n.s.*	1.1	*n.s.*	1.3	*n.s.*
DSST	0.9	*n.s.*	0.9	*n.s.*	0.3	*n.s.*	1.7	*n.s.*

[a] df = 18, 2268

[b] df = 3, 378

[c] df = 6, 756

Table 5.
Statistical Analysis Results for Subjective, Performance and Physiological Measures Collected During Four Conditions – AUC.

	Dose[a]		Gender[b]		Dose * Gender[a]	
	F	P	F	P	F	P
Physiological measures						
Heart rate	123.2	<.001	3.5	*n.s.*	3.5	<.05
Plasma nicotine	994.9	<.001	0.5	*n.s.*	1.2	*n.s.*
Subjective effects						
Hughes Hatsukami Questionnaire						
Urges to smoke	13.3	<.001	0.2	*n.s.*	0.8	*n.s.*
Irritability/Frustration/Anger	4.1	<.05	0.4	*n.s.*	0.5	*n.s.*
Anxious	2.8	<.05	0.0	*n.s.*	0.6	*n.s.*
Difficulty concentrating	1.8	*n.s.*	1.1	*n.s.*	2.1	*n.s.*
Restlessness	1.3	*n.s.*	0.9	*n.s.*	1.1	*n.s.*
Hunger	1.9	*n.s.*	0.1	*n.s.*	2.2	*n.s.*
Impatient	4.6	<.01	0.0	*n.s.*	0.6	*n.s.*
Craving a cigarette/Nicotine	15.0	<.001	0.1	*n.s.*	1.7	*n.s.*
Drowsiness	1.7	*n.s.*	1.8	*n.s.*	2.0	*n.s.*
Depression/Feeling blue	2.2	*n.s.*	0.0	*n.s.*	0.3	*n.s.*
Desire for sweets	2.4	*n.s.*	0.7	*n.s.*	5.0	<.005

(table continues)

(Table 5 continued)

	Dose[a]		Gender[b]		Dose * Gender[a]	
	F	P	F	P	F	P
Tiffany Drobes QSU						
Factor 1	21.0	<.001	0.3	*n.s.*	3.2	<.05
Factor 2	14.8	<.001	0.9	*n.s.*	1.4	*n.s.*
Direct Effects of Nicotine						
Nauseous	25.1	<.001	0.9	*n.s.*	3.4	*n.s.*
Dizzy	19.2	<.001	1.5	*n.s.*	0.9	*n.s.*
Lightheaded	19.6	<.001	1.4	*n.s.*	3.2	<.05
Nervous	10.7	<.001	0.8	*n.s.*	1.7	*n.s.*
Sweaty	16.01	<.001	0.4	*n.s.*	2.6	*n.s.*
Headache	3.6	<.05	1.0	*n.s.*	0.4	*n.s.*
Excessive Salivation	6.5	<.005	0.6	*n.s.*	1.1	*n.s.*
Heart Pounding	9.4	<.001	0.7	*n.s.*	0.0	*n.s.*
Confused	3.8	<.05	1.6	*n.s.*	1.3	*n.s.*
Weak	21.5	<.001	3.5	*n.s.*	2.1	*n.s.*
DSST	2.0	*n.s.*	3.5	*n.s.*	0.4	*n.s.*

[a] df = 3, 378

[b] df = 1, 126: all participants, N=128

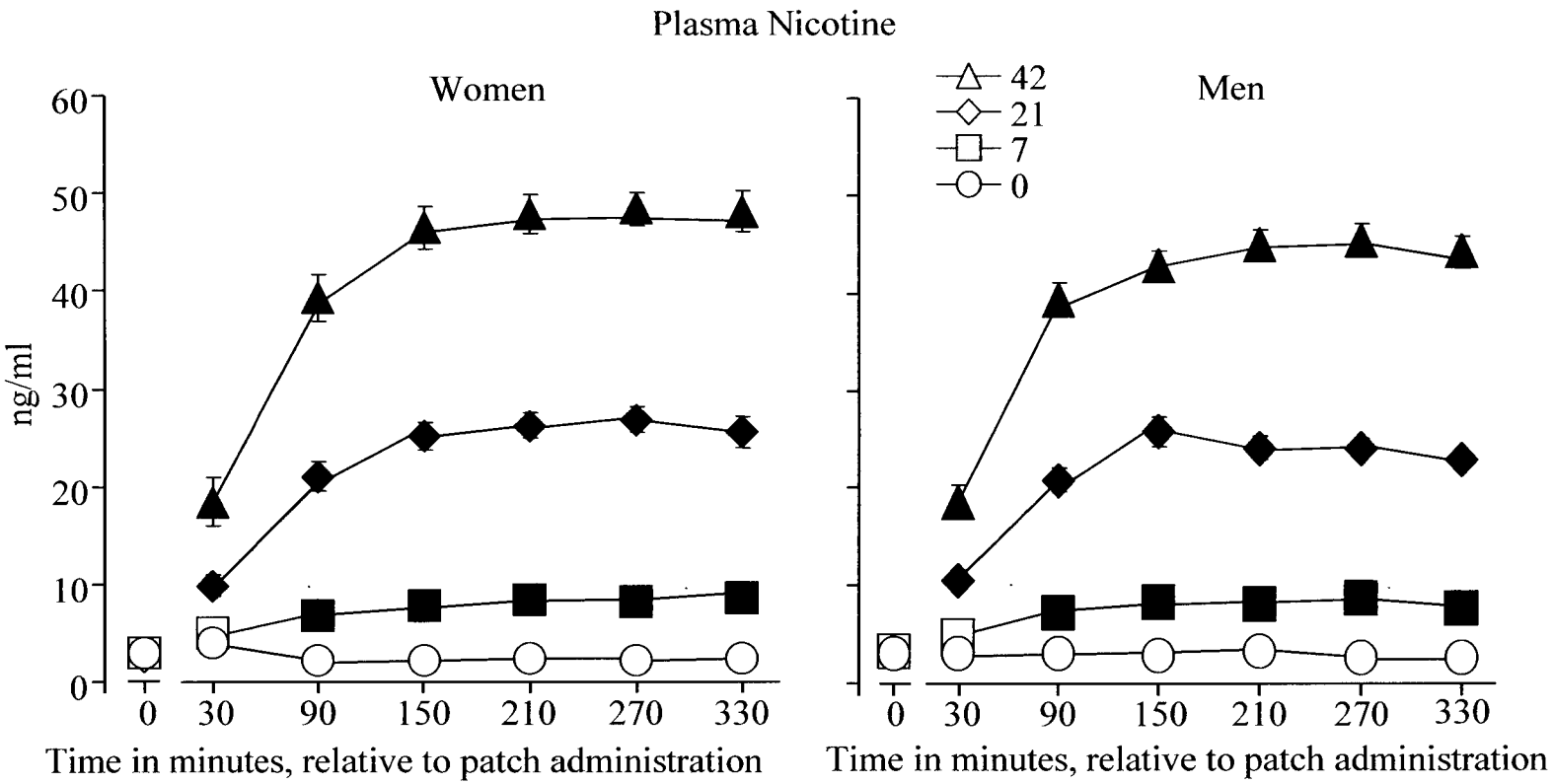

Figure 3. Mean data (+/- 1 SEM) for plasma nicotine for women (left; N=51) and men (right; N=72) by dose and time. Filled symbols indicate a significant difference relative to baseline.

Primary Outcome Measures

Primary outcome measures included plasma nicotine level (an indicator of TN dosing), heart rate (a tobacco abstinence sign influenced by nicotine administration), and subjective measures of withdrawal that address the study's primary hypothesis.

Plasma Nicotine Level. As can be seen in the tables, for plasma nicotine there was a highly significant interaction of dose and time (Table 4) and main effect of dose (Table 5), but no significant main effects or interactions involving the gender factor. Figure 3 shows plasma nicotine levels for men and women by dose. Each panel shows a significant increase of nicotine starting at 90 minutes and peaking 3-4 hours after patch administration. Nicotine levels increased with each increasing dose and there was a significant increase relative to placebo at these active doses.

Heart Rate. As seen in Table 4, for heart rate, two significant interactions involving the gender factor were observed: time by gender and dose by gender (Ps < .05). For the time by gender interaction, the mean data for men and women at each time point (collapsed across TN dose) are presented in Figure 4. While the figure shows some variability in average heart rate for men and women over time, post hoc analyses revealed that heart rate differed significantly by gender at only one time point, 360 minutes after TN administration: women's mean heart rate (73.85 bpm, SD = 9.57) was significantly greater than men's (69.85, SD = 8.90; P < .05, Tukey's HSD).

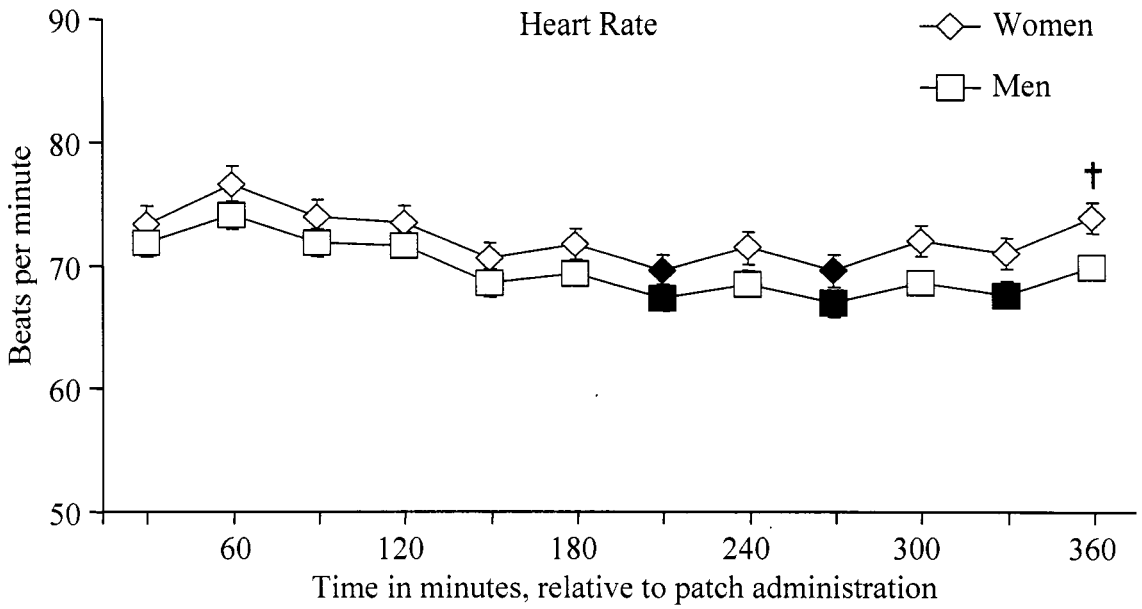

Figure 4. Mean data (+/- 1 SEM) for heart rate for 75 men and 53 women by time. Filled symbols indicate a significant difference relative to baseline (+30 minutes) and sword (†) indicates a significant difference between men and women at that time point. All Ps < .05, Tukey's HSD.

AUC data were used to explore further the influence of dose on heart rate. Table 5 shows a significant AUC dose by gender interaction for this outcome measure, and Figure 5 shows the data. As can be seen in the figure, heart rate increased significantly at each active dose relative to placebo (P < .05; Tukey's HSD). Women's heart rate was significantly greater than men's at the 7mg and 21 mg TN patch doses (P < .05; Tukey's HSD).

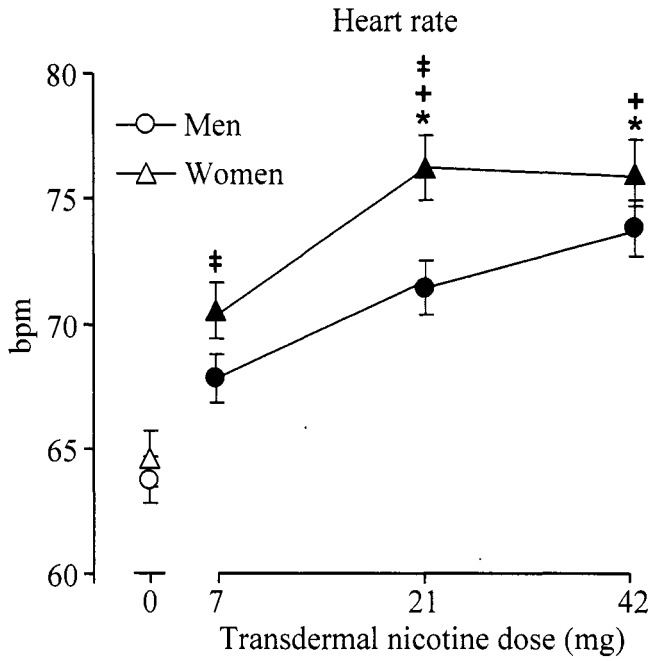

Figure 5. Mean AUC data (+/- 1 SEM) for heart rate for 75 men and 53 women by dose (0, 7, 21 or 42 mg TN), collapsed across time. Filled symbols indicate a significant difference at that dose relative to placebo; asterisk (*) indicates a significant difference from 7 mg for women; plus sign (+) indicates a significant difference from 7 mg for men; and double sword (‡) indicates a significant difference between women and men at that dose. All Ps < .05, Tukey's HSD.

Hughes and Hatsukami Questionnaire. Table 4 reveals that gender interacted significantly with at least one other factor for three items of the Hughes & Hatsukami Questionnaire: for Irritability/frustration/anger it interacted with dose and time ($P < .005$); for Hunger it interacted with time ($P < .05$); and for Desire for Sweets it interacted with dose ($P < .005$). Figure 6 shows averaged data for Irritability/frustration/anger VAS scores by time for women (left panel; N=53) and men (right panel; N=75). As the figure shows, Tukey's HSD revealed the baseline score for 42 mg TN for women (31.98, SD = 35.42) was significantly higher than the baseline score for 42 mg TN for men (17.52, SD = 24.71; $P < .05$).

The post-baseline pattern of results for this measure appeared different for men and women. For women, the mean Irritability/frustration/anger VAS scores for active TN doses at most time points were significantly lower as compared to baseline (see Figure 6, left). That is, relative to baseline, mean scores for 42 mg TN decreased 70.8% 360 minutes after patch administration. Similarly, relative to baseline, mean scores for 21 mg TN decreased 61.9% and mean scores for 7 mg TN decreased 36.4% 360 minutes after patch administration. In addition, 120 minutes after patch administration the 7mg TN score (10.25, SD = 16.12) was significantly lower than the 42 mg TN score (18.89, SD = 24.10) and by 360 minutes after patch application the 42 mg TN score (9.34, SD = 15.18) and 21 mg TN score (11.81, SD = 20.52) was significantly lower from the placebo score (all Ps < .005).

A different post-baseline pattern was observed for men: for active transdermal nicotine doses, the mean VAS scores at only a few time points (120 minutes after patch application for 7 mg TN; 60, 120, 180, 240, 300 and 360 minutes after patch application for 21 mg TN) were significantly lower as compared to baseline VAS scores. In addition, there were no significant differences of any active dose as compared to placebo.

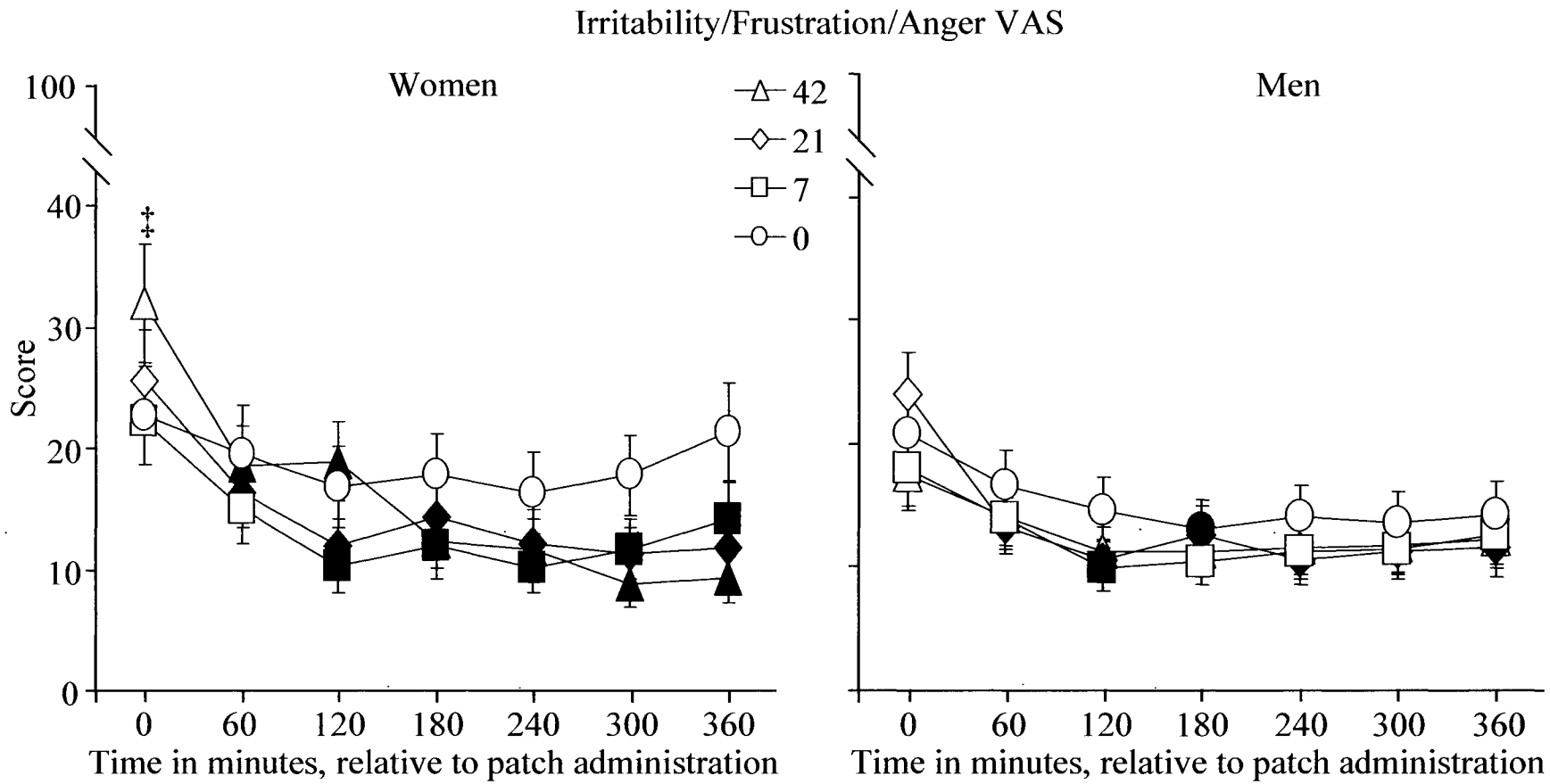

Figure 6. Mean data (+/- 1 SEM) for Irritability/Frustration/Anger VAS for women (left; N=53) and men (right; N=75) by dose and time. Double sword (‡) indicates a significant difference between women and men for the 42 mg dose at that time point and filled symbols indicate a significant difference relative to baseline. All Ps < .05, Tukey's HSD.

A significant interaction of time by gender was observed for the VAS item Hunger (see Figure 7, below), where, relative to women's ratings, men's were slightly higher at baseline (n.s.), and slightly lower (n.s.) at the end of the 6.5-hour session. Specifically, for men, mean ratings in this measure were 24.99 (SD = 30.63) as compared to 20.26 (SD = 25.97) for women at session onset, but, by the end of the session, women's mean scores were higher (49.69, SD = 33.18) than men's (44.21, SD = 36.32).

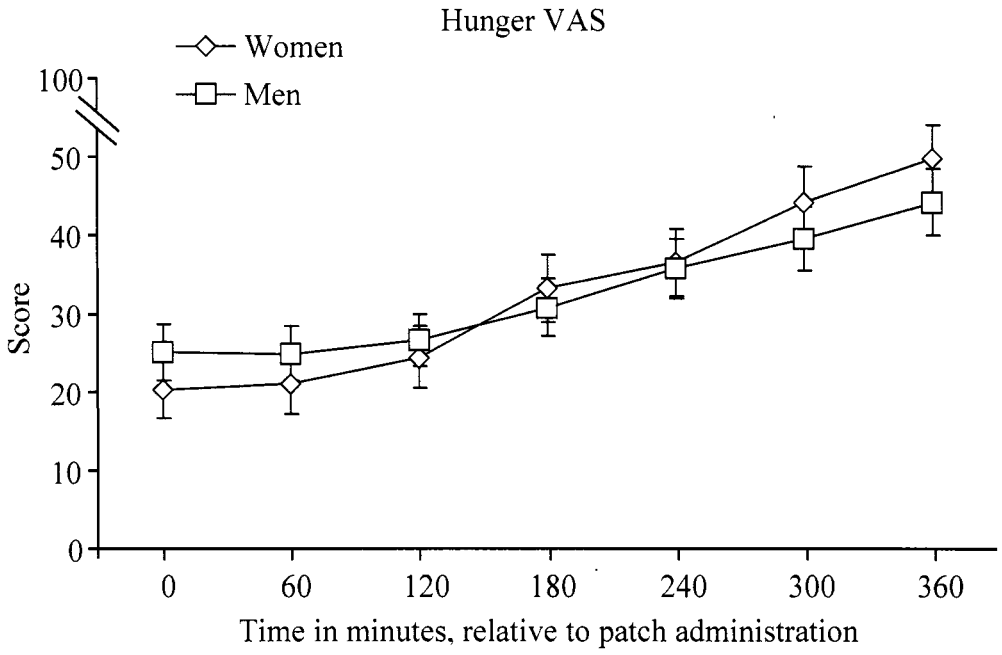

Figure 7. Mean data (+/- 1 SEM) for Hunger VAS for 75 men and 53 women by time.

For the Desire for Sweets VAS, a gender by dose interaction was observed, and Figure 8 shows average VAS scores, using AUC data, for each of the four doses (0, 7, 21, and 42 mg) for women and men. As seen in Figure 8, women's mean Desire for Sweets VAS scores at baseline (28.34, SD = 30.26) were significantly higher than men's mean scores at baseline (19.21, SD = 27.29; $P < .005$). In addition, for women (but not for men)

the mean Desire for Sweets VAS scores for the 7 mg (21.17, SD = 26.87), 21 mg (19.36, SD = 24.48) and 42 mg (16.93, SD = 22.18) doses were significantly lower than the mean Desire for Sweets VAS score for placebo (28.34, SD = 30.26; P < .005).

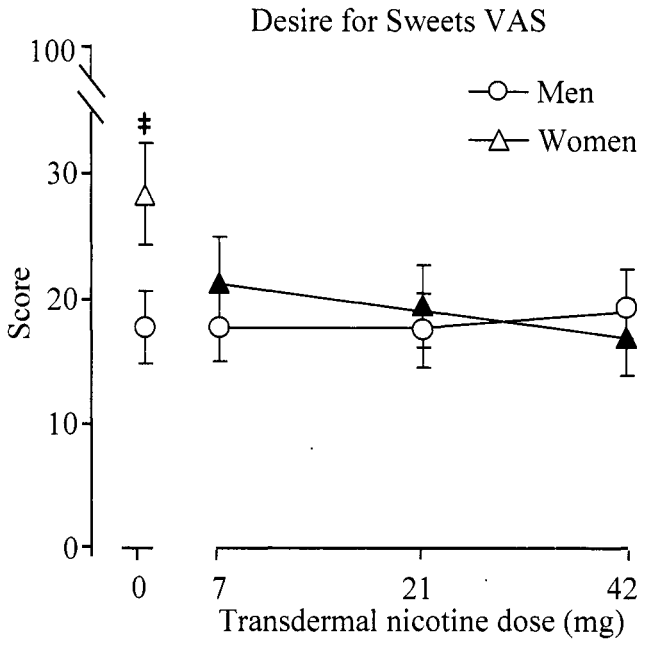

Figure 8. Mean AUC data (+/- 1 SEM) for Desire for Sweets for 75 men and 53 women by dose (0, 7, 21 or 42 mg TN), collapsed across time. Filled symbols indicate a significant difference at that dose relative to placebo and double sword (‡) indicates a significant difference between women and men at that dose. All Ps < .05, Tukey's HSD.

Tiffany-Drobes Questionnaire of Smoking Urges. Tables 4 (interactions of time course data) and 5 (main effects and interactions for AUC data) show that a significant dose by gender interaction for QSU Factor 1 was observed. AUC data were used to explore this dose by gender interaction further. As seen in Figure 9, there was a significant gender difference at the 42 mg dose, with women's average AUC score (44.67, SD = 26.03) being significantly lower than men's average AUC score (52.29, SD = 19.45; P < .05, Tukey's HSD).

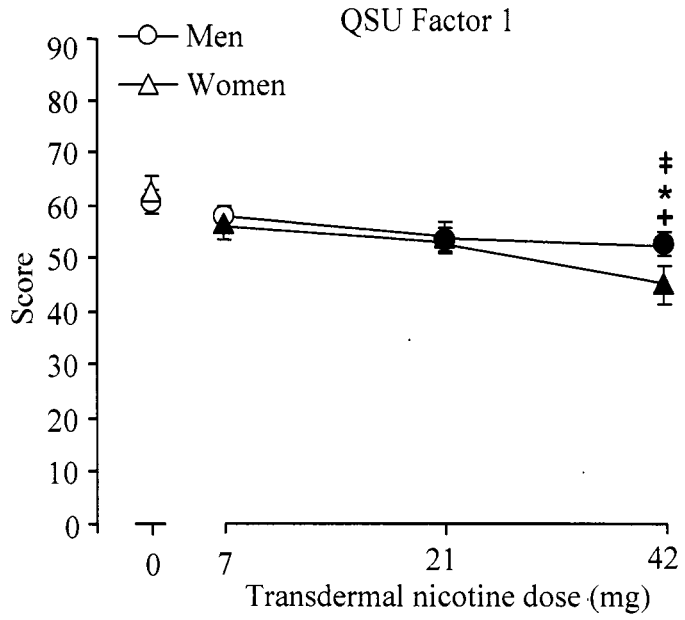

Figure 9. Mean AUC data (+/- 1 SEM) for QSU Factor 1 for 75 men and 53 women by dose (0, 7, 21 or 42 mg TN), collapsed across time. In all other aspects the figure is similar to Figure 5.

Secondary Outcome Measures

Secondary outcome measures included the Direct Effects Scale (a measure of the subjective effects of transdermal nicotine) and the Digit Symbol Substitution Test (DSST; a performance measure).

Direct Effects Scale. Table 4 reveals that gender interacted significantly with at least one other factor for two Direct Effects Scale items: for Dizzy it interacted with dose and time ($P < .05$); and for Sweaty it interacted with dose ($P < .05$). Figure 10 shows that, for "Dizzy", there was one significant between-gender difference. While there was substantial variability, women reported greater levels of dizziness after they had received 42 mg TN, especially within the first hour post-dosing. Women's mean VAS scores for 42 mg TN at 60 minutes after patch application (20.49, SD = 29.87; left panel) were significantly greater

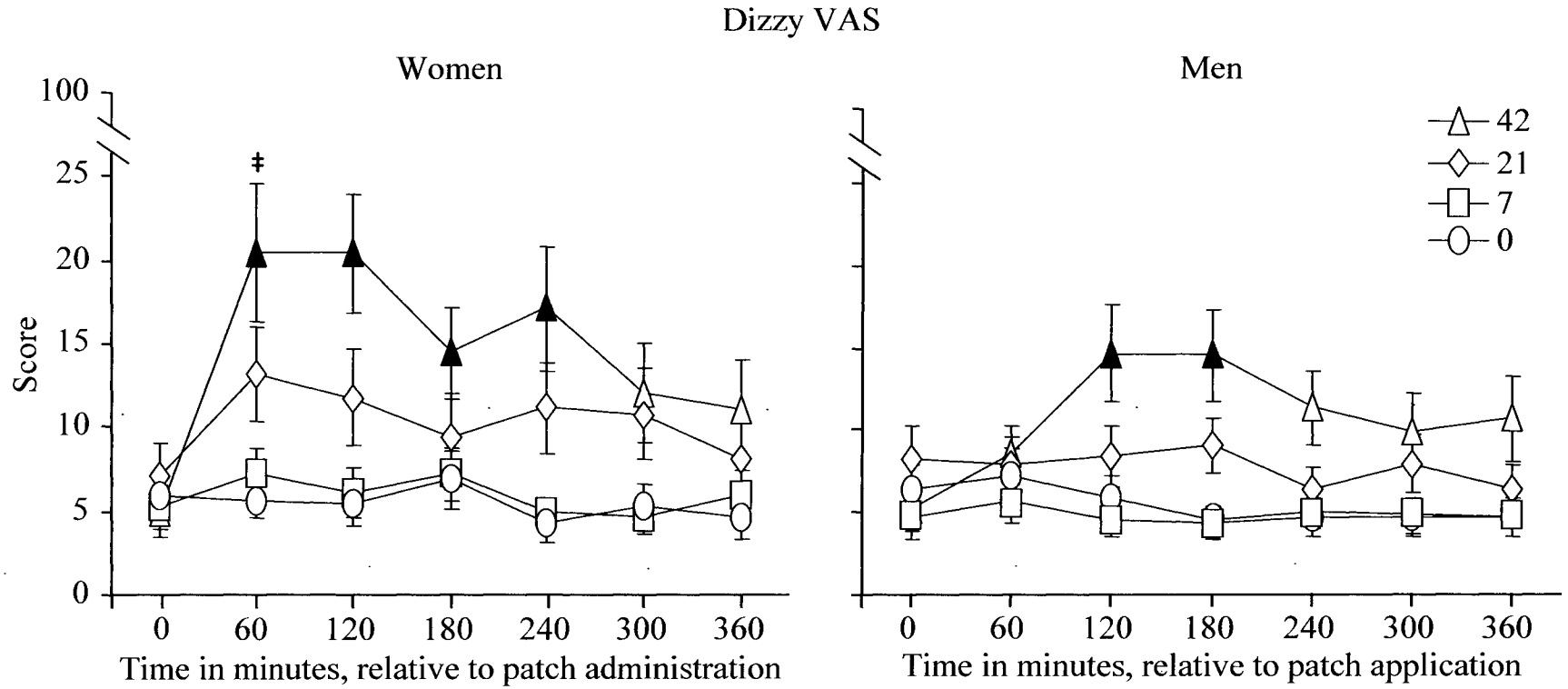

Figure 10. Mean data (+/- 1 SEM) for Dizzy VAS for women (left; N=53) and men (right; N=75) by dose and time. Double sword (‡) indicates a significant difference between women and men for the 42 mg dose at that time point and filled symbols indicate a significant difference relative to baseline. All Ps < .05; Tukey's HSD.

than men's mean VAS score at that dose and time (8.48, SD = 15.73; P < .05, Tukey's HSD; right panel).

For women, 42 mg TN differed significantly from other doses at several time points. That is to say, the mean VAS scores for Dizzy for 42 mg TN were significantly greater than mean scores observed for at least one other active dose at 60, 120, 180, 240 and 300 minutes after patch administration.

For men, mean scores observed after 42 mg TN differed significantly at two time points: 120 and 180 minutes after patch administration.

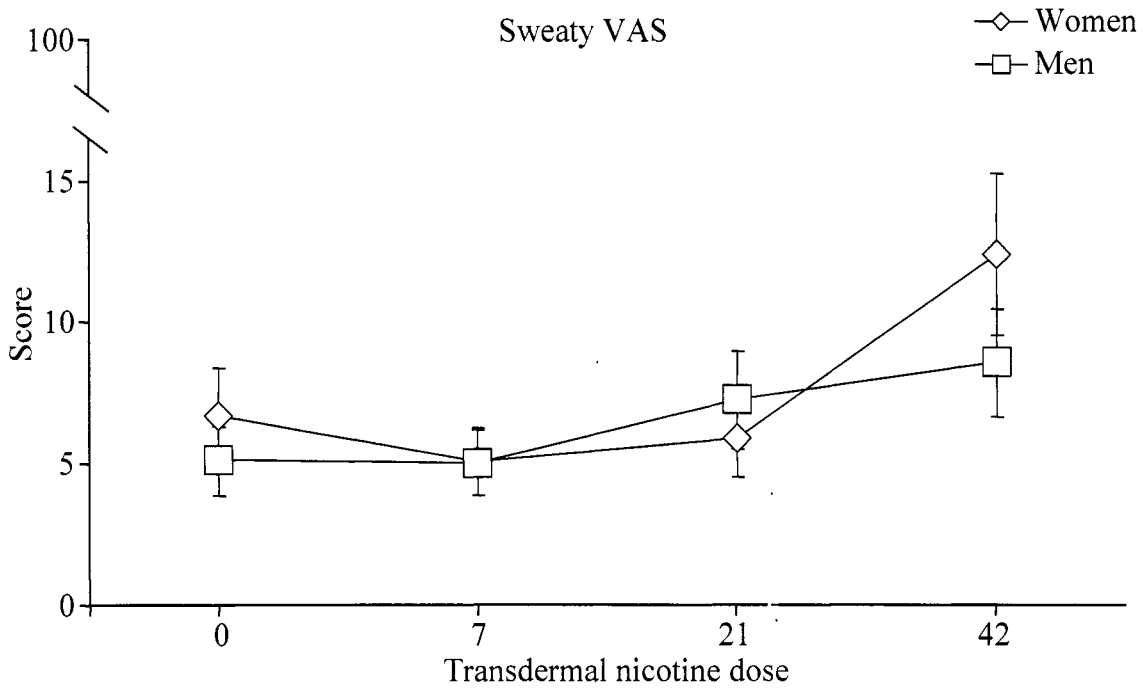

Figure 11. Mean data (+/- 1 SEM) for Sweaty VAS for 75 men and 53 women by dose (0, 7, 21 or 42 mg nicotine), collapsed across time.

Table 4 reveals that gender interacted significantly with dose (P < .05) for the Direct Effect Scale item of "Sweaty." Figure 11 shows average scores for this item, collapsed across time, for each of the four doses (0, 7, 21, and 42 mg) for women and

men (AUC analysis did not reveal any significant gender by dose interactions, see Table 5). As seen in Figure 11, the greatest between-gender difference was observed at 42 mg TN with women reporting greater mean scores (12.39, SD = 20.80) as compared to men (8.55, SD = 16.46; n.s., Tukey's HSD).

Table 5 reveals that gender interacted significantly with dose ($P < .05$) for the Direct Effect Scale item of "Lightheaded." Figure 12 shows average AUC scores for this item, for each TN dose for women and men. As seen in Figure 12, the greatest between-gender difference was observed at 42 mg TN with women (20.41, SD = 21.53) reporting significantly greater scores, on average, as compared to men (12.98, SD = 19.06; $P < .05$, Tukey's HSD). Women also reported that 42 mg TN (20.41, SD = 21.53) and 21 mg TN (13.25, SD = 19.38) were significantly greater than 7mg TN (7.15, SD = 10.89) and placebo (7.0, SD = 10.22; $P < .05$, Tukey's HSD).

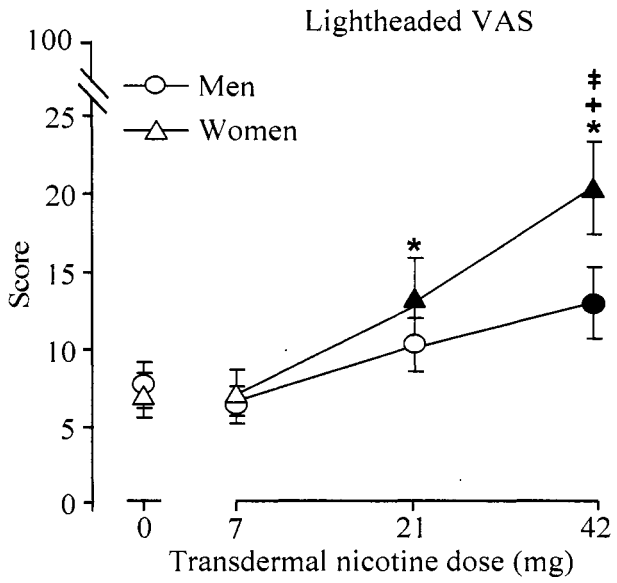

Figure 12. Mean AUC data (+/- 1 SEM) for Lightheaded VAS for 75 men and 53 women by dose (0, 7, 21 or 42 mg nicotine), collapsed across time. In all other aspects the figure is similar to Figure 5.

Digit Symbol Substitution Task (DSST). As seen in Table 4, there were no significant interactions of gender for the DSST outcome measure.

The Effects of Transdermal Nicotine Dose on Study Outcome Measures

An additional goal of this study was to determine the effects of dose on TN-induced withdrawal suppression. Results from physiological, subjective and/or performance measures may differ depending on TN dose. To expand on the effect of TN's effects over time, AUC analysis was used. The results showing the effects of dose on study outcome measures are presented below.

Primary Outcome Measures

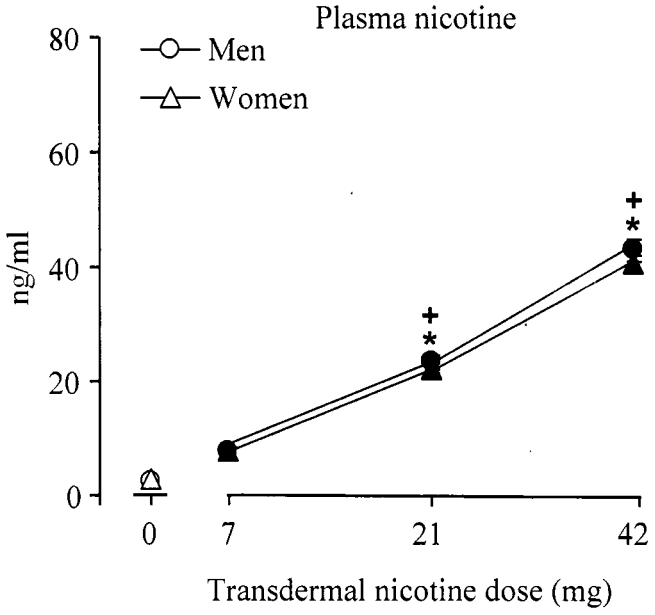

Figure 13. Mean AUC data (+/- 1 SEM) for plasma nicotine for 72 men and 51 women by dose (0, 7, 21 or 42 mg TN), collapsed across time. Filled symbols indicate a significant difference at that dose relative to placebo; asterisk (*) indicates a significant difference from 7 mg for women; and plus sign (+) indicates a significant difference from 7 mg for men. All Ps < .05; Tukey's HSD.

Plasma Nicotine Level. As seen in Table 5, there was a significant interaction of dose for plasma nicotine ($P < .001$). Figure 13 shows the averaged plasma nicotine AUC data for the four conditions (0, 7, 21 and 42 mg TN).

As can be seen in Figure 13 (above), when participants received active transdermal nicotine, plasma nicotine levels increased, relative to placebo. These increases were clearly dose-related, and there were no significant differences between men and women.

Heart Rate. Figure 14 shows the results for heart rate data, on which a significant interaction of dose by time was observed (see Table 4). Relative to baseline (+30 minutes after patch application), heart rate significantly decreased over time for the placebo condition. For example, heart rate was 70.67 bpm (SD = 9.56) at baseline and decreased to 65.49 (SD = 9.49) at 90 minutes and remained at approximately this level for the remainder of the session (i.e., 65.78 bpm, SD = 9.38 at 360 minutes after patch application; relative to baseline, Ps < .05, Tukey's HSD). Thus bradycardia was observed in the placebo condition, consistent with the notion that decreased heart rate is a sign of nicotine/tobacco withdrawal. In contrast, for 21 and 42 mg TN, patch administration increased heart rate significantly in the period from 60 to 90 minutes, relative to baseline. Relative to placebo, in these two conditions heart rate was significantly elevated for the rest of the 6.5-hour session (i.e., for every time point from 120 minutes to 360 minutes).

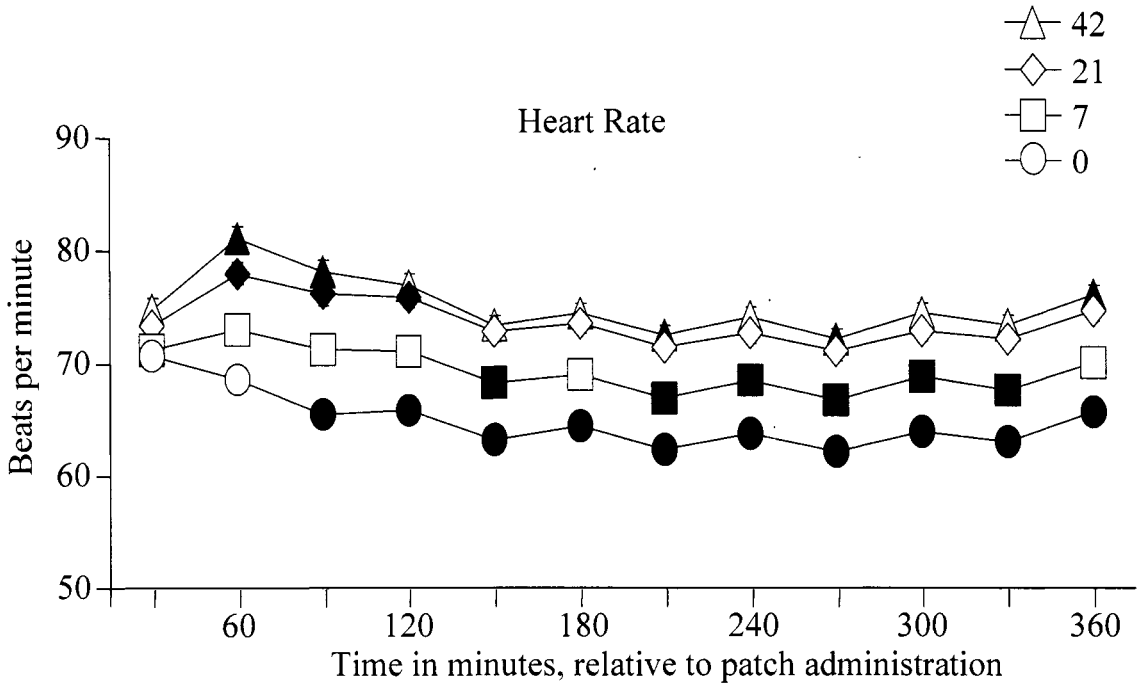

Figure 14. Mean data (+/- 1 SEM) for heart rate for 75 men and 53 women, by dose and time. Filled symbols indicate a significant difference relative to baseline. All Ps < .05; Tukey's HSD.

Hughes and Hatsukami Questionnaire. Results of the statistical analyses for the Hughes & Hatsukami VAS items are presented in Tables 3, 4, and 5. As can be seen in Table 3, a significant dose by time interaction was observed on three items: Craving ($P < .001$), Urges to smoke ($P < .005$) and Irritability/frustration/anger ($P < .05$).

The left panel of Figure 15 displays the results from the Craving VAS item for all doses and all time points. As the figure shows, at the baseline assessment, participants across all four dose conditions (0, 7, 21 and 42 mg TN) reported moderate Craving with a mean (collapsed across condition) of 58.47 (SD = 35.06) out of a 100 point scale (Tukey's HSD revealed no significant between condition differences at this time point). Relative to baseline, mean scores for all conditions (0, 7, 21 and 42 mg TN) on this

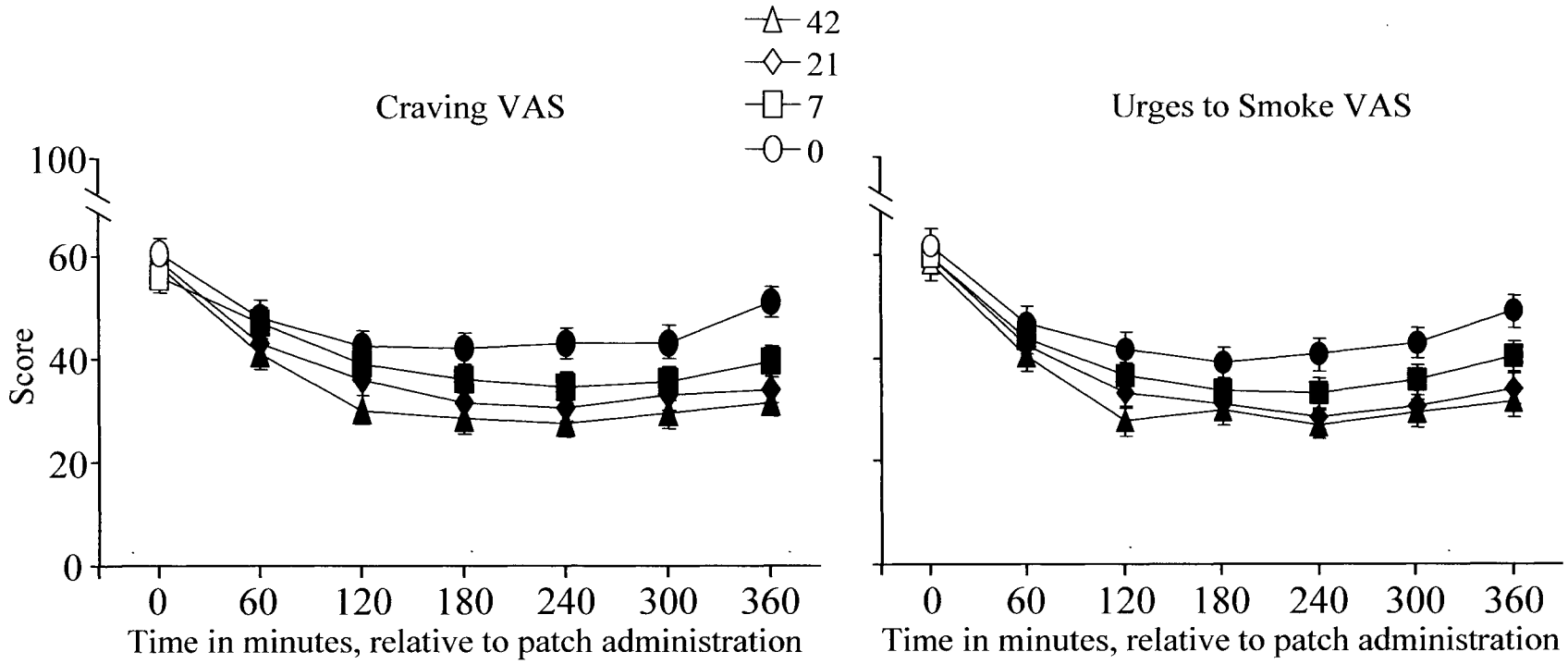

Figure 15. Mean data (+/- 1 SEM) for Craving VAS (left panel) and Urges to Smoke VAS (right panel); N=128 (75 men) for dose by time. Filled symbols indicate a significant difference relative to baseline (Craving: $P < .001$; Urge: $P < .05$; Tukey's HSD).

measure decreased significantly 1 hour after patch application. In addition, beginning at 120 minutes after patch application, self-reported Craving was significantly lower for participants in the 42 mg TN dose as compared to placebo. For example, for 42 mg TN, mean Craving scores at 180 minutes after patch administration (when plasma nicotine levels neared their peak) were 28.29 (SD = 30.09). In contrast, for placebo, mean Craving scores were 41.90 (SD = 33.62) at 180 minutes ($P < .001$). Similarly, the mean Craving scores for 21 mg (31.26, SD = 31.21) at 180 minutes after patch administration also differed significantly from placebo at that time point ($P < .001$). Similar differences were also observed at the end of the session, when mean Craving scores observed in all active conditions were significantly lower than that observed for the placebo condition.

As can be seen in Table 5, there was a significant main effect of dose for Craving ($P < .001$) using the AUC data, and these data are displayed in Figure 16 (top left panel). As the figure shows, there was a significant decrease in reports of Craving for 42 mg TN (collapsed across gender, mean = 29.91, SD = 28.39) and 21 mg TN (mean = 34.22, SD = 28.69) doses as compared to placebo (mean = 44.3, SD = 30.95, all Ps < .001).

A similar pattern of time course results was observed for the Urges to smoke VAS item. At the baseline assessment, participants in all four conditions reported moderate Urges to smoke with a mean (collapsed across condition) of 59.70 (SD = 34.90) out of a 100 point scale (Tukey's HSD revealed no significant between condition differences at this time point). As seen in Figure 15 (right panel), relative to baseline, mean scores for all conditions (0, 7, 21 and 42 mg TN) on this measure decreased significantly 1 hour after patch application. In addition, beginning at 120 minutes after patch application, self-reported Urges to smoke were significantly lower for most active TN doses as compared

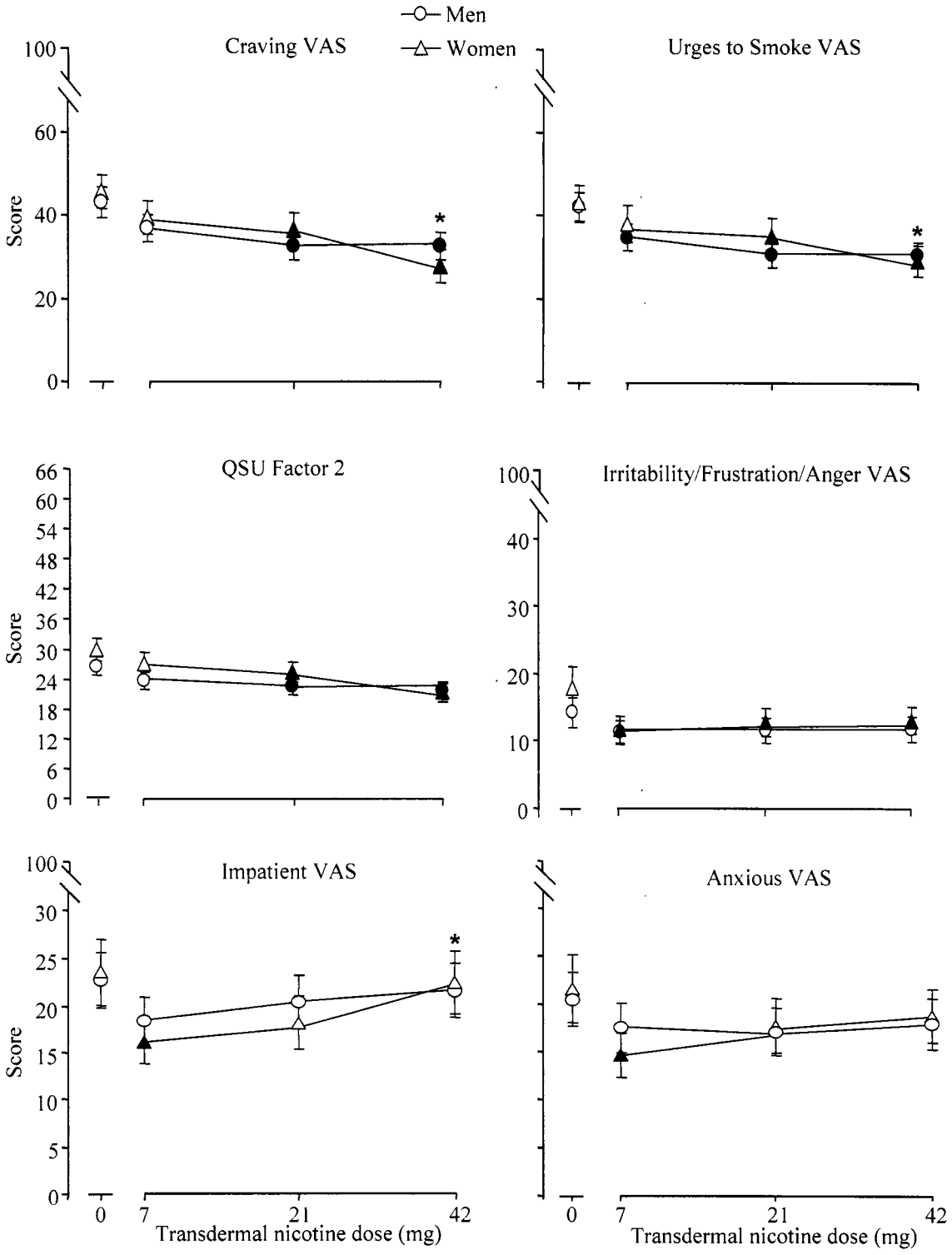

Figure 16. Mean AUC data (+/- 1 SEM) for 72 men and 51 women by dose (0, 7, 21 or 42 mg TN), collapsed across time for Craving VAS, Urge VAS, QSU Factor 2, Irritability/Craving/Anger VAS, Impatient VAS and Anxious VAS. In all other aspects the figure is similar to Figure 12.

to placebo. For example, for 42 mg TN, the mean Urges to smoke score at 240 minutes after patch administration (collapsed across gender) was 26.93 (SD = 30.56). In contrast, for placebo at 240 minutes, the mean Urges to smoke score was 40.54 (SD = 34.60). Similarly, the mean Urges to smoke scores for 21 mg (collapsed across gender, mean = 28.45, SD = 30.28) at 240 minutes after patch administration also differed significantly from placebo at that time point.

As can be seen in Table 5, there was a significant main effect of dose for the AUC data for Urges to smoke; these data are displayed in Figure 16 (top right panel). As the figure shows, there was a significant decrease in reports of Urges to smoke when participants received 42 mg TN (collapsed across gender, mean = 29.74, SD = 27.54) or 21 mg TN (mean = 32.62, SD = 27.46), as compared to placebo (mean = 41.90, SD = 31.90).

Also seen in Table 5, there was a significant main effect of dose for the Impatient VAS; these data are displayed in Figure 16 (bottom left panel). As the figure shows, the largest difference in reports of Impatient was between 7 mg TN (collapsed across genders, mean score = 17.30, SD = 19.40) and placebo (mean score = 23.16, SD = 19.40).

Similar results were observed for the Anxious VAS. As seen in Figure 16 (bottom right panel) the largest difference in scores for Anxious were between 7 mg TN (collapsed across genders, mean = 16.08, SD = 19.76) and placebo (mean = 21.02, SD = 24.92). This finding of the largest difference between 7 mg TN (mean = 11.49, SD = 15.35) and placebo (mean = 16.03, SD = 21.51) was also true for

Irritability/frustration/anger, as seen in Figure 16 (middle right). For the remaining Hughes & Hatsukami VAS items, which included Difficulty concentrating, Restlessness, Hunger, Impatient, Drowsiness, Depression/Feeling blue and Desire for sweets, AUC analysis revealed there were no significant dose effects.

Tiffany-Drobes Questionnaire of Smoking Urges. Table 4 shows there was a significant dose by time interaction for QSU Factor 2. This interaction indicated significant reduction in scores when participants received active TN versus placebo. AUC data were used to explore these differences further, and the AUC data are displayed in Figure 16 (middle panel, left). The figure shows that 42 mg TN (collapsed across gender, mean = 21.18, SD = 16.37) and 21 mg TN (mean = 23.90, SD = 14.96) were significantly lower than placebo (mean = 21.39, SD = 14.88).

Secondary Outcome Measures

Direct Effects Scale. As can be seen in Tables 3 and 4, a significant dose by time interaction was observed on five Direct Effect Scale items (Nauseous, Dizzy, Lightheaded, Sweaty and Weak). This interaction indicated significant increases in DES scores when participants received active TN versus placebo. AUC analysis was used in order to examine further the influence of dose. As Figure 17 shows, these interactions reflect dose-related increases on these measures.

For example, Figure 17 (top left) shows the results of Nauseous. On this measure, the mean score for placebo, collapsed across gender, was 5.36 (SD = 9.38), and the mean decreased slightly to 4.78 for 7 mg (SD = 7.23, n.s.), then increased to 9.31 for 21 mg

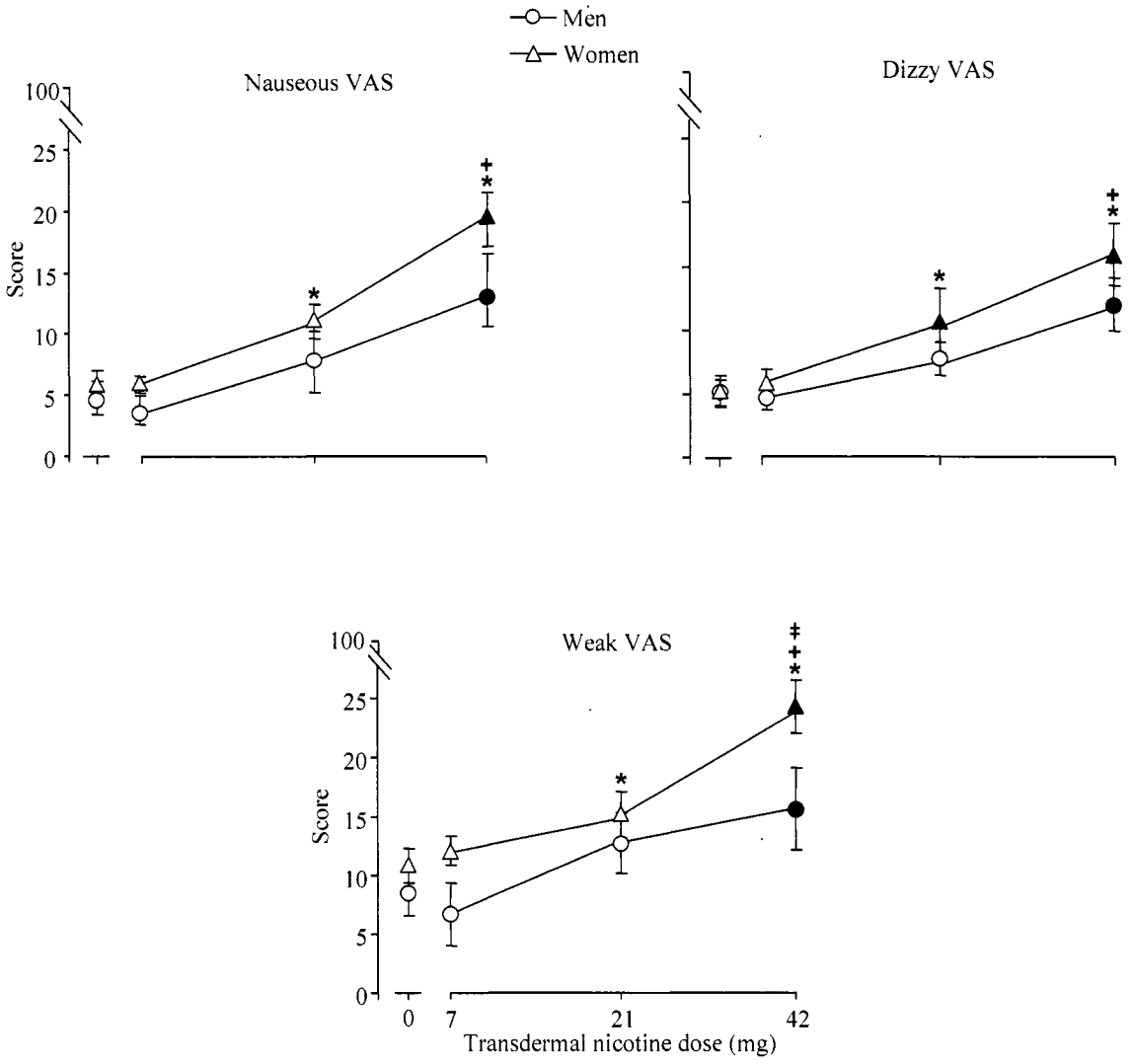

Figure 17. Mean AUC data (+/- 1 SEM) for 75 men and 53 women for Nauseous VAS (top left), Dizzy VAS (top right), and Weak VAS (bottom middle). In all other aspects the figure is similar to Figure 12.

(SD = 14.97, n.s.), and 16.30 for 42 mg (SD = 20.31, P < .001). As seen in Figure 17, a nearly identical pattern can be seen for the direct effects of Dizzy, (top right), and Weak (bottom center). A difference for Weak was also observed at 42 mg TN, with women (mean = 24.10, SD = 25.10) reporting significantly greater scores, on average, as compared to men (mean = 15.38, SD = 19.44).

Digit Scale Substitution Task (DSST). Finally, results of the statistical analyses revealed that there were no significant main effects or interactions observed for the DSST "percent correct" data except for a significant improvement over time: collapsed across session, mean percent correct increased from 93.48% (SD = 12.54) at baseline to 95.62% (SD = 7.81) at 360 minutes after patch application (P < .005).

Chapter 4

Discussion

In many tobacco cigarette smokers, periods of tobacco abstinence, such as those that accompany a quit attempt, result in a well-defined, quantifiable syndrome that includes observable signs (decreased heart rate, increased caloric intake and weight, EEG changes), behavioral decrements, and aversive symptoms (irritability, headache, hunger, restlessness, impatience). This syndrome, often referred to as "nicotine/tobacco withdrawal" (Jarvis, 2004; Buchhalter, Schrinel & Eissenberg, 2001; Jorenby et al., 1996; Hatsukami, LaBounty, Hughes & Laine, 1993) likely contributes to the difficulty in quitting smoking reported by treatment-seeking smokers (Fagerström, Schneider & Lunell, 1993; Killen, Fortmann, Kraemer, Varady & Newman, 1992; Hughes & Hatsukami, 1996). Suppressing nicotine/tobacco withdrawal is one putative mechanism of action underlying the effectiveness of smoking cessation pharmacotherapies (Wetter, Fiore, Young, McClue & deMoor, 1999; Hatsukami, McBride, Pirie, Hellerstedt & Lando, 1991; Hajek, Jarvis, Belcher, Sutherland & Feyerabend, 1989), including NRT (West & Shiffman, 2001; Molander, Lunell & Fagerström, 2000; Hurt et al., 1998; Leischow et al., 1997; Hughes et al., 1984; West, Jarvis, Russell, Carruthers & Feyerabend, 1984). NRT, and specifically TN, is an efficacious smoking cessation pharmacotherapy (Kalman et al., 2004; Hughes, Shiffman, Callas & Zhang, 2003; Kotlyar & Hatsukami, 2002), though some clinical trials suggest that, relative to men, abstinence rates are lower for women using TN (Bohadana, Nilsson, Rasmussen & Martinet, 2003; Swan, Jack & Ward, 1997; Gourlay, Forbes, Marriner, Pethica &

McNeil, 1994; Nørregaard, Tonnesen & Petersen, 1993; Transdermal Nicotine Study Group, 1991). Because suppressing nicotine/tobacco withdrawal is relevant to TN's efficacy, and because TN may be less effective for women, gender may influence NRT-induced nicotine/tobacco withdrawal suppression in abstinent smokers. Indeed, some studies are consistent with the notion that relative to men, women report less NRT-induced withdrawal suppression (Wetter, Fiore, Young, McClure & deMoor, 1999a), though these studies were limited by use of small samples and single NRT doses (Killen, Fortmann, Newman & Varady, 1990) and thus may not have had optimal sensitivity (Hatsukami, Skoog, Allen & Bliss, 1995). Larger sample studies that compare the withdrawal suppressing effects of a wide range of NRT doses may help reveal the extent to which gender influences NRT's withdrawal-suppressing effects, and thus may be relevant to understanding differences in treatment efficacy in men and women. This study was designed to examine the extent to which 0, 7, 21, and 42 mg TN suppressed acute withdrawal in abstaining smokers (75 men and 53 women) in a laboratory setting, using empirically validated assessment instruments. Results revealed that tobacco abstinence produced a variety of observable signs and symptoms, some of these symptoms were suppressed by active TN, and gender had little influence on TN-induced withdrawal suppression. TN also produced a range of side effects, and gender had some influence on these effects. These results are discussed below, as are some important study limitations.

Signs and Symptoms of Nicotine/Tobacco Abstinence

In this study, 8-12 hours of objectively-verified tobacco abstinence was required before each of the four sessions, in order to maximize the chances that participants would

experience withdrawal that might be suppressed by TN. Signs and symptoms of withdrawal were evident in this study. For example, as seen in Figure 13, when participants received placebo TN, their heart rate decreased significantly across the 6-hour session, and bradycardia is a sign of nicotine/tobacco withdrawal. These findings are consistent with previous reports which revealed a reliable decrease in heart rate in smokers undergoing tobacco abstinence (e.g., Eissenberg, Griffiths & Stitzer, 1996; Pickworth, Fant, Butschky & Henningfield, 1996; Hughes, Higgins & Hatsukami, 1990; Shiffman, 1979) and in a placebo-control study in which smokers used denicotinized cigarettes (Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005).

Participants also reported symptoms of nicotine/tobacco withdrawal. For example, mean pre-session scores for many withdrawal measures were elevated relative to scores observed in smokers who are not undergoing a period of tobacco abstinence (e.g., Irritability/frustration/anger; see Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005). For some symptoms, such as Hunger, magnitude increased over time when placebo was administered (in cigarette smokers, tobacco abstinence is associated with increased appetite: American Psychiatric Association, 1994; Hughes, Gust, Skoog, Keenan & Fenwick, 1991; Hughes, Gust, Skoog, Keenan & Fenwick, 1991).

Overall, the signs and symptoms observed at baseline in this study are consistent with those observed in previous research where nicotine/tobacco withdrawal has been documented under controlled conditions (Buchhalter, Acosta, Evans, Breland & Eissenberg, 2005; Gilbert et al., 2004; Teneggi et al., 2002; Persico, 1992; West & Russell, 1987; Hatsukami, Hughes & Pickens, 1985; Hatsukami, Hughes, Pickens & Svikis, 1984; Gilbert & Pope, 1982; Myrsten, Elgerot & Edgren, 1977; Knapp, Bliss &

Wells; 1963). Importantly, as has been reported elsewhere (Ward, Swan & Jack, 2001; Shiffman, Khayrallah & Nowak, 2000; Foulds et al., 1997; Hughes, Gust, Skoog, Keenan & Fenwick, 1991; Hughes & Hatsukami, 1986), the signs and symptoms of nicotine/tobacco withdrawal observed in this study were largely independent of gender. While these effects are consistent with nicotine/tobacco withdrawal, this study did not include a control condition in which participants' heart rate and withdrawal symptoms were assessed immediately after smoking a tobacco cigarette (i.e., a non-abstinence condition). Inclusion of this control condition would have helped demonstrate unequivocally that the decreased heart rate and increased symptom magnitude observed at baseline were due to tobacco abstinence.

Trandermal Nicotine-Induced Suppression of Nicotine/Tobacco Withdrawal.

TN increased plasma nicotine levels in a dose-dependent manner, and active TN suppressed nicotine/tobacco withdrawal signs and symptoms, at least partially. First, as has been reported previously (e.g. Mendelson, Sholar, Goletiani, Siegel & Mello, 2005; Ingram et al., 2004; Fant, Henningfield, Shiffman, Strahs & Reitberg, 2000; Henningfield & Kennan, 1993), plasma nicotine levels were low at baseline in all conditions (consistent with pre-session abstinence) and, after dosing, increased as TN dose increased (peak plasma nicotine levels occurred at approximately 3-4 hours after TN administration; see Figures 3 and 13). These results are important, as they demonstrate: 1) participants' compliance with study smoking restrictions; 2) the effectiveness of the TN preparation used in the study; and 3) the fact that, under placebo dosing conditions, participants did not receive nicotine in this study.

Second, TN suppressed, in a dose-dependent manner, the bradycardia observed under placebo conditions (see Figure 4), as reported elsewhere with a variety of methods of nicotine delivery (e.g. Garrett & Griffiths, 2001; Jones, Garrett & Griffiths, 1999; Krivokapich, Schneider, Child & Jarvik, 1985). The TN-induced increases in heart rate occurred within the first 60 minutes after TN administration, consistent with increases in plasma nicotine levels observed at this time. This time course of nicotine's physiological effects is consistent with previous studies that indicate that transdermal nicotine can increase heart rate even after 30 minutes (Rose, Herskovic, Trilling & Jarvik, 1985).

Third, in this study, AUC data revealed that TN reliably suppressed many nicotine/tobacco withdrawal symptoms; in some cases, this TN-induced withdrawal suppression was dose-related, though for many symptoms, it was not. For example, Craving and Urges to Smoke were two measures on which dose-dependent effects were observed (see Figures 15 and 16). That is to say, as the TN dose increased, the reports of Craving and Urges to Smoke decreased. Collapsed across gender, the mean AUC VAS scores for Craving were 29.91 (SD = 28.39) for 42 mg TN, 34.22 (SD = 28.69) for 21 mg TN and 37.94 (SD = 29.55) for 7 mg TN [a paired samples t-test revealed a significant difference between 7 and 42 mg, $t(127) = 3.66$, $P < .01$]. Similar dose-related withdrawal suppression was reported for Urges to Smoke with VAS scores of 29.74 (SD = 27.54) for 42 mg TN, 32.65 (SD = 27.46) for 21 mg TN and 36.30 (SD = 42.42) for 7 mg TN 21 [the difference between 7 and 42 mg was significant, $t(127) = 3.05$, $P < .01$]. While not a DSM-IV withdrawal symptom, Craving for cigarettes is the most commonly reported reason for relapse (Nørregaard, Tonnesen & Petersen, 1993), can increase in intensity after one hour of cigarette deprivation, and may reach peak levels within 6-24 hours of

abstinence (Maude-Griffin & Tiffany, 1996). Therefore suppression of Craving and Urges to Smoke is important in cessation efforts.

TN-induced withdrawal suppression was observed for Irritability/frustration/anger, Anxious and QSU Factor 2, but withdrawal suppression was dose-related for QSU Factor 2 only. Collapsed across gender, the mean AUC VAS scores for QSU Factor 2 were 21.39 (SD = 14.88) for 42 mg TN, 23.90 (SD = 14.96) for 21 mg TN and 25.28 (SD = 16.26) for 7 mg TN (all comparisons n.s.). In contrast, for Irritability/frustration/anger the mean AUC VAS scores (collapsed across gender) were 12.44 (SD = 15.58) for 42 mg TN, 12.11 (SD = 15.79) for 21 mg TN and 11.49 (SD = 15.35) for 7 mg TN (all comparisons n.s.). For Anxious the mean AUC VAS scores (collapsed across gender) were 18.35 (SD = 21.74) for 42 mg TN, 17.41 (SD = 21.18) for 21 mg TN and 16.08 (SD = 19.76) for 7 mg TN (all comparisons n.s.).

In summary, TN-induced withdrawal suppression was observed for Craving and Urges to smoke, as well as some DSM-IV nicotine/tobacco withdrawal symptoms (Irritability/frustration/anger, Anxious; Hughes & Hatsukami, 1998). The failure to observe TN suppression on some withdrawal measures is inconsistent with results from some clinical trials (Dale et al., 1995; Transdermal Nicotine Study Group, 1991) and may reflect a difference in participants (i.e., non-treatment seeking versus actively trying to quit smoking) and/or time course (i.e., assessments over 6 hours versus over several days). The current results and previous reports (Shiffman, Khayrallah & Nowak, 2000; Leischow et al., 1997; Jorenby et al., 1996) support the notion that TN suppresses many symptoms reported by abstinent smokers (i.e., Craving, Urges to smoke,

Irritability/frustration/anger, and Anxious). Thus, this study highlights one mechanism by which TN helps abstinent smokers avoid relapse. However, these results also suggest that some symptoms are not suppressed by TN under the conditions reported here (e.g., Difficulty concentrating, Restlessness, Hunger, Impatient). To the extent that TN does not suppress some withdrawal symptoms in a dose-related manner, and does not suppress other symptoms at all, clinicians recommending TN may want to consider identifying the symptoms reported by their abstinent patients before recommending a specific TN dose. Thus, the results of this study may be taken as support for individualizing clinician-recommended pharmacotherapy for smoking cessation, based on patient reports of abstinence symptoms, either during a quit attempt or based upon previous attempts.

The Effects of Gender on Transdermal Nicotine-Induced Suppression of Nicotine/Tobacco Withdrawal

This study was designed to examine the effects of gender on TN-induced withdrawal suppression. Of the 260 total F tests performed in this study (with an alpha level of 0.05; see Tables 3, 4 and 5), only 12 involving a gender factor were significant (three for physiological effects, six for withdrawal symptoms, and three for direct effects). By chance, 13 significant F tests might be expected. Thus, these results provide little support for the notion that gender differences in TN-induced withdrawal suppression underlie differential treatment outcomes that have been reported in some clinical trials.

In the current study, some observed differences between men and women were likely not due to TN. For example, gender differences for Irritability/frustration/anger involved women's higher baseline (i.e., pre-dosing) scores in the 42 mg TN condition.

This result, recorded prior to TN administration, could not be a TN-induced effect, and may reflect the observation that women are more likely than men to report subjective states of withdrawal (Franklin, 2005). Importantly, this high baseline in the 42 mg condition may indicate greater TN-induced suppression of Irritability/frustration/anger with the 42 mg TN dose for women, as they reported a mean 70.8% decrease from baseline to end of session scores, as opposed to a 29.91% decrease for men. Also, a significant interaction of time and gender was observed for the Hunger VAS; because no significant main effects or interactions involving the dose factor were observed for this measure, these results cannot be explained by a differential response to TN.

Other observed differences between men and women may reflect a differential effect of TN. For example, women's heart rate was significantly higher than men's at all active TN doses (see Figure 5). These results may be a function of the higher nicotine dose/kilogram that women received. Also, a gender difference in the pattern of response was observed on the VAS measures of Desire for Sweets (see Figure 8). Mean ratings in the placebo condition were greater for women, and, relative to placebo were significantly lower in active patch conditions for women only. These results may suggest that TN is effective at suppressing Desire for sweets for women, a suggestion that is contrary to the study hypothesis and thus cannot explain TN's apparent lower efficacy for women.

Gender differences in TN-induced withdrawal suppression were also observed for QSU Factor 1 "Intention to smoke". As shown in Figure 9, significantly lower QSU Factor 1 scores were observed for women relative to men in the highest TN dose condition. Thus, on this measure, greater withdrawal suppression was observed for

women at the 42 mg TN dose. This result is contrary to the study hypothesis that women experience less withdrawal suppression at some or all TN doses.

Overall, the pattern of results for men and women observed in this study does not provide strong support for a gender difference in TN-induced withdrawal symptom suppression. Thus, this study, by itself, cannot explain why NRT, the most widely used treatment strategy for smoking cessation, appears to be less effective for women. However this study did not address TN's ability to blunt the effects of a concurrently administered cigarette or the influence of smoking-related stimuli. Gender differences related to these factors may help understand a differential treatment outcome.

Also, gender differences in the effectiveness of TN could be related to individual genotype (Johnstone et al., 2004). Women with the variant T allele of the dopamine D2 receptor *DRD2* 32806 showed a higher quit rate in a 12-week cessation study than women with the more common CC genotype, though the opposite effect was true for men (Yudkin et al., 2004). Consequently, NRT may work through different processes and may be subject to different genetic influences in men and women. Therefore, genotype may be an important factor in targeting smoking cessation interventions. In addition, social support (Carlson, Goodey, Bennett, Taenzer & Koopmans, 2002) and behavioral counseling in combination with bupropion may lead to improved cessation rates for women (Collins et al., 2004). Thus, in terms of devising more successful smoking cessation programs for women, targeted interventions that make use of genotype, behavioral and/or pharmacotherapies may be particularly valuable.

Transdermal Nicotine-Induced Side Effects

While TN ameliorated signs (heart rate) and symptoms (QSU Factor 1, Hunger, Desire for Sweets) associated with tobacco abstinence, it also increased reports of the direct effects of nicotine. In fact, with 42 mg TN, reports of these negative side effects began as soon as 60 minutes after patch administration for five of the ten Direct Effect Scale items: Nauseous, Dizzy, Lightheaded, Sweaty and Weak. These results are consistent with previous studies of high dose TN (e.g. Kalman et al., 2004; Dale et al., 1995). In addition, when participants received the highest active TN dose (42 mg) there were significant increases ratings of Nauseous, Dizzy, and Weak as compared to placebo (see Figure 16).

The Effects of Gender on Trandermal Nicotine-Induced Side Effects

Gender differences in response to the direct effects of nicotine were evident with 42 mg TN for three of the ten Direct Effect Scale items including: Dizzy, Sweaty and Lightheaded. The 42 mg dose, twice the highest available over-the-counter dose of 21 mg TN, was chosen to ensure that dose effect functions covered the highest doses that could be delivered safely in a short-term study (Benowitz, Zevin & Jacob, 1998; Fredrickson et al., 1995). For women, 42 mg TN produced higher ratings of Dizzy, Sweaty and Lightheaded as compared to men, indicating symptoms of nicotine intoxication. For example, women's reports for Dizzy (mean = 20.49, SD = 29.87) were greater than men's reports (mean = 8.48, SD = 15.73) for 42 mg TN beginning one hour after patch administration.

These results support the suggestion that in the short-term, as compared to men, women may be more sensitive to the direct effects of nicotine (Grunberg, Winders &

Wewers, 1991). However, the finding from this study that women are more sensitive than men to the acute direct effects of nicotine is in contrast to preclinical research that suggests that female mice may be less sensitive to the acute effects of nicotine than male mice (Damaj, 2001). The clinical relevance of some preclinical outcome measures is uncertain, and the acute effects of nicotine in non-human animals may be less relevant to smokers, who are exposed to nicotine chronically.

In summary, results from this laboratory study revealed women reported a more intense side effect profile after receiving 42 mg TN. This observation has important therapeutic implications for clinicians who recommend high dose NRT (Kalman et al., 2004; Hughes et al., 1999; Frederickson et al., 1995; Dale et al., 1995). To the extent that these laboratory results generalize to the natural environment, women may find compliance with a daily dose of 42 mg TN challenging, due to the side effects that it may produce. Taken in combination with the lack of a dose effect observed on some withdrawal measures, the benefits of high dose NRT for women may not outweigh the costs.

Study Limitations

At least three potential limitations may have influenced the study results: 1) some significant effects observed in this study may not reflect real differences across conditions/genders (i.e., Type I error); 2) some real differences between conditions and/or genders may not have been detected (i.e., Type II error); and 3) the laboratory setting may limit the generalizability of the results. These limitations are discussed below.

Type I Error. The probability of a Type I error, alpha (α, may be an important study limitation. The probability of a Type I error, or a false rejection of a true null

hypothesis, can increase in studies, like this one, where many comparisons are conducted (i.e. experiment-wise error rate, Pagano, 1990). Two hundred sixty within-subjects (dose) and between-subjects (gender) F tests were generated for this study, as can be seen in Tables 3, 4 and 5, and each F test had an alpha level of 0.05. Experiment-wise error rate was controlled in this study by use of Tukey's HSD, a conservative post hoc test that maintains the Type I error rate at a chosen alpha level across all possible comparisons within a single outcome measure. For dose comparisons, the pattern of observed differences was consistent across many measures suggesting that the many effects that attained conventional levels of statistical significance may reflect the real state of the world: active doses of transdermal nicotine likely increase plasma nicotine levels and heart rate in a dose dependent manner, and also, relative to placebo, suppress withdrawal. In contrast to dose comparisons, results of gender comparisons were less consistent. Out of 160 gender comparisons, only 12 significant results were observed (with an α of 0.05, approximately 8 might be expected by chance). In addition, the pattern of the gender differences observed was not clear cut (i.e., some were related to baseline responding, others to TN-induced effects, etc.). Thus, some or all of the gender effects observed in this study may reflect Type I error.

Type II Error. The probability of a Type II error may have also been a study limitation. A Type II error occurs when the null hypothesis has not been rejected when it should have been, and thus real differences are not detected. The probability of committing a Type II error, beta (β), varies inversely with the study's alpha level (α; Type I error), effect size (ES), and sample size. In this study, effect size may have limited study sensitivity (or power, 1-α), thus increasing the likelihood of a Type II error

for the interactions and main effects involving the gender factor (leading to a failure to reject the null hypothesis of gender equivalence). For this study, the ES (partial eta squared, or η_p^2) for dose by gender interactions for virtually all subjective withdrawal measures was, at best, small (i.e., $\eta_p^2 < .010$; Cohen, 1977; see Table 6). As the study was designed to detect a medium ES, and the ES was, at best, small, a study with a much larger N (e.g. N = 400, Cohen, 1988) would be needed to detect a gender effect. The clinical significance of such a small gender effect must be balanced across the costs of an adequately powered study.

Laboratory Setting. The clinical laboratory offers many advantages over more naturalistic studies (such as clinical trials), including precise control over environmental variables (e.g., smoking-related stimuli like the sight, smell, and taste of a cigarette) and/or other factors (e.g., concurrent drug administration, activity level, social situation, food intake). However, this high level of control can also be a limitation, as factors that precipitate or contribute to tobacco withdrawal symptoms in the natural environment may be eliminated intentionally from the laboratory setting. For example, environmental cues such as the sight and smell of a lit cigarette can increase a smoker's Urges to smoke (Niaura, Abrams, Pedraza, Monti, Rohsenow, 1992; Niaura et al., 1998; Abrams, Monti, Carey, Pinto & Jacobus, 1988), but the laboratory setting of this study avoided the presence of these cues rigorously. To the extent that cues and other factors were

Table 6.
Statistical Analysis Results for Subjective Effects and Physiological Measures Collected During Four Transdermal Patch Doses – AUC η_p^2 and Power Estimates.

	Dose		Gender		Dose * Gender	
	η_p^2	Power estimate	η_p^2	Power estimate	η_p^2	Power estimate
Physiological measures						
Heart rate	0.494	1.000	0.027	0.457	0.027	0.457
Plasma nicotine	0.892	1.000	0.004	0.104	0.010	0.233
Subjective effects						
Hughes Hatsukami Questionnaire						
Urges to smoke	0.095	1.000	0.006	0.207	0.001	0.071
Irritability/Frustration/Anger	0.032	0.784	0.004	0.143	0.003	0.097
Anxious	0.022	0.655	0.005	0.177	0.000	0.050
Difficulty concentrating	0.014	0.447	0.009	0.185	0.016	0.499
Restlessness	0.010	0.327	0.007	0.155	0.090	0.291
Hunger	0.014	0.476	0.017	0.551	0.001	0.060
Impatient	0.035	0.861	0.005	0.162	0.000	0.055
Craving a cigarette/Nicotine	0.107	1.000	0.013	0.430	0.001	0.058
Drowsiness	0.014	0.441	0.014	0.269	0.015	0.493
Depression/Feeling blue	0.017	0.508	0.000	0.051	0.003	0.112
Desire for sweets	0.019	0.589	0.038	0.908	0.005	0.130

(table continues)

(Table 6 continued)

	Dose		Gender		Dose * Gender	
	η_p^2	Power estimate	η_p^2	Power estimate	η_p^2	Power estimate
Tiffany Drobes QSU						
Factor 1	0.143	1.000	0.002	0.081	0.025	0.722
Factor 2	0.105	1.000	0.011	0.353	0.007	0.150
Direct Effects of Nicotine						
Nauseous	0.166	1.000	0.026	0.443	0.007	0.215
Dizzy	0.132	1.000	0.011	0.223	0.007	0.209
Lightheaded	0.142	1.000	0.026	0.681	0.012	0.221
Nervous	0.078	0.998	0.006	0.140	0.013	0.425
Sweaty	0.113	1.000	0.020	0.546	0.003	0.098
Headache	0.027	0.727	0.008	0.165	0.003	0.119
Excessive Salivation	0.052	0.944	0.005	0.119	0.009	0.259
Heart Pounding	0.069	0.989	0.006	0.136	0.000	0.057
Confused	0.029	0.774	0.012	0.240	0.011	0.331
Weak	0.146	1.000	0.027	0.460	0.016	0.474
DSST	0.015	0.474	0.027	0.457	0.011	0.340

controlled in this study, and to the extent that these factors underlie the gender differences that have often been observed in outpatient (i.e., naturalistic environment) smoking cessation trials, the study's generalizability may be limited. However, laboratory studies of potential drug dependence pharmacotherapies often predict clinical outcome (Shiffman et al., 2002; Bollinger et al., 2000; Molander, Lunnell & Fagerström, 2000; Wallstrom, Nilsson & Hirsch, 2000; Blondal, Franzon & Westin, 1997; Blondal, 1989; Nemeth-Coslett & Henningfield, 1986; Russell, Wilson, Feyerabend & Cole, 1976) so there is evidence that the controlled laboratory environment has real world relevance. Studying the individual and combined effects of nicotine and smoking-related stimuli (as well as other non-pharmacological factors) in the laboratory may be one way to maximize the value of this setting.

Summary

One hundred twenty eight overnight-abstinent smokers (75 men) completed four, double-blind, randomized, 6.5-hour laboratory sessions in which further cigarette abstinence was required. Sessions differed by TN dose (0, 7, 21, or 42 mg). This study revealed clear nicotine dose-related effects for plasma nicotine and heart rate, symptoms of nicotine intoxication (e.g. Nausea, Lightheaded) and suppression of Urges to smoke and Craving. Many DSM IV nicotine/tobacco withdrawal symptoms were also suppressed by active TN, but this suppression was not dose-related (e.g. Irritability/frustration/anger, Anxious, Difficulty concentrating). Therapeutically, knowing the doses that best suppress specific nicotine/tobacco withdrawal symptoms may prove useful in developing relapse-prevention programs that incorporate information gained from a smoker's previous (unsuccessful) quit attempt.

One goal of this study was to compare men's and women's responses to TN-induced suppression of the nicotine/tobacco withdrawal syndrome. Overall, only a few gender effects were observed. Gender differences were evident in TN-induced cardiovascular response and some direct effects of nicotine (e.g., Dizzy, Weak, Lightheaded); gender influenced TN's effects on only three withdrawal-related measures (QSU Factor 1, Desire for Sweets, Hunger). To the extent that TN-induced withdrawal suppression is related to successful smoking cessation with this pharmacotherapy, results from this large-sample laboratory study that used specific, validated outcome measures, are inconsistent with the notion that gender differences in TN-induced withdrawal suppression underlie differential treatment outcomes that have been reported in many clinical trials. Future research addressing this important issue may benefit from focusing on a potential interaction between gender and other effects of TN (i.e., blunting the effects of a concurrently administered cigarette) and/or on other triggers for relapse (i.e., smoking-related stimuli).

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Appendix A

Effects of nicotine patch in men and women

Introduction. You are being asked to participate in a research study that is being conducted by Dr. Thomas Eissenberg of the VCU Department of Psychology. The purpose of the study is to examine the effects of the nicotine patch on men and women who smoke.

Study Procedures. If you agree to join the study, we will ask you to let us perform an electrocardiogram to ensure that your heart is healthy, allow a study physician to complete a brief physical examination to make certain that you are in general good health, and then we will ask you to complete four approximately 6.5-hour experimental sessions. Before each session we will ask you to abstain from smoking for about 12 hours. For example, you may begin a session in the morning if you have not smoked since dinnertime the day before. Before each session we will test your breath to find out when you last smoked; the result of this test will determine if the session can begin. If the breath test indicates that a session may not begin, you may wait or reschedule the session for another day.

At the beginning of each session a research nurse will insert a thin needle into your arm (catheter) that will stay there for the duration of the session. This needle will be used to draw blood (about a tablespoonful) periodically. We use this method because participants tell us that it is more comfortable than repeated "sticks" with a needle whenever we need a blood sample. Although we take several blood samples in each session, the total that we take each day is about ¼ of what is taken when you donate blood. The amount of blood that we take in the entire study (1 pint + 1 ounce) is only one ounce more than the pint that you would donate all at once during a blood drive.

In addition, near the beginning of each session, three patches will be placed on your upper back and covered with gauze. These patches may or may not contain nicotine and the gauze is used to make sure that neither you nor the laboratory staff know which patches have been used. Some nicotine patch doses that you will receive will be larger than those normally used to help smokers quit and these doses may make you feel sick (nauseous) or uncomfortable (dizzy or lightheaded). Please inform us at any time if you begin to feel any unpleasant effect. At regular intervals during each session you will also participate in other data collection procedures. These procedures will include describing how you feel using several computerized questionnaires and tasks. Also, throughout each session we will monitor your heart rate, blood pressure, and skin temperature.

Benefits. You will derive no personal benefit from this study. However, your participation will help us in the future as we try to better understand how to make nicotine patches more effective for smokers who want to quit smoking.

Alternative Therapy. This is not a therapeutic study. You have the alternative not to participate.

Risks, Inconveniences, Discomforts. There are minimal risks associated with this study. Eight or more hours of cigarette abstinence may cause mild discomfort that is not medically dangerous. The blood drawing procedure involves minimal risks of infection that are reduced by the research nurse who will use sterile, disposable equipment. The nicotine patches may cause a variety of side effects that include a mild rash at the site where the patch was applied, increased heart rate and blood pressure, sweating, lightheadedness, dizziness, nausea and nervousness. These effects may be more likely at higher than normal patch doses. If you find any effects or data collection procedures unacceptable, you may stop your participation at any time.

Costs of Participation. Participating in this study will take about 25 hours of your time. You will be paid $100 in cash after your completion of sessions 1, 2, and 3 and $200 after your completion of session four. Thus, you will have received a total of $500 when you complete the study.

Pregnancy. Every effort will be made to have women enter this study on an equal basis with men. Nicotine may harm a fetus, and pregnant women should not participate in this study. Women who choose to participate will need to provide a urine sample before each session. We will use this sample for a pregnancy test that must be negative before the session can begin.

Confidentiality of Records. The researchers involved in this study will treat your identity with professional standards of confidentiality. The information obtained in this study may be published, but your identity will not be revealed.

Withdrawal. Participation is voluntary. The investigators will answer any questions that you may have. You are free to withdraw your consent and discontinue participation at any time. If you choose not to participate or to discontinue your participation, this choice will in no way affect any medical care you receive now or in the future at this institution. If you choose to withdraw from the study without completing all four scheduled sessions, call Dr. Eissenberg and you will be paid $10/hour for the sessions that you completed. If during the course of the study you experience adverse effects, your participation may be stopped by Dr. Eissenberg without your consent. If Dr. Eissenberg stops your participation before you have completed all four scheduled sessions, you will be paid $10/hour for the sessions that you completed.

Current Telephone Numbers. You can call Dr. Eissenberg at 225-3562 for information about the research or about research-related injury.

Subjects' Rights Information. If you have any questions concerning your rights as a research subject, you may contact the VCU Office of Research Subjects Protection at 828-0868 for information or assistance. You will receive a copy of this consent form.

If you agree to join this study, please sign your name below.

_____	_____
Signature of Participant	Date
_____	_____
Signature of Person Performing Consent	Date
_____	_____
Signature of Investigator	Date

Appendix B

Effects of Nicotine Patch In Men And Women

Personal Information and Health Status Form

Personal Information
Name _____

Address _____

Home phone _____

What time/day is best to call you? _____

Date of birth _____ (years)

Height _____ (feet and inches) Weight _____ (pounds)

General health status:
Are you under a doctor's care for a medical condition?_____ (If yes, please describe below)

Are you taking any prescription medications?_____ (If yes, please identify below)

Do you have any chronic health concerns or problems?_____ (If yes, please describe below)

Do you have any heart conditions?_____ (yes or no)

Do you have any psychiatric conditions?_____ (If yes, please describe below)

Do you have high or low blood pressure?_____ (If yes, please specify high or low)

Do you have fainting spells or seizures?_____ (If yes, please specify fainting or seizures)

Do you have glacuoma?_____ (yes or no)

Do you have any kidney problems?_____ (yes or no)

Alcohol use:
Do you use (drink) alcoholic beverages?_____ (yes or no)

How many alcoholic drinks do you have on a typical day?_____ (number of drinks)

How many days out of the last 30 have you used alcohol?_____ (number of days)

Have you ever been treated for alcohol abuse/dependence?_____ (yes or no)

Have you ever felt you ought to cut down on your drinking?_____ (yes or no)

Alcohol use (cont):

Have people annoyed you by criticizing your drinking?_____ (yes or no)

Have you ever felt bad or guilty about your drinking?_____ (yes or no)

Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)?_____ (yes or no)?

Marijuana use:
Have you ever, in your lifetime, smoking marijuana or hashish? _____ (yes or no)

Have you smoked marijuana in the past month? _____ (yes or no)

How many days of the last 30 have you smoked marijuana? _____ (number of days)

Can you estimate how much money you spend each month on marijuana? _____(dollars)

Other Drug Use:
Have you used any other illicit drugs within the past month? _____ (yes or no)

If yes, please identify which drug or drugs: _____

Cigarette use:
What brand of cigarettes do you smoke?_____

Hard pack or soft pack? _____

King size or 100s? _____

How many cigarettes/day do you smoke? _____ (number of cigarettes)

For how long have you smoked this number? _____ (months or years)

Have you ever felt a need to cut down or control your smoking, but had difficulty doing so?_____ (yes or no)

Do you ever get annoyed or angry with people who criticize your smoking or tell you that you ought to quit moking?_____ (yes or no)

Have you ever felt guilty about your smoking or about something you did while smoking?_____ (yes or no)

Do you ever smoke within half an hour of waking up (eye-opener) ?_____ (yes or no)

For women only:
Are you currently pregnant?_____ (yes or no)

Are you currently breast-feeding a child?_____ (yes or no)

Which contraceptive method(s) are you currently using (including abstinence)?_____

What was the first day of the onset of your last period?_____

By signing this form below, you indicate that you have answered the above questions truthfully.

_____ _____

Participant's Signature Today's Date

_____ _____

Investigator's Signature Today's Date

Appendix C

Smoking Behavior Questionnaire

For each of the questions below, please circle one of the listed responses.

	Circle one response
1. How soon after you wake up do you smoke your first cigarette?	Within 30 minutes After 30 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in cinema, etc.)?	No Yes
3. Which cigarette would you hate most to give up?	The first one in the morning Any other
4. How many cigarettes/day do you smoke?	15 or less 16 - 25 26 or more
5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?	No Yes
6. Do you smoke if you are so ill that you are in bed most of the day?	No Yes
7. What is the nicotine level of your usual brand of cigarette (written on each pack)	0.9 mg or less 1.0-1.2 mg 1.3 mg - more
8. Do you inhale?	Never Sometimes Always

Additional research
May we call you if there are additional studies for which you are qualified? _____

By signing this form below, you indicate that you have answered the above questions truthfully.

_____ _____
Participant's Signature Today's Date

_____ _____
Investigator's Signature Today's Date

Appendix D

Demographic Information

Effects of Nicotine Patch in Men and Women
Protocol # 01974

Participant's Name Today's Date

Age

Years: _____ Exact date of birth _____

Ethnicity

o Hispanic or Latino o Not Hispanic or Latino

Race

o American Indian/Alaskan Native o White o Black or African American

o Asian/Native Hawaiian or other Pacific Islander o Other/Unknown (_____)

Gender

o Male o Female

Marital status

o Single o Married o Separated o Divorced o Widowed

Education

Years: _____ (For example, High school = 12, College degree = 16, etc.)

Primary employment

o unemployed o PT (0-30 hrs/wk) o FT (>30 hrs/wk) o Student

History of quit attempts

o Never tried to quit o Tried to quit _____ times o Trying to quit now

Previous experience with nicotine medications

o No experience o At least one experience o Nicotine gum

o Nicotine patch o Nicotine spray o Nicotine inhaler

By signing this form below, you indicate that you have answered the above questions truthfully.

Participant's Signature Today's Date

Investigator's Signature Today's Date

Appendix E

Nicotine/tobacco withdrawal VASs (Hughes & Hatsukami, 1986)

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you have felt over the last 24 hours by drawing a vertical mark anywhere along the horizontal line.

	Not at all	**Extremely**
1. URGES to smoke		
2. Irritability/frustration/anger		
3. Anxious		
4. Difficulty concentrating		
5. Restlessness		
6. Hunger		
7. Impatient		
8. CRAVING a cigarette/nicotine		
9. Drowsiness		
10. Depression/feeling blue		
11. Desire for sweets		

Appendix F

Questionnaire of Smoking Urges (Tiffany & Drobes, 1991)

For each item please indicate how you feel RIGHT NOW by placing an X in the appropriate level.

1. Smoking would make me feel very good right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

2. I would be less irritable now if I could smoke.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

3. Nothing would be better than smoking a cigarette right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

4. I am not missing smoking right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

5. I will smoke as soon as I get the chance.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

6. I don't want to smoke right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

7. Smoking would make me less depressed.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

8. Smoking would not help me calm down right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

9. If I were offered a cigarette, I would smoke it immediately.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

10. Starting now, I could go without smoking for a long time.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

11. Smoking a cigarette would not be pleasant.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

12. If I were smoking this minute, I would feel less bored.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

13. All I want right now is a cigarette.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

14. Smoking right now would make me feel less tired.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

15. Smoking right now would make me feel happier now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

16. Even if it were possible, I probably wouldn't smoke right now.

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

17. I have no desire for a cigarette right

Strongly disagree ○ ○ ○ ○ ○ ○ ○ Strongly agree

now.

18. My desire to smoke seems overwhelming.

Strongly disagree — Strongly agree

19. Smoking right now would make things seem just perfect.

Strongly disagree — Strongly agree

20. I crave a cigarette right now.

Strongly disagree — Strongly agree

21. I would not enjoy a cigarette right now.

Strongly disagree — Strongly agree

22. A cigarette would not taste good right now.

Strongly disagree — Strongly agree

23. I have an urge for a cigarette.

Strongly disagree — Strongly agree

24. I could control things better right now if I could smoke.

Strongly disagree — Strongly agree

25. I am going to smoke as soon as possible.

Strongly disagree — Strongly agree

26. I would not feel better physically if I were smoking.

Strongly disagree — Strongly agree

27. A cigarette would not be very satisfying right now.

Strongly disagree — Strongly agree

28. If I had a lit cigarette in my hand I probably would not smoke it.

Strongly disagree — Strongly agree

29. If I were smoking right now I could think more clearly.

Strongly disagree — Strongly agree

30. I would do almost anything for a cigarette now.

Strongly disagree — Strongly agree

31. I need to smoke now.

Strongly disagree — Strongly agree

32. Right now, I am not making plans to smoke.

Strongly disagree — Strongly agree

Appendix G

Direct Effects of Nicotine

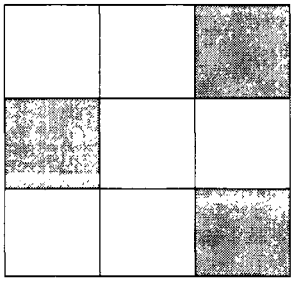
These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

	Not at all	**Extremely**
1. Nauseous		
2. Dizzy		
3. Lightheaded		
4. Nervous		
5. Sweaty		
6. Headache		
7. Excessive salivation		
8. Heart Pounding		
9. Confused		
10. Weak		

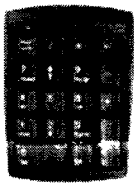
Appendix H

Digit Symbol Substitution Test (McCleod et al., 1982)

4



DSST as it appears on computer monitor



Numeric keypad on laptop computer

7	8	9
4	5	6
1	2	3

Close-up of numbers on keypad

In this case, a participant would press the 9, 4 and 3 keys

Vita

Sarah Ellen Evans was born in Baltimore, Maryland on October 21st, 1970. She is a graduate of James Madison High School in Vienna, VA, and has a B.A. in Psychology from The College of William and Mary in Williamsburg, Virginia, which she received in 1992. She began the Biopsychology Program at Virginia Commonwealth University in August 2001 and received her Masters of Science degree in August, 2003. She is currently pursuing her Doctorate of Philosophy.