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27	Vector Tobacco, Inc. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of Quest alone and in combination with nicotine replacement therapy as a smoking cessation aid, protocol number Vector-201, IND Number 69,185. Clinical Study Report dated October 13, 2006.....	8	113
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GLOSSARY OF ABBREVIATIONS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
APHIS	Animal and Plant Health Inspection Service
BOLD	blood oxygen level dependence
bpm	beats per minute
CI	confidence interval
CO	carbon monoxide
CRF	case report form(s)
CRO	Contract Research Organization
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EEG	Electroencephalogram
FDA	(U.S.) Food and Drug Administration
fMRI	functional magnetic resonance imaging
FTND	Fagerström Test of Nicotine Dependence
g	gram(s)
GCP	Good Clinical Practice (Guidelines)
GWA	genome wide association
HDPE	high-density polyethylene
HIPPA	Health Insurance Portability Accountability Act of 1996
IB	investigator brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	institutional review board
ITT	intent-to-treat (population)
IV	intravenous
MAOI	Monoamine oxidase inhibitor
mg	milligram(s)
mL	milliliter(s)
MOR	mu opioid receptor
MRI	magnetic resonance imaging
nAChR	nicotinic acetylcholine receptors
NCSU	North Carolina State University

NDA	new drug application
ng	nanogram
NIDA	National Institute on Drug Abuse
NRT	nicotine replacement therapy
PAS	platelet activation state
PE	physical examination
PET	positron emission tomography
PP	per protocol (population)
ppm	parts per million
PREP	potential reduced exposure products
QD	once daily
QPT	technology to reduce nicotine biosynthesis in tobacco
QSU	Questionnaire of Smoking Urges
RNC	reduced nicotine cigarette
RTI	Research Triangle Institute International
SAE	serious adverse event
SEM	standard error of the mean
SNP	single nucleotide polymorphism
TID	three times daily
UB	usual brand
USDA	United States Department of Agriculture
VLN	very low nicotine
μg	microgram

1. INTRODUCTION

1.1. Medical Need

It has been well established that cigarette smoking is toxic and poses health risks to subjects, namely cardiovascular disease, multiple cancers, pulmonary disease, adverse reproductive outcomes, and exacerbation of other chronic health conditions.[1] Cigarette smoking is the leading cause of preventable morbidity and mortality in the United States, causing approximately 440,000 premature deaths annually.[2] In 2009, 20.6% of adults in the United States were current cigarette smokers.[2] It is the goal of the US Department of Health and Human Services, as outlined in the program *Healthy People 2010*[3], to reduce smoking to 12% among adults aged 18 years and older by the year 2020. This goal was previously set, but not attained, for the year 2010.

Cigarette smoking is a complex behavior that is sustained by the pharmacological properties of nicotine and reinforcing behavioral and sensory cues.[4,5] Smokers report reduced satisfaction when sensory signals are blocked or altered using methods such as local airway anesthesia[6] and addition or elimination of menthol.[7] Furthermore, nicotine delivered intravenously in the absence of the sensory and behavioral aspects of cigarette smoking is rated a less satisfying experience than delivery via inhalation from a cigarette.

Currently available pharmacological approaches for smoking cessation in combination with counseling and education (maximal intervention) are effective in a minority of smokers, with the probability of initial success with all types of approved pharmacotherapy increased 1.5 to 2.5 fold compared to placebo.[8,9] Relapse is common following use of currently approved treatments, and 75 to 80 percent of smokers who receive treatment are unable to achieve long-term abstinence at 6 or 12 months.[10,11] Therefore, there is an important public health need to provide additional smoking cessation treatments, reduce relapse, and to provide alternative treatments for smokers who may not succeed with, or do not have access to, treatment that includes approved pharmacotherapies.

1.2. Rationale for the Use of Very Low Nicotine Cigarettes

Cigarettes containing very low levels of nicotine consistently reduce craving for cigarettes and withdrawal in smokers.[12,13,14,15,16,17,18,19,20,21] In contrast to conventional low-yield ("light" or "ultra light") cigarettes that have reduced tar and nicotine yields as measured by smoking machines mainly due to smoke dilution, smoke from cigarettes containing very low levels of nicotine contains greatly reduced ratios of nicotine to other smoke components.[22] The data from studies of the behavioral and pharmacodynamic properties of cigarettes

containing very low levels of nicotine indicate that a product that delivers the sensory and behavioral cues associated with cigarette use but does not deliver a satisfying amount of nicotine breaks the association of those cues with the contingent delivery of nicotine reinforcement and promotes extinction of smoke cues.

Much of the early research cited in the paragraph above was conducted with denicotinized cigarettes. Denicotinized cigarettes differ from cigarettes such as X-22 cigarettes in that denicotinized cigarettes are manufactured with conventional tobacco from which nicotine has been removed by chemical processes. Several types of denicotinized cigarettes have been produced in the past several decades. In 1989, Philip Morris Inc. (Richmond, VA) tested the market acceptability of a de-nicotinized cigarette (Next®). Nicotine was removed from the tobacco in Next® using high-pressure carbon dioxide. Although the cigarette was not well accepted in the retail market, it proved useful in clinical studies to estimate the effects of smoking with minimal nicotine delivery.

In response to the need among tobacco researchers for a cigarette containing very low levels of nicotine, the National Institute on Drug Abuse (NIDA) contracted with a private firm (Ultratech/Lifetech Corporation, Lafayette Hill, PA) to develop and manufacture de-nicotinized cigarettes. According to Pickworth *et al*[15], the de-nicotinized cigarettes had the nicotine removed with a mild alkaline (ammonium solution) wash and had similar characteristics to commercial cigarettes, but contained and delivered very low nicotine. Four types of cigarettes were developed and tested: reduced- and full-tar standard cigarettes and identically appearing reduced- and full-tar denicotinized cigarettes that delivered carbon monoxide (CO) and tar, but very small amounts of nicotine.

Processes involved in removing nicotine from tobacco have been found not to be specific for nicotine and other leaf components are also removed, resulting in changes in taste and other factors.[23] Levels of monoamine oxidase inhibitors (MAOIs) such as β-carboline alkaloids, naphthoquinone, and acetaldehyde are also affected by extracting nicotine from tobacco. Besides nicotine, the following compounds or compound classes have been known to be simultaneously extracted from denicotinized tobacco:

- Isoprenoids, a class of compounds that are acyclic terpenes such as solanesol and neophytadiene.

- Oils and waxes, which cover a number of compound classes and a larger number of specific compounds analogous to essential oils in other plants such as citrus fruit, these compounds in tobacco are largely responsible for the characteristic “tobacco” flavor and aroma. Removal of these compounds, or even a change in the

concentration ratios, can destroy the characteristic flavor or aroma of a plant, including tobacco.

- Carboxylic Acids - Tobacco contains many, however, palmitic acid, oleic acid, and a number of C18-fatty acids were specifically identified.
- Hydrocarbons in the range C27H50 to C33H68.
- Other compounds, including cembranoids and stigmasterol.

In contrast to denicotinized tobacco, the tobacco used in X-22 cigarettes is produced from a very low nicotine (VLN) tobacco variety that when grown to maturity using conventional practices contains approximately 95 percent less nicotine than conventional tobacco plants. X-22 cigarettes may therefore offer benefits relative to cigarettes manufactured with conventional tobacco that has had nicotine chemically removed.

Quest® cigarettes, manufactured using the same VLN tobacco as X-22 cigarettes, were sold by Vector Tobacco Inc. from December 2002 to December 2007, and Quest® menthol cigarettes were sold by Vector Tobacco Inc. from November 2003 through December 2007. Consumers purchased these Quest® and Quest® menthol cigarettes for at least another year. Both Quest® and Quest® menthol cigarettes were produced in brand styles containing 3 levels of nicotine in the tobacco filler, resulting in the following nicotine yields per cigarette: Quest 1® (0.60 milligrams [mg]), Quest 2® (0.3 mg) and Quest 3® (≤0.05 mg).

Most recently, NIDA in 2009 included an option to develop and produce research cigarettes with different levels of nicotine (from very low to high) in its request for proposals for a 5-year contract for Preparation and Distribution of Research and Drug Products. 22nd Century agreed, as a subcontractor to Research Triangle Institute International (RTI), in RTI's contract with NIDA for the Research Cigarette Option, to supply 9 million cigarettes having 8 different nicotine contents to NIDA. These research cigarettes, Spectrum™, are expected to be delivered to RTI in July of 2011.

1.3. X-22 Smoking Cessation Product

The X-22 Smoking Cessation Product is a tobacco-based (botanical) medical product consisting of VLN cigarettes. X-22 cigarettes, like conventional cigarettes, consist of filler, filter, and wrapper components. X-22 cigarettes contain menthol, which is added to the filter. The menthol is included in part to compensate for the reduced sensory impact of the X-22 cigarettes in the mouth and throat due to the very low nicotine content.

The filler in X-22 cigarettes is comprised primarily of cured tobacco leaf and does not contain other non-tobacco material other than relatively small quantities added as flavorings. The tobacco in the filler of X-22 cigarettes is produced from a proprietary VLN tobacco variety. All processing of tobacco is carried out by processors of conventional tobacco. All manufacturing of cigarette components and cigarettes is carried out by manufacturers of conventional cigarette components and cigarettes.

Like conventional cigarettes, X-22 cigarettes are toxic and pose health risks to subjects, namely cancer, cardiovascular disease, respiratory disease and reproductive effects. X-22 cigarettes are similar to conventional cigarettes except that the filler contains tobacco from a tobacco plant variety that has very low levels of nicotine due to genetic modification of the nicotine biosynthesis pathway in the plant. X-22 cigarettes have a tobacco content and tar yield comparable to typical commercial cigarettes, but have a nicotine content and yield ≤0.05 mg. This represents a reduction in nicotine of more than 95% compared to typical commercial cigarettes, including compared to low-yield cigarettes such as "lights" and "ultra lights."

Except for the use of the VLN tobacco variety, the growing, curing and processing of tobacco for X-22 cigarettes are the same as for conventional cigarettes, and X-22 cigarettes have the same physical and chemical properties as conventional cigarettes, except for the reduction in nicotine and related compounds. The composition of smoke from X-22 cigarettes is chemically similar to smoke from conventional cigarettes.[22]

In addition to being sold commercially, Quest 3® cigarettes have been used in clinical studies, including trials evaluating their usefulness as an aid to smoking cessation. These trials are described below in Section 2.1.

1.4. History of the Vector-21-41 Very Low Nicotine Tobacco Variety

The VLN tobacco used in X-22 cigarettes is the genetically engineered tobacco variety Vector-21-41.[24] Vector-21-41 was deregulated by the by the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA) on December 3, 2002.[25] Vector-21-41 is the same very low nicotine tobacco variety used in Quest® cigarettes from December 2002 to December 2007 and Quest® menthol cigarettes from November 2003 through December 2007, all of which were manufactured by Vector Tobacco. Quest® and Quest® menthol remained in the tobacco trade pipeline through 2009, including sales by retailers. Both Quest® and Quest Menthol® were available in 3 varieties: Quest 1®, Quest 2® and Quest 3®. Quest 3® only contained Vector-21-41, Quest 2® contained approximately 75% Vector-21-41 and 25% conventional tobacco, and Quest 1® contained

approximately 25% Vector-21-41 and 75% conventional tobacco. According to filings by Vector Group Ltd. (parent company of Vector Tobacco Inc.) with the Securities and Exchange Commission, sales of Quest® by Vector Tobacco Inc. from 2002 to 2007 were approximately $60 million. This equates to approximately 26 million packs (520 million cigarettes) sold or 14,246 pack-a-day smokers using Quest® for 5 years. A clinical trial with Quest® cigarettes was conducted under Investigational New Drug Application (IND) 69,185.

The tobacco variety Vector-21-41 and related technology to reduce nicotine biosynthesis in tobacco ("QPT Technology") was developed at North Carolina State University (NCSU) in a 5-year research program funded by 22nd Century. 22nd Century was in turn granted an exclusive worldwide license to the QPT Technology and in 1999, 22nd Century exclusively sublicensed its rights to the QPT Technology to Liggett Group, Inc., the fifth largest cigarette company in the United States, and in 2001 to Liggett Group's affiliate Vector Tobacco Inc. Liggett Group, Inc. and Vector Tobacco are both wholly-owned subsidiaries of Vector Group Ltd.

In November 2006, Vector Group Ltd. publically announced that Vector Tobacco was no longer pursuing the development of Quest® as a smoking cessation aid (IND 69,185), which led to an arbitration proceeding between Vector Tobacco and 22nd Century and a binding arbitration award the from the American Arbitration Association to 22nd Century in 2008 that (i) confirmed the termination of the prior exclusive license between 22nd Century and Vector Tobacco for the proprietary QPT Technology; (ii) reverted all rights of the QPT Technology back to 22nd Century; (iii) provided 22nd Century with copies of Vector's United States Food and Drug Administration (FDA) submissions relating to the QPT Technology in Vector's IND 69,185, including the right to use the data and information; (iv) awarded 22nd Century a right of reference to Vector's IND 69,185; and (v) awarded monetary damages to 22nd Century. Vector Tobacco subsequently took Quest® off of the market. The arbitration award was fully fulfilled by Vector Tobacco in 2009.

2. CLINICAL DATA SUMMARY

The X-22 cigarette has not been previously tested in humans. However, various research studies have been conducted on Quest 3® and Quest 3® menthol, the VLN cigarettes sold by Vector Tobacco Inc. from 2002 to 2007, described above (Sections 1.3 and 1.4). Quest 3® and Quest 3® menthol cigarettes only contained Vector-21-41, which is the same tobacco variety used in the manufacture of X-22 cigarettes.

Additionally, a phase II trial currently in progress entitled "Innovative Interventions for Smoking Cessation" (NCT01050569, principal investigator Dorothy Hatsukami, PhD at the University of Minnesota) is using VLN cigarettes designed by 22nd Century containing Vector 21-41.

Although other components of X-22 cigarettes, including cigarette paper and filter, are not identical to those used in the manufacture of Quest® cigarettes or the VLN cigarettes used in the NCT01050569 phase II clinical trial, the cigarette papers and filters used in all of these studies and X-22 cigarettes are produced and supplied by manufacturers that are major suppliers of cigarette components, and 22nd Century maintains that data from these studies are fully applicable to X-22 cigarettes. These studies are described below in Section 2.1.

2.1. Previous Clinical Studies Using Very Low Nicotine Cigarettes

2.1.1. Studies of Smoking Cessation

The following studies were primarily conducted to evaluate the use of VLN cigarettes for smoking cessation.

2.1.1.1. A Study of Quest 1®, Quest 2®, and Quest 3® in a Step-down Treatment Schedule With and Without Nicotine Replacement Compared to a Conventional Cigarette and the Influence of Genetics on Treatment Success

A randomized, double-blind, active controlled, parallel group, multi-center phase II clinical trial was reported by Becker *et al* to evaluate the efficacy of reduced-nicotine cigarettes as a novel smoking cessation treatment under IND 69,185.[26,27] This study was previously submitted to FDA by Vector Tobacco, Inc. in an End-of-Phase II Meeting Package for IND 69,185 on June 12, 2006.

Treatment consisted of 6 weeks of smoking a series of cigarettes with progressively lower nicotine content (Quest 1®, Quest 2®, and Quest 3®, with smoking yields of 0.6, 0.3 and

≤0.05 mg nicotine/cigarette), either in combination with nicotine patch therapy (NRT) or placebo patches. Three hundred forty-six smokers of non-menthol cigarettes who were motivated to quit were randomized to one of 3 treatments:

- Group 1: Quest® plus NRT patch,
- Group 2: Quest® plus placebo patch, or
- Group 3: active control (conventional cigarette) plus NRT patch.

The design of the study is presented in Table 2-1, below

Table 2-1 Design of Study Published by Becker *et al*, 2008

	Weeks																					
							Primary endpoint 4-week Abstinence															
Group	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	----	32
1	Usual Brand all groups	Quest 1		Quest 2		Quest 3													3-month post-quit follow-up		6 month post-quit follow-up
						21 mg patch		21 mg patch				14 mg patch		7 mg patch		placebo patch					
2		Quest 1		Quest 2		Quest 3															
						placebo patch		placebo patch				placebo patch		placebo patch		placebo patch					
3		Active Control		Active Control		Active Control															
						placebo patch		21 mg patch				21 mg patch		14 mg patch		7 mg patch					

The primary endpoint was 4 weeks of continuous abstinence (Weeks 7 to 10), with follow-up at 3 and 6 months. Group 1 had a higher continuous abstinence during weeks 7-10 than Group 3, 32.8% vs. 21.9% (p = 0.04). Group 2 had an abstinence rate similar to that of Group 3, 16.4% vs. 21.9% (p = 0.89). Abstinence rates at the 3-month follow-up were 17.2%, 10.3%, and 14.9% in Groups 1, 2, and 3, respectively. At the 6-month follow-up, abstinence rates were 11.2%, 7.8%, 9.6% in Groups 1, 2, and 3, respectively. The differences in abstinence among groups were not statistically significant at 3 months and 6 months. Mean exhaled CO levels increased moderately compared to baseline after subjects smoked Quest 1® (Group 1, +1.5 parts per million [ppm]; Group 2, +2.5 ppm) and Quest 2® (Group1, +2.9 ppm; Group 2, +2.9 ppm), and was reduced compared to baseline after smoking Quest 3® (Group 1, -5.4 ppm; Group 2, -3.0 ppm). No serious adverse events (SAEs) were attributed to the investigational product.

2.1.1.2. A Study of Quest 3® or Quest 2® Compared to Nicotine Lozenge

Another controlled cessation phase II trial conducted by Hatsukami *et al*[28] compared the effects of smoking VLN cigarettes or low nicotine cigarettes to the use of nicotine lozenges. Smokers were randomly assigned to 1 of 3 treatment groups which were each administered for 6 weeks:

- Group 1: Quest 3® cigarettes having a nicotine yield of ≤0.05 mg (n=53)
- Group 2: Quest 2® cigarettes having a nicotine yield 0.30 mg (n=52)
- Group 3: 4 mg nicotine lozenge (n=60)

Four week continuous abstinence in the Hatsukami trial was measured after the treatment period, as shown in Figure 2-1 below, rather than during the last four weeks of the treatment period. (According to the prescription Chantix® label, 4-week continuous abstinence in the Chantix® phase III clinical trials was measured during the last 4 weeks of the 12-week treatment period, while patients were still taking Chantix®.)

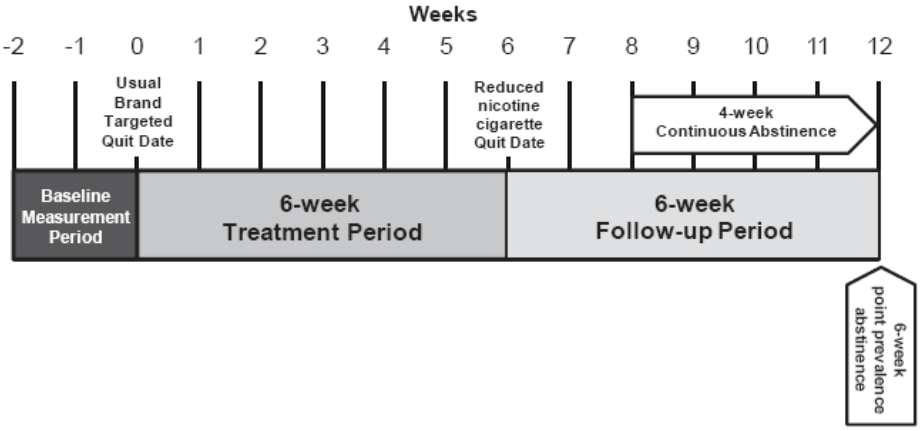


Figure 2-1 Design of Smoking Cessation Study Published by Hatsukami *et al*, 2010

Continuous abstinence 4-weeks post-treatment was 43% for the VLN cigarette group, 35% for the nicotine lozenge group, and 21% for the low nicotine cigarette group. Point abstinence rates at 6 weeks post-treatment were 47% for the VLN cigarette group, 37% for the nicotine lozenge group, and 23% for the low nicotine group. Unlike the Quest 2® cigarette, the Quest 3® VLN cigarette was not associated with compensatory smoking behaviors. Furthermore, Quest 3® VLN cigarettes and nicotine lozenges were associated with reduced carcinogen exposure, nicotine dependence and product withdrawal scores. The Quest 3® VLN cigarette was associated with greater relief of withdrawal from usual brand cigarettes than the nicotine lozenge. The Quest 3® VLN cigarette led to a significantly higher rate of cessation than the Quest 2® 0.3 mg nicotine cigarette and a similar rate as nicotine lozenge.

Patients who used the VLN Quest 3® cigarette over the 6-week treatment period significantly reduced their smoking as compared to their usual brand of cigarettes. The number of VLN cigarettes smoked per day on average decreased from 19 (the baseline number of cigarettes of

the smoker's usual brand) to 12 by the end of the 6-week treatment period, even though participants in this clinical trial were instructed to smoke *ad libitum* (as many cigarettes as desired) during treatment. As depicted in Figure 2-2 below, carbon monoxide (CO) levels, an indicator of smoke exposure, significantly decreased from 20 ppm (baseline) to 15 ppm. Cotinine, a metabolite and biomarker of nicotine, significantly decreased from 4.2 micrograms/milliliter (mL) (baseline) to 0.2 micrograms/mL. All differences in the above three measurements were statistically significant ($p<0.05$).

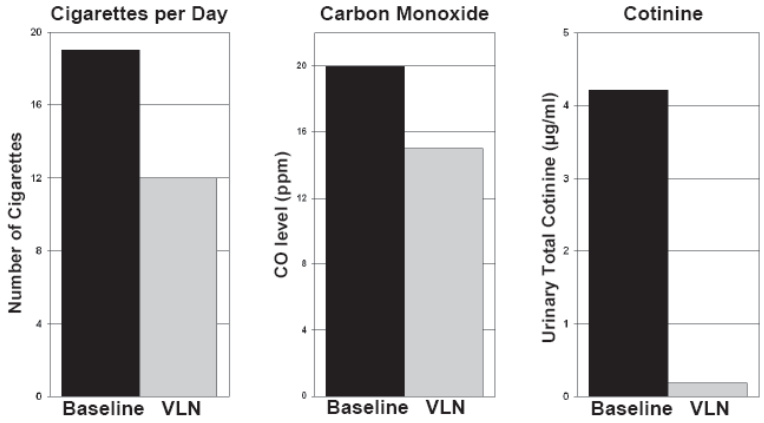


Figure created by 22nd Century from data published by Hatsukami *et al*, 2010

Figure 2-2 Number of Cigarettes Smoked, Carbon Monoxide, and Cotinine Results Published by Hatsukami *et al*, 2010

Additional biomarkers of smoke exposure were significantly reduced on average from baseline measurements (taken before the 6-week treatment period) in patients who used the Quest 3® VLN cigarette (see Figure 2-3).

BIOMARKER	DESCRIPTION	LEVEL IN PATIENTS (pmol/mg creatinine)		REDUCTION
		Baseline	VLN Cigarette	
NNAL	Metabolites of the tobacco-specific carcinogen NNK	0.92	0.2	78%
NNN	Metabolites of the tobacco-specific carcinogen NNN	0.09	0.03	67%
1-HOP	Metabolite of pyrene, a marker for uptake of carcinogenic polycyclic aromatic hydrocarbons	0.89	0.57	36%
3-HPMA	Metabolite of the smoke toxicant acrolein	3320	1453	56%
S-PMA	Metabolite of the carcinogen benzene	2.46	0.76	69%
	All differences were statistically significant (P<0.05).			

Figure created by 22nd Century from data published by Hatsukami *et al*, 2010

Figure 2-3 Biomarkers Measured after Smoking Quest 3® Cigarettes by Hatsukami *et al*, 2010

No significant differences were observed in biomarkers for cardiovascular risk between groups.

In a separate publication, Drgon *et al*[29] reported genome wide association (GWA) results from participants in the above clinical trial. GWA studies have previously demonstrated haplotypes that distinguish successful quitters from individuals who were not able to quit smoking using smoking cessation methods other than VLN cigarettes.[30,31] In this study, DNA extracted from the blood of self-reported European-American subjects was pooled into: i) three pools (n = 16 in each) containing DNA from "successful quitters"; and ii) 6 pools of "unsuccessful quitters" who were selected based on matches to features noted for the successful quitters. When the authors compared data from unsuccessful versus successful quitters, there was significant clustering of nominally positive single nucleotide polymorphisms (SNPs) in small chromosomal regions. The authors concluded that these data support the idea that ability to quit in a circumstance in which most participants used VLN cigarettes shares strong overall genetic influences with ability to quit when other pharmacological strategies were used.

2.1.1.3. A Comparison of Quest 1® Without Nicotine Replacement Therapy Versus Quest 3® With Nicotine Replacement Therapy on Cessation Success

In a randomized, controlled clinical trial conducted at Roswell Park Cancer Institute in Buffalo, New York, Rezaishiraz *et al*[32] investigated the effect of smoking a VLN cigarette in combination with a nicotine patch for 2 weeks prior to the quit date. Ninety-eight adult heavy smokers (using 20 or more cigarettes/day) were randomized to 1 of 2 treatments:

- Group 1: 2 weeks of Quest 3®, nicotine yield ≤0.05 mg, and 21-mg nicotine patch before the quit date; or
- Group 2: Quest 1®, nicotine yield 0.6 mg, during the 2 weeks before the quit date.

After the quit date, all subjects received counseling for smoking cessation and nicotine patch therapy for up to 8 weeks (4 weeks of 21-mg patches, 2 weeks of 14-mg patches, and 2 weeks of 7-mg patches). Group 1, which used VLN cigarettes and nicotine patch before quitting had lower combined craving score during the 2 weeks before ($p = 0.001$) and after ($p = 0.013$) the quit date. Self-reported point prevalence of smoking abstinence at the 3- and 6-month follow-ups was higher in Group 1 (43% vs. 34% and 28% vs. 21%, respectively), although the difference was not statistically significant at the $p < 0.05$ level.

2.1.1.4. Study of Quest 3® With or Without Nicotine Replacement Therapy or With Quest 1® and Quest 2® in a Step-down Treatment Schedule

A small study was carried out by Jed Rose *et al* at Duke University[33] comparing the following groups:

- Group 1: Quest 3® (nicotine yield ≤0.05 mg, tar yield 9 mg) with NRT;
- Group 2: Quest 3® without NRT;
- Group 3: Use of a series of cigarettes of decreasing nicotine content and the following nicotine yields: (Quest 1®, 0.6 mg, Quest 2®, 0.3 mg, and Quest 3®, ≤0.05 mg)

During the first week of the study, subjects smoked only their usual brand (UB) of cigarette. From Weeks 2 through 5, subjects gradually reduced the amount of usual brand and increased the amount of Quest 3® smoked (Groups 1 and 2), or smoked cigarettes with decreasing amounts of nicotine per cigarette (Group 3). During Weeks 6 through 11, subjects were to smoke Quest 3® exclusively. During Week 12 through Week 14, subjects were gradually weaned off Quest 3®, and subjects using NRT were weaned off of nicotine replacement. In Group 2, 33% of subjects achieved 4-week continuous abstinence. Group 3 attained a 13% abstinence rate. In Group 1 no subjects achieved abstinence.

2.1.1.5. Ongoing Clinical Trials Registered on ClinicalTrials.gov

There are currently 2 clinical trials recruiting subjects for smoking cessation studies using VLN cigarettes that are registered on ClinicalTrials.gov. The first is NCT01050569, entitled "Innovative Interventions for Smoking Cessation", principal investigator Dorothy Hatsukami, PhD at the University of Minnesota. VLN cigarettes containing Vector 21-41 and designed

by 22nd Century are being used in this phase II clinical trial currently in progress. The Hatsukami study plans to enroll approximately 200 subjects to evaluate the effect of a combination of the 21 mg nicotine patch and a VLN cigarette compared to the 21 mg nicotine patch only and VLN cigarette only on abstinence and withdrawal symptoms.

The second is NCT00960778, entitled "Gender Differences in Response to Nicotine Replacement Therapy and 'De-nicotinized Cigarettes' (BIRCWH)", principal investigator Karen Hartwell, MD at the Medical University of South Carolina. The Hartwell study plans to enroll 20 subjects to investigate the underlying neurobiology of differences between male and female smokers. Quest 3® VLN cigarettes and the nicotine patch will be utilized in the study.

2.1.2. Other Studies of Quest 3® Cigarettes

The following studies evaluated Quest 3® cigarettes but did not directly research their use as a tool for smoking cessation.

2.1.2.1. A Study of the Effects of Inhaled Nicotine, Very Low Nicotine Cigarettes, and Regular Cigarettes on Craving, Withdrawal, Self-Administration in Male and Female Smokers

This study by Barett[34] examined the acute subjective effects of nicotine in the absence of tobacco (through nicotine inhalers and placebo inhalers), tobacco with greatly reduced nicotine (Quest 3® cigarettes, nicotine yield ≤0.05 mg), and nicotine-containing tobacco (Quest 1® cigarettes, nicotine yield 0.60 mg), and their effects on subsequent smoking behavior. A total of 22 smokers (12 male, 10 female; 11 low dependent, 11 high dependent) were enrolled. During 4 randomized blinded sessions, participants self-administered inhaled nicotine, inhaled placebo, Quest 1® cigarettes, or Quest 3® VLN cigarettes and assessed their effects using Visual Analogue Scales and the Brief Questionnaire of Smoking Urges. They could then self-administer their preferred brand of cigarettes using a progressive ratio task. Quest 1® cigarettes and Quest 3® VLN cigarettes were each associated with increased satisfaction and relaxation as well as decreased craving relative to the inhalers, and Quest 1® cigarettes increased ratings of stimulation relative to each of the other products. Both Quest 1® and Quest 3® cigarettes delayed the onset of preferred tobacco self-administration relative to inhaled nicotine and inhaled placebo, but only Quest 3® cigarettes reduced the total amount self-administered. Sex differences were evident in the effects of VLN cigarettes on withdrawal-related cravings with women experiencing greater VLN cigarette-induced craving relief than men. The authors concluded that these findings suggest that VLN tobacco is effective in acutely reducing many smoking abstinence symptoms, especially in women, but a

combination of nicotine and non-nicotine tobacco ingredients may be necessary to suppress smoking behavior.

2.1.2.2. An Evaluation of Affect Relief Produced by Smoking

Perkins *et al*[35] conducted a study to determine if smoking relieved negative affect only due to smoking abstinence or also from other sources. Dependent smokers (n=104) randomly assigned to one of three smoking conditions (Quest 1®, nicotine yield 0.60 mg; VLN Quest 3®, nicotine yield ≤0.05 mg; or no smoking) completed four negative mood induction procedures (one per session): 1) overnight smoking abstinence, 2) challenging computer task, 3) public speech preparation, and 4) watching negative mood slides. A fifth session involved a neutral mood control. The 2 smoking groups took 4 puffs on their assigned cigarette and then smoked those same cigarettes *ad libitum* during continued mood induction. All subjects rated their level of negative affect and positive affect on several measures and also craving and withdrawal.

Results indicated that negative affect relief from smoking depended on the negative affect source (i.e., mood induction procedure) and the affect measure. Smoking robustly relieved negative affect due to abstinence on all 4 measures but only modestly relieved negative affect due to the other sources and typically on only some measures. Smoking's effects on positive affect and withdrawal were similar to effects on negative affect, but relief of craving depended less on negative affect source. Smoking reinforcement only partly matched the pattern of negative affect relief. Few responses differed between the Quest 1® and VLN Quest 3® smoking groups. The authors concluded that acute negative affect relief from smoking depends on the situation and the affect measure used but may not depend on nicotine intake.

2.1.2.3. A Comparison of the Acute Effects of Potential Reduced-Exposure Products Marketed to Smokers

This study by Cobb *et al*[36] compared the acute effects of various noncombustible potential reduced exposure products (PREPs) (Ariva compressed tobacco tablet, Camel Snus, Marlboro Snus, and Commit® 2 mg nicotine lozenge) and various combustible tobacco products (Subjects' OWN brand, SHAM [puffing on an unlit cigarette], and Quest 3® [nicotine yield ≤0.05 mg]) on plasma nicotine levels, expired CO, heart rate, and subjective effects in 28 participants during 7 laboratory sessions (one session for each product with 2 administration periods per product). Subjects abstained from smoking overnight before each session.

Nicotine: On average, 5 minutes after beginning to smoke a single OWN brand cigarette, participants' mean plasma nicotine level increased by approximately 18 nanograms (ng)/ml. Non-combustible PREPs included in this study delivered a nicotine dose an order of magnitude less, and any significant increases were observed later, if at all. Neither Quest 3® nor SHAM increased plasma nicotine level reliably.

CO: Expired CO increased to a greater extent in the OWN condition compared to Quest 3® after the first administration (OWN, mean 12.8 parts ppm (standard error of the mean [SEM] 0.7); Quest 3®, 11.0 ppm (SEM 0.6)) and second product administration (OWN, mean 17.5 ppm (SEM 1.0); Quest 3®, 14.4 ppm (SEM 0.8). There were no significant changes in any other condition.

Heart Rate: For OWN, mean baseline heart rate was 67.8 beats per minute (bpm) (SEM 1.9), which increased significantly to 82.3 bpm (SEM 2.3) 5 minutes after the first product administration and remained significantly elevated. Significant increases relative to baseline also were observed after the second administration. For Quest 3®, mean baseline heart rate was 68.7 bpm (SEM 2.1), which increased significantly but to a lesser extent than OWN to 73.1 bpm (SEM 2.1) 5 minutes after the first but not the second product administration. Mean heart rate in the SHAM condition was stable or decreased over both administration periods. For the non-combustible conditions, a significant increase in heart rate was observed during the Camel Snus condition; heart rate at baseline was 67.8 bpm (SEM 2.3), which increased significantly to 72.0 bpm (SEM 2.4) 15 minutes after the first product administration. No significant increases were observed for ARIVA, COMMIT® or Marlboro Snus.

Subjective Effects: OWN brand was associated with significant decreases in craving scores relative to baseline at nearly every time point. Quest 3® was associated with a similar pattern, while mean craving scores during SHAM were relatively high and stable. During all non-combustible conditions, craving scores were significantly higher relative to OWN at 5 and 15 minutes after the first product administration and at 5, 15, 30 and 45 minutes after the second product administration

2.1.2.4. Evaluation of the Effect of Puff Volume and Compensatory Smoking on Changes in Filter Tar Staining in Quest® Cigarettes

Strasser *et al*[37] conducted a study to describe the physical characteristics of the Quest® cigarettes, to evaluate the effect of puff volume on filter tar staining, and to examine the effect of compensatory smoking on changes in filter tar staining. In this study, 50 adult smokers smoked four 4 cigarettes in a laboratory setting. The first cigarette was always their

own preferred brand cigarette followed by Quest 1® (nicotine yield 0.6 mg), Quest 2® (nicotine yield 0.3 mg), and Quest 3® (nicotine yield ≤0.05 mg) cigarettes. Nicotine level was blinded to researcher and participant, and order of presentation was randomized and counterbalanced across participants to minimize order effects. All cigarettes were smoked 30 minutes apart. Spent cigarette filters were analyzed digitally. Results suggest that compensatory smoking may be detectable by darkening and reddening of the tar stain. The authors concluded that this type of measure could be useful in quantifying the extent to which human smokers smoke differently than standard testing protocols and in assessing the prevalence of compensatory smoking in population samples.

2.1.2.5. Evaluation of Compensatory Smoking with Reduced Nicotine Cigarettes

Strasser *et al*[38] also conducted a study to test the hypothesis that compensatory smoking will occur as nicotine levels of cigarettes decrease, increasing exposure to tobacco toxins using a smoking topography machine. In this study, 50 adult smokers participated in a single laboratory session. Subjects first smoked one of their own brand cigarette through the device. Thirty minutes after smoking their own brand cigarette, participants smoked the first of three Quest® cigarettes (Quest 1® [nicotine yield 0.6 mg], Quest 2® [nicotine yield 0.3 mg] or Quest 3® [nicotine yield ≤0.05 mg]) with a 30-minute interval between cigarettes. The Quest® cigarettes were presented in randomized order, counter-balanced across participants to minimize potential order effects. Subjects and researcher were blind to nicotine level. Puff volume was measured using the smoking device. Prior to and 4 minutes after smoking each cigarette, participants provided breath CO samples. Upon extinguishing each cigarette, participants completed a 14-item subjective rating of the cigarette they had just finished smoking, including which had the most and least amount of nicotine.

Mean total puff volumes measured were 832.0 ml, 540.3 ml, 518.1 ml, and 570.5 ml in the Own brand, Quest 1®, Quest 2®, and Quest 3® cigarette groups. Mean number of puffs per cigarette were 14.3, 9.8, 9.9, and 10.0 in the Own brand, Quest 1®, Quest 2®, and Quest 3® cigarette groups. Fifty-four percent correctly identified the Quest 1® cigarette as the highest nicotine cigarette. Fifty-eight percent correctly identified the Quest 3® cigarette as the least nicotine-containing cigarette. Only 38% correctly identified both the Quest 1® cigarette and the Quest 3® cigarette. Ability to discriminate nicotine levels did not affect total puff volume or CO boost.

2.1.2.6. Inpatient Study of Reduced Nicotine Cigarettes, Very Low Nicotine Cigarettes, or No Cigarettes over 11 Days

Smoking behavior with reduced nicotine cigarettes (RNCs) and VLN cigarettes under controlled, inpatient, conditions over 11 days was studied by Donny *et al*.[39] Thirty adult regular smokers were assigned randomly to 1 of 3 groups:

- Group 1: RNCs (Quest 1®, nicotine yield 0.6 mg),
- Group 2: VLN cigarettes (Quest 3®, nicotine yield ≤0.05 mg), or
- Group 3: No smoking.

Subjects in the VLN cigarette group smoked fewer cigarettes (a decrease of 3.8 cigarettes/day compared to baseline vs. an increase of 2.1 cigarettes/day in the RNC group), took fewer puffs per cigarette (8.8 vs. 11.5, $p = 0.10$), tended to leave larger butts (0.54 grams vs. 0.45 grams, $p = 0.11$), and had significantly lower expired CO levels. Subjects smoking VLN cigarettes also demonstrated a 31% decline in the number of puffs earned on a progressive ratio, a measure of the motivation to smoke, during the study. Acute craving suppression following smoking was evident throughout the study regardless of nicotine content.

2.1.2.7. Modulation of Smoking-Induced Platelet Activation by Nicotine

In a previous *in vitro* study, Girdhar *et al*[40] exposed human blood cell platelets and cultured endothelial cells to smoke extracts from nicotine-containing cigarettes and VLN cigarettes, and found that nicotine has a protective effect on platelet activation induced by exposure to cigarette smoke. In this in vivo study, Girdhar *et al*[66] reported that RNCs increase platelet activation in smokers. In this study, 32 smokers smoked 3 cigarettes with moderately reduced nicotine (Quest 1®, nicotine yield 0.6 mg) in 1 hour. Following the first 1 hour of smoking, 16 of these subjects continued smoking with 5 of the same cigarettes over the next 1.5 hours, while the other 16 subjects smoked 5 VLN cigarettes (Quest 3®, nicotine yield ≤0.05 mg). (Consuming 8 cigarettes over 2.5 hours equates to approximately 51 cigarettes/16-hour day and 5 VLN cigarettes over 1.5 hours equates to approximately 53 cigarettes/16-hour day.) The percentage of platelets scored as activated increased in both groups, but the increase was larger in the group smoking VLN cigarettes during the second period ($p < 0.02$). No measure of smoke exposure was made, so it cannot be determined whether nicotine content of the cigarettes affected the intake of smoke under the rapid smoking schedule.

To determine whether nicotine modulates platelet activation by secondhand smoke, 16 nonsmokers were exposed to medium-nicotine smoke and 16 to low/zero-nicotine smoke for 1.5 hours on 2 consecutive days. Exposure to second hand smoke increased platelet activation by 60%, but no difference between the medium and zero nicotine groups was observed ($p>0.09$). The authors concluded that in smokers, nicotine modulates platelet activation. See further discussion of this study in Section 2.3.1.3.4.

2.1.2.8. The Influence of Instructions and Nicotine Dose on Subjective and Reinforcing Effects of Smoking

Perkins *et al*[41] conducted a study in 2004 to examine the subjective and reinforcing effects of smoking. In this study, 96 healthy smokers whose preferred brand had a nicotine yield of at least 0.7 mg were assigned to 1 of 4 treatment groups and evaluated during a single laboratory session. Participants smoked one of their preferred brand cigarettes *ad libitum* upon arrival and then rested quietly for 1 hour. At the end of the 1-hour rest period, they completed baseline measures of craving and withdrawal. They then were introduced to the designated cigarette (regular nicotine or very low nicotine) and were given the following instructions, depending on their group assignment:

- Told regular nicotine: "We are interested in why smokers like certain brands of cigarettes. Regular Full-Flavor brands, those higher in nicotine, often are liked. So, nicotine levels may have something to do with brand liking. Today, you will be smoking a regular higher nicotine cigarette that is well-liked."

- Told low nicotine: "We are interested in why smokers do not like certain brands of cigarettes. Low nicotine brands often are not liked, so nicotine levels may have something to do with brand liking. Today, you will be smoking a low nicotine cigarette that is not well-liked."

Subjects rated the cigarette according to "how much nicotine" it included and completed craving and withdrawal measures.

In this study, instructions about the nicotine content and expected likeability of a cigarette influenced ratings of the cigarette on items relevant to the perceived nicotine content and strength of the cigarette, as well as on some measures of smoking reward. The greater ratings for the VLN cigarette among those told regular nicotine versus those told low nicotine support a significant placebo effect. Similarly, the lower ratings for the regular nicotine cigarette among those told low nicotine versus those told regular nicotine support a significant antiplacebo effect. Instructions had comparable effects regardless of the nicotine

dose of the cigarette. Under the conditions of this study, instructions did not affect craving or withdrawal. Women showed similar responses to instructions compared with men, but results indicated greater effects due to nicotine on ratings regarding perception in women compared with men.

2.1.2.9. The Influence of the Airway Sensory Effect of Nicotine on the Reward Obtained from Cigarette Puffs

Naqvi and Bechara[42] examined the extent to which reward from puffs can be derived from the airway sensory effect of nicotine, in the absence of a direct central nervous system effect of nicotine. To do this, the self-reported reward obtained from individual puffs from Quest 1® (nicotine yield 0.6 mg), VLN Quest 3® (nicotine yield ≤0.05 mg) and unlit cigarettes within 7 seconds of inhalation, which is before nicotine had an opportunity to reach the brain, was assessed. Results indicated that nicotinized puffs were rated as both stronger and more rewarding than VLN and unlit puffs. Furthermore, the extent to which nicotine elicited reward was directly correlated with the extent to which nicotine elicited airway sensations. The authors concluded that the airway sensory effects of nicotine contribute to the reward from puffs, above and beyond the reward derived from the airway sensory effects of nonnicotine constituents.

2.1.2.10. Evaluation of Naltrexone or Bupropion on the Reinforcing Value of Nicotine

Rukstallis *et al*[43] evaluated the effect of naltrexone or bupropion on the self-reported reinforcing effects of nicotine. This study explored the effects of an acute dose of naltrexone, bupropion, or placebo on the relative reinforcing value of nicotine from cigarette smoking using Quest 1® (nicotine yield 0.6 mg) and VLN Quest 3® (nicotine yield ≤0.05 mg) cigarettes. In a double-blind, within-subjects design, 26 dependent smokers participated in 3 experimental cigarette smoking sessions following pretreatment with either naltrexone (50 mg), bupropion (300 mg), or placebo. After medication administration and 2 hours of monitored deprivation from cigarettes and food, participants rated their responses to the initial exposure to the cigarettes and then participated in 4 choice sessions over a 2-hour period during which they could take 4 puffs from either cigarette. The relative reinforcing value of nicotine, as measured by the number of Quest 1® puffs chosen out of 16, was significantly lower following naltrexone compared to placebo. There were no effects of an acute dose of bupropion on cigarette choices. The authors concluded that naltrexone may reduce the relative reinforcing effects of nicotine via cigarette smoking and support ongoing investigation of opioid antagonists as potential smoking cessation pharmacotherapies.

2.1.2.11. Evaluation of Gender Differences in the Effect of Dose Instructions on the Reinforcing Effects of Nicotine

Perkins *et al*[44] conducted a study in 2006 comparing the influence of the presence versus absence of dose instructions on the subjective and reinforcing effects of nicotine via cigarette smoking in men and women. A total of 120 subjects were randomly assigned to 1 of 4 groups. Subjects abstained overnight from smoking. Half of the subjects received Quest 1® (nicotine yield 0.6 mg), and the other half received VLN Quest 3® (nicotine yield ≤0.05 mg) cigarettes. Furthermore, half of each subsample was accurately instructed they were receiving a "normal nicotine" or a "no nicotine" cigarette, while the other half received no instructions. Subjects completed baseline measures of craving and mood (positive and negative affect), took 2 puffs from the cigarette after receiving dose instructions or no instructions, and then rated the cigarette's "reward" value (liking, satisfying) and other characteristics. They also repeated the craving and mood measures. Subjects then smoked more of that same brand *ad libitum* over the next 30 minutes to measure reinforcement (puff number and latency to first puff). Overall, nicotine increased reward, other cigarette ratings, and positive affect, but did not affect craving or smoking behavior. However, results varied by sex. Dose instructions enhanced the effects of nicotine on smoking reward and reinforcement in women, while instructions tended to dampen or even reverse these effects of nicotine in men. The authors concluded that in women but not in men, the influence of nicotine on smoking reward and reinforcement is enhanced by accurate verbal information about the cigarette's nicotine dose.

2.1.2.12. A Study of the Effect of Genetic Variants of the Mu Opioid Receptor on the Reinforcing Effects of Nicotine

Noting the importance of the endogenous opioid system in nicotine reward, Ray *et al*[45] conducted a study to elucidate the possible role of genetic variation in the mu opioid receptor (MOR) in smoking behavior. Specifically, this study examined (1) the association between polymorphisms of the gene encoding the MOR (ie, gene OPRM1; specifically, SNP 118A to G substitution) with the relative reinforcing value of nicotine using a validated nicotine cigarette choice paradigm and (2) the influence of the MOR antagonist naltrexone on nicotine reinforcement. A total of 156 subjects were screened and genotyped at the A118G SNP to obtain a final sample of 60 eligible subjects; 30 with the AA genotype and 30 with either the AG genotype (26 subjects) or GG genotype (4 subjects). In a within-subject, double-blind design, subjects participated in 2 experimental sessions following 4 days of orally administered naltrexone 50 mg or placebo. Participants completed a validated assessment of the relative reinforcing value of nicotine. This cigarette choice paradigm assessed self-administration of Quest 1®(nicotine yield 0.6 mg) vs. Quest 3® (nicotine yield ≤0.05 mg)

cigarettes after a brief period of nicotine abstinence. The relative reinforcing value of nicotine (number of nicotine cigarette puffs) was predicted by a significant OPRM1 by gender interaction. Among women, the low activity G allele (A/G and G/G) was associated with a reduced reinforcing value of nicotine; among male smokers, there was no association with genotype. Smokers carrying a G allele were also significantly less likely to differentiate the Quest 1® vs. Quest 3® cigarettes by subjective ratings of satisfaction and strength. No evidence for an effect of naltrexone on nicotine reinforcement was found in the overall sample or in the genotype or gender subgroups.

2.1.2.13. A Study of the Expectancy of Nicotine and the Pharmacological Effects of Nicotine on Memory and Subjective Effects of Cigarettes

In this double-blind, 2-hour, laboratory study, Kelemen and Kaighobadi[46] evaluated the expectancy and pharmacological effects of nicotine on memory and the subjective effects of cigarettes. A total of 120 smokers who had abstained from nicotine for 8 hours prior to the study were randomly assigned to one of the following 4 groups:

- Told nicotine - Received nicotine (Quest 1®, yield 0.60 mg nicotine/cigarette)
- Told nicotine - Received VLN (Quest 3®, yield ≤0.05 mg nicotine/cigarette)
- Told no nicotine - Received nicotine (Quest 1®, yield 0.60 mg nicotine/cigarette)
- Told no nicotine - Received VLN (Quest 3®, yield ≤0.05 mg nicotine/cigarette)

Each subject was informed of which kind of cigarette they would receive as shown above, then smoked 1 entire cigarette, and then rated the cigarette on a number of dimensions and completed questionnaires on smoking urges, tension, and energy. Participants also completed tests of memory as well as predictions of memory. Pharmacology played a stronger role than expectancy in most ratings of the cigarettes, but significant effects of expectancy did emerge for feelings of increased wakefulness, concentration, calming, cigarette satisfaction, and hunger reduction. The higher level of nicotine significantly reduced smoking urges, but expectancy alone reduced tension after smoking. Neither variable produced significant effects on memory or memory predictions.

2.1.2.14. The Acute Effects of Smoking on the Brain as Measured by Functional Magnetic Resonance Imaging

Lindsey *et al*[47] studied the acute effects of smoking on the brain using functional magnetic resonance imaging (fMRI) during tobacco cigarette and placebo tobacco smoking. Subjects smoked either a Marlboro Red brand cigarette or a VLN Quest 3® cigarette during fMRI

scanning with concurrent assessment of heart rate and changes in subjective mood state. Visual analog scales for mood states were presented every 2.5 minutes throughout the functional scan. Using General Linear Modeling techniques, changes in subjective sensation of "high" after smoking tobacco were found to be most highly correlated with blood oxygen level dependence (BOLD) signal change in the bilateral anterior nucleus of the thalamus, bilateral caudate head and tail, bilateral posterior cingulate (these and all subsequent correlations were found to be significant at $p<0.0001$). These findings are consistent with both the reinforcing properties of nicotine and the anatomical distribution of terminals emanating from regions of high nicotinic acetylcholine receptor density. Changes in subjective sensation of "high" after smoking placebo tobacco were most highly correlated with BOLD signal change in the orbitofrontal cortex, and dorsolateral prefrontal cortex. The authors noted that these findings are consistent with the cognitive components of reward mediated by conditioned reinforcers only in the absence of active drug.

2.1.2.15. The Effect of an Extinction-based Smoking Cessation Treatment (Quest 3® plus Nicotine Patch) on Brain Responses to Smoking Cues

McClernon *et al*[48] reported that the combination of smoking VLN cigarettes and a nicotine patch has been reported to extinguish brain responses to smoking cues. In this study, blood oxygen level-dependent functional magnetic resonance imaging of 16 dependent smokers were scanned at baseline, after 2-4 weeks of smoking Quest 3® nicotine yield ≤0.05 mg cigarettes while wearing a 21-mg nicotine patch, and 2-4 weeks following quitting smoking altogether. The treatment attenuated responses to smoking cues in the amygdala while potentiating responses to control cues. Exploratory analysis indicated that this pattern was also observed in the thalamus of future abstinent but not relapsing smokers. The results of this preliminary study suggest that an extinction-based treatment for smoking cessation alters brain responses to smoking and control cues in amygdala.

2.1.2.16. Pharmacological, Stimulus Expectancy, and Response Expectancy Effects of Nicotine-Free Cigarettes

Kelemen[49] conducted a study to evaluate the pharmacological, stimulus expectancy, and response expectancy effects of Quest 1® (nicotine yield 0.60 mg) compared with Quest 3® (nicotine yield ≤0.05 mg). In this double-blind study, 103 smokers who had abstained from smoking for at least 5 hours were told that they would be given a cigarette to smoke and that the cigarette may or may not have nicotine in it. Subjects were offered an additional $5 if they could guess whether the cigarette contained nicotine after smoking it. Subjects completed a series of pre-tests (baseline measurement of smoking urges, baseline measure of energy and tension, and baseline assessment of cognitive performance) and then smoked a

single cigarette (Quest 1® or Quest 3®). After smoking, subjects guessed whether or not their cigarette contained nicotine and predicted how it would influence their subsequent cognitive performance. The also repeated the baseline questionnaires and a second round of cognitive testing.

Cigarettes with nicotine were preferred on most dimensions, and stimulus expectancy partially mediated the relationship between nicotine and subjective effects of the cigarettes. Stimulus expectancy also mediated the effect of nicotine on tension reduction immediately after smoking, but not 30 minutes later. Response expectancy effects of nicotine were related to predicted and actual recall performance, such that participants who performed well tended to attribute the effect to the cigarette they smoked.

2.1.2.17. A Study of the Effects of Nicotine on Ratings of Attractiveness

Attwood *et al*[50] conducted this double-blind study to test the hypothesis that nicotine enhances the hedonic impact of behaviors performed in the presence of nicotine, using ratings of facial attractiveness. Male (n=24) and female (n=24) participants attended a single testing session and were randomized to smoke either Quest 1® (nicotine yield 0.60 mg) or Quest 3® (nicotine yield ≤0.05 mg) cigarette, after which they completed ratings of attractiveness of 20 male and 20 female faces. A 2 × 2 × 2 mixed-model repeated measures analysis of variance indicated a significant main effect of cigarette, reflecting higher attractiveness ratings in the Quest 1® compared with the Quest 3® condition There was no evidence that these effects differed between males and females. There were also no effects on subjective ratings of mood, suggesting that the effects observed on ratings of attractiveness may not simply reflect global hedonic effects, or a positivity bias in questionnaire responding, in the nicotine condition.

2.1.2.18. Effect of Nicotine on Smoking-dependent Dopamine Release

Brody *et al*[51] studied the effect of dopamine release in response to cigarette smoking and nicotine gum administration. This study used VLN cigarettes and ^{11}C-raclopride positron emission tomography (PET) scanning to investigate whether nicotine is necessary for smoking-induced dopamine release. A total of 62 subjects were enrolled, and an MRI scan of the brain was obtained within 1 week of the study PET sessions. Subjects were instructed to smoke one of their usual brand cigarettes immediately prior to testing. They then were interviewed, filled out rating scales, and underwent a session of bolus-plus-continuous-infusion ^{11}C-raclopride PET scanning for evaluation of ventral striatal ^{11}C-raclopride binding potential, an indirect measure of dopamine release in this area of the brain. Three hours after their previous cigarette, subjects took a 10-minute break from the PET scan during which

they smoked either a regular (the subject's own brand, de-identified) or VLN Quest 3® (nicotine yield ≤ 0.05 mg) cigarette under double-blind conditions. Rating scales evaluating craving, anxiety, and mood were administered immediately before and after smoking.

Smoking a regular cigarette resulted in a significantly greater mean reduction in ^{11}C-raclopride binding potential in the ventral striatum than smoking a VLN cigarette. Although both groups had reductions in craving and anxiety with smoking, the regular cigarette group had a greater improvement in mood. For the total group, change in binding potential correlated inversely with change in mood, indicating that greater smoking-induced dopamine release was associated with more smoking-related mood improvement. Thus, nicotine delivered through cigarette smoking appears to be important for ventral striatal dopamine release. Study findings also suggest that mood improvement from smoking is specifically related to ventral striatal dopamine release.

2.1.2.19. Effect of Nicotine Inhalation on Nicotinic Acetylcholine Receptor Occupancy in the Brain

Brody *et al*[52] conducted this study in follow-up to a previous report that smoking regular cigarettes resulted in 88% occupancy of $\alpha_4\beta_2$ brain nicotinic acetylcholine receptors (nAChRs). This study investigated whether nicotine is solely responsible for the previously observed receptor occupancy, or whether other factors related to smoking are involved. The authors hypothesized that if nicotine was solely responsible for the receptor occupancy, then smoking a cigarette without nicotine should decrease receptor binding to within the range of 22% to 24%. To investigate this hypothesis, 24 PET sessions were performed on tobacco-dependent smokers, using 2-[F-18]fluoro-A-85380 (2-FA), a radiotracer that binds to $\alpha_4\beta_2$ nAChRs. 2-FA displacement was determined from before to 3.1 hours after either: no smoking, smoking a VLN cigarette (Quest 3®, ≤0.05 mg nicotine yield), or smoking a reduced nicotine cigarette (Quest 1®, 0.60 mg nicotine yield). Analysis of this PET data revealed that smoking a VLN and a low-nicotine cigarette resulted in 26% and 79% $\alpha_4\beta_2$ nAChR occupancies, respectively, across three regions of interest. Therefore, the authors concluded that nicotine inhalation during smoking appears to be solely responsible for $\alpha_4\beta_2$ nAChR occupancy.

2.1.2.20. A Study of the Effects of Nicotine and Gender on Alcohol-induced Increases in Smoking Behavior

Alcohol is known to increase smoking urges and smoking behavior. To evaluate if nicotine content of cigarettes or gender of subjects influences this effect, King *et al*[53] enrolled male and female smokers who were non-dependent heavy social drinkers in 2 double-blind laboratory sessions. Subjects were randomized to receive either an alcohol (n=29) or placebo

(n=13) beverage and then smoked either VLN Quest 3® (≤0.05 mg nicotine yield), or Quest 1® (0.60 mg nicotine yield) cigarettes over a 3-hour period. Results showed that alcohol, compared with placebo beverage, increased both men's and women's smoking urge, as well as subjective ratings of smoking reference puffs for either nicotinized or VLN cigarettes. Regardless of cigarette type, alcohol (more than placebo) increased men's smoking behavior, including puff count, volume, and duration. In contrast, for women, smoking topography measures did not differ between alcohol and placebo conditions. The authors concluded that the results indicate that the mechanisms underlying co-use of alcohol and tobacco in women may be more complex than in men.

2.1.2.21. Evaluation of Silver Acetate Interactions with Nicotine and Non-nicotine Smoke Components

Oral topical silver-containing formulations were marketed in the 1970s and 1980s as smoking deterrents, based on the finding that when using such formulations, an unpleasant taste occurs upon smoking. This study by Rose *et al*[54] explored the basic mechanistic question of whether topical oral silver acetate solution interacts with nicotine as opposed to non-nicotine smoke constituents. A total of 20 smoking volunteers were recruited to rate higher nicotine (Usual brand or Quest 1®, yield 0.60 mg nicotine) or VLN (Quest 3®, yield ≤0.05 mg nicotine) cigarettes, as well as the Nicotrol nicotine vapor inhaler and sham (air) puffs. In 2 sessions, subjects rated the sensory and hedonic qualities of puffs after rinsing their mouths with either silver acetate solution or deionized water (placebo). Silver acetate relative to placebo solution substantially reduced liking and satisfaction ratings for the usual brand and VLN cigarettes; in contrast, for the nicotine inhaler these ratings were unaffected by the silver-based treatment. These results support the conclusion that silver acetate not only renders the taste of cigarette smoke less appealing, but also that the compound appears to interact selectively with non-nicotine smoke constituents. Moreover, these data suggest silver acetate would be compatible with buccal nicotine delivery systems (e.g., nicotine lozenge or gum).

2.1.3. Studies of Other Low Nicotine Cigarettes

The following studies were conducted with reduced nicotine cigarettes other than Quest® that did not contain Vector 21-41 tobacco (see also Section 1.2 for a summary of non- Quest® low nicotine cigarettes and methods of nicotine removal).

2.1.3.1. The Effect of Nicotine and Menthol on the Self-reported Reward of Smoking

Rose and Behm[7] evaluated several pharmacological and behavioral treatments designed to promote extinction of the responses to rewarding cigarette smoke cues. Treatments

administered in this study included nicotine patch, mecamylamine, or placebo and in addition, subjects were assigned to smoke either their usual brand or were switched from their usual brand of cigarette to another cigarette that was either denicotinized, mentholated, or a low tar, low nicotine nonmentholated cigarette for a two-week treatment period. During weekly test sessions, subjects rated the rewarding effects of their usual brands of cigarettes or cigarettes with different menthol content (mentholated vs. nonmentholated). Treatments and numbers of subjects are summarized in Table 2-2.

Table 2-2 Treatments and Number of Subjects in Study Published by Rose and Behm, 2004

Brand switch	NIC/MEC	NIC only	MEC only	Placebo
Usual brand	30	8	43	12
Denicotinized cigarette	31	12	–	7
Menthol cigarette	32	–	–	13
Low tar and nicotine cigarette	28	9	–	8
Total *n*	121	29	43	40

MEC, mecamylamine; NIC, nicotine; NIC/MEC, nicotine plus mecamylamine.

Over the 2-week treatment period, all pharmacological treatments reduced ratings of reward for the usual-brand test cigarettes. Switching to smoking denicotinized cigarettes for 2 weeks similarly decreased rewarding effects of the usual-brand test cigarettes. Subjects also strongly preferred cigarettes with the same menthol content to which they were accustomed. However, manipulating the menthol content of the cigarettes smoked during the 2 weeks of treatment had different effects, depending on whether smokers habitually smoked mentholated or nonmentholated cigarettes. For menthol smokers, removal of the menthol cue hampered extinction of reward ratings for the usual brand (mentholated) test cigarette. For nonmenthol smokers, addition of the menthol cue did not affect the progress of extinction of nonmenthol smoke cues. These findings demonstrate the importance of sensory cues in determining subjective reward and show that the reward value of these cues can be altered by removal of nicotine from tobacco or by pharmacological manipulations that interfere with the reinforcing effects of nicotine.

2.1.3.2. Smoking-related Stimuli Delivered by Denicotinized Cigarettes Manufactured by Ultratech/Lifetech

Buchhalter *et al*[20] conducted this study to clarify the impact of smoking-related stimuli on tobacco withdrawal, and to explore the duration of their ability to suppress withdrawal in smokers. Male (n=19) and female (n=13) smokers participated in 3 double-blind, within-subjects, Latin square-ordered, 5-day conditions in which they smoked nicotinized, denicotinized or no cigarettes. The nicotinized and denicotinized cigarettes were developed and manufactured for the National Institute on Drug Abuse (NIDA) by Ultratech/Lifetech Corporation (Lafayette Hill, PA, USA). The smoke of the nicotinized cigarettes yielded 0.6 mg nicotine and 10.0 mg tar, while the smoke of the denicotinized cigarettes yielded 0.07 mg nicotine and 12.1 mg tar.

Subjective and physiological performance measures were collected. The authors found that smoking-related stimuli are sufficient for suppressing some symptoms of tobacco abstinence over a 5-day period (i.e. Questionnaire of Smoking Urges [QSU] factor 1, 'Desire for sweets', 'Hunger' and 'Urges to smoke'), while in this study a combination of nicotine and smoking-related stimuli suppressed other symptoms (i.e., 'Difficulty concentrating', 'Increased eating', 'Restlessness' and 'Impatient'). The authors concluded that while some tobacco abstinence symptoms may be suppressed with nicotine, suppressing others may also require strategies that address the absence of smoking-related stimuli.

2.1.3.3. Pharmacodynamic Effects of Ultratech/Lifetech Corporation Denicotinized Cigarettes

In a study by Pickworth *et al*[15], pharmacological effects of the denicotinized cigarettes manufactured by Ultratech/Lifetech Corporation (Lafayette Hill, PA, USA) were compared with standard cigarettes. The de-nicotinized cigarettes had the appearance, draw, and taste or standard cigarettes but contained and delivered virtually no nicotine (0.06 mg), but delivered tar and CO. Twenty subjects (10 men, 10 women) participated in 4 experimental sessions in which they smoked either a standard cigarette or a de-nicotinized cigarette after either 3 or 12 hours of tobacco deprivation. Heart rate, blood pressure, and electroencephalogram (EEG) were recorded before, and for I hour after, ad lib smoking. Plasma nicotine concentrations verified that de-nicotinized cigarettes did not deliver nicotine. The denicotinized cigarettes did not increase heart rate or activate the EEG. The subjects preferred the cigarettes that delivered nicotine compared to the de-nicotinized cigarettes. However, both types of cigarettes reduced subjective measures of tobacco craving and withdrawal and the time to smoke and the number of puffs to smoke the cigarette did not differ between the de-nicotinized and standard cigarettes. The boost in exhaled CO was similar after standard and

de-nicotinized cigarettes. The authors concluded that denicotinized and standard cigarettes both reduced acute measures of tobacco withdrawal.

2.1.3.4. A Study of the Subjective Effects from Smoking the Next® Denicotinized Cigarette by Philip Morris

In this study by Gross *et al*,[14] 10 smokers smoked 20 puffs from their own brand (1.1 mg nicotine delivery, commercial cigarettes), a 0.7 mg nicotine "light" cigarette, or the Next® de-nicotinized cigarette manufactured by Philip Morris (<0.1 mg nicotine) during independent experimental test sessions. The Next® cigarette did not deliver any appreciable nicotine, did not elevate heart rate during smoking, and was rated as less satisfying than the smokers' own brand. Subjective ratings of cigarette craving and tobacco withdrawal symptoms increased during a 90 minute post-smoking abstinence period. However, there were no measurable differences on these subjective ratings across the 3 cigarette test brands. It is concluded that nicotine can be removed from cigarettes without affecting the onset time course or intensity of cigarette cravings and other tobacco withdrawal symptoms in an acute abstinence model.

2.1.3.5. A Study of the Effects of Nicotine Content on Smoking Pace and Subsequent Craving and Smoking Using Denicotinized Cigarettes Manufactured by the Ultratech/Lifetech

This study by Dallery *et al*[19] utilized denicotinized cigarettes manufactured by Ultratech/Lifetech Corporation (Lafayette Hill, PA, USA) to investigate the effects of nicotine content of cigarettes on smoking pace and subsequent craving and smoking behavior. Participants (n=15) engaged in one session each of rapid smoking (up to 9 cigarettes with puffs taken every 6 seconds) and normal paced smoking with nicotinized and denicotinized cigarettes (total of 4 sessions). During the next 3 hours, craving and withdrawal assessments and smoking opportunities were scheduled every 15 minutes. Plasma nicotine levels were measured at baseline, immediately and 15 minutes after the smoking interventions, and subsequently at the time when the participant first chose to smoke. Craving ratings were equally suppressed immediately after all conditions. After self-paced conditions, both types of cigarettes produced equivalent effects on latency to smoke. Latency to smoke was significantly longer after rapid smoking of nicotinized cigarettes compared to all other conditions. Finally, changes in craving were associated with choices to smoke. The authors concluded that the sensory cues associated with smoking suppressed craving ratings regardless of the smoking pace or nicotine content. Only at high doses did nicotine levels play an additional role in acutely suppressing smoking behavior. Small elevations in craving ratings were associated with choices to smoke.

2.1.3.6. A Study of Withdrawal Symptoms Using Next® Denicotinized Cigarettes Manufactured by Philip Morris and a "Lettuce" Cigarette Manufactured by Safer Smokes, Inc.

Butschky *et al*[12] studied the contribution of sensory factors to smoking satisfaction and nicotine withdrawal symptoms was assessed by evaluating responses to three types of cigarettes: a regular cigarette, a denicotinized cigarette (Next® cigarette manufactured by Philip Morris, nicotine yield 0.09 mg), and "lettuce leaf" cigarette Bravo®, a non-tobacco cigarette manufactured by Safer Smokes, Inc., Ft. Lee, NJ). Doses were varied by requiring subjects to smoke cigarettes using a five-port cigarette manifold. The ratio of the regular or denicotinized cigarettes to the "lettuce" cigarettes was varied across the following values: zero, one, two, and four of five. Seven male smokers were tobacco-deprived for 12 hours before testing. On one test day they smoked the denicotinized cigarettes, and on another day they smoked the regular cigarettes. Ratings of satisfaction and cigarette liking were directly related to the number of regular or denicotinized cigarettes, but were generally higher after the regular cigarette. The regular and denicotinized cigarettes were equivalent in reducing acute withdrawal symptoms. Expired CO was similar on both experimental days. The regular cigarette dose dependently increased plasma nicotine, but the denicotinized cigarette did not increase plasma nicotine. The authors concluded that sensory characteristics of cigarettes contribute to the abuse liability of smoke-delivered nicotine and that smoking cigarettes that do not provide nicotine may temporarily suppress cigarette withdrawal symptoms.

2.1.3.7. Evaluation of the Accord® System Compared to Own Brand or Denicotinized Cigarettes Manufactured by Ultratech/Lifetech

This study by Buchhalter *et al*[18] was undertaken to evaluate the Accord® smoking system, which consists of a handheld device and specially constructed 'cigarettes', that allows a maximum of 8 puffs. This system is intended to reduce secondhand smoke and possibly decrease the mutagenicity and cytotoxicity associated with normal tobacco smoke. Smokers of light or ultra-light cigarette brands (16 men and 16 women) participated in this within-subjects protocol. Prior to each of the four, Latin-square ordered, approximately 2.5-hour sessions, subjects abstained from smoking for at least 8 hours. In each session, subjects smoked eight puffs at 30-min intervals from one of the following:

- The Accord® - 0.20 mg nicotine
- Subjects' own brand of cigarettes - on average, 0.75 mg nicotine
- Merit Ultra Light®; Phillip Morris, Richmond, VA - 0.40 mg nicotine

- De-nicotinized cigarettes (Ultratech/Lifetech Corporation, Lafeyette Hill, PA) - 0.07 mg nicotine

Subjective and physiological effects were assessed regularly.

Subjective Results: Results indicated that relative to baseline, all treatments significantly reduced cravings; however, the greatest reductions were achieved with own brand, followed by Merit Ultra light®, denicotinized cigarettes, and the Accord®. Compared to baseline scores, significant reductions of self-reported 'Irritability/frustration/anger' were observed after all smoking bouts when subjects used normally marketed cigarettes, and after the second, third, and fourth smoking bouts when subjects used de-nicotinized cigarettes, but only after the fourth bout with Accord®.

Physiological Results: When subjects were smoking normally marketed brands, heart rate increased significantly after the first smoking bout and then remained elevated relative to pre-smoking levels. Heart rate increases produced by normally marketed cigarette brands were significantly greater relative to those produced by Accord®; however, heart rate never increased significantly when subjects smoked de-nicotinized cigarettes, and was significantly lower at every time after the baseline measurement, relative to the other three smoking conditions. Expired air CO also depended upon cigarette type, number, and time. CO levels rose reliably whenever subjects used the two normally marketed cigarette brands or de-nicotinized cigarettes. No significant CO increase was observed when subjects used the Accord®.

2.1.3.8. Evaluation of Nicotine and Carcinogen Exposure During a Tapered Nicotine Cessation Protocol

Benowitz *et al*[21] conducted this 10-week longitudinal study of 20 healthy smokers involved smoking their usual brand followed by different types of research cigarettes manufactured by Philip Morris with progressively lower nicotine content, each smoked for 1 week. Subjects were followed for 4 weeks after returning to smoking their usual brand (or quitting). Smoking behaviors, chemical biomarkers of tobacco smoke exposure, and cardiovascular effect biomarkers were measured. Findings: Intake of nicotine declined progressively as the nicotine content of cigarettes was reduced, with little evidence of compensation. Cigarette consumption and markers of exposure to carbon monoxide and polycyclic aromatic hydrocarbons, as well as cardiovascular biomarkers remained stable, whereas urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol excretion decreased. Twenty-five percent of participants had spontaneously quit smoking 4 weeks after completing the research cigarette taper.

2.1.3.9. Individual Differences in Smoking Reward from Denicotinized Cigarettes

Brauer *et al*[17] presented the results of a pooled analysis of 9 studies conducted at Duke University in Durham, NC, in order to explore the influence of demographic and smoking-related variables on ratings of de-nicotinized as compared to nicotine-containing cigarettes. The primary dependent measures explored in this analysis were smoking satisfaction and craving reduction obtained from smoking nicotine-containing as compared to denicotinized cigarettes. As a group, subjects reported substantial reward (i.e., the mean of craving reduction and smoking satisfaction ratings) from both nicotine-containing and denicotinized cigarettes, but ratings were highest after smoking cigarettes containing nicotine. Results also showed that there were significant individual differences in cigarette ratings, with some individuals assigning approximately equal ratings to the 2 kinds of cigarettes, and others reporting greater reward from nicotine-containing cigarettes. Second, cigarette ratings also tended to vary as a function of gender. On average, males were more indifferent to the effects of nicotine than females. A major finding of this analysis was that ratings of smoking derived from de-nicotinized, but not nicotine-containing, cigarettes appear to vary with level of tobacco dependence as evaluated using the Fagerström Test of Nicotine Dependence (FTND), suggesting that sensory factors may be more important to highly dependent, as compared to less-dependent, smokers.

2.1.3.10. A Study to Discern the Nicotine versus Airway Sensory Effects of Smoking

Westman *et al*[13] conducted this study to examine the subjective and cardiovascular effects of two of the components of cigarette smoking when given separately: nicotine and airway sensations. Using a within-subjects design, 6 healthy volunteer smokers, age 18-45 years, who smoked at least 20 cigarettes per day were given 6 conditions in a randomized, counterbalanced order. The effects of intravenous (IV) nicotine, IV saline, and denicotinized cigarettes were compared to a standard 1-mg cigarette. The standard cigarette produced more of a calming effect and more irritability reduction than either the nicotine or airway sensations alone. The denicotinized cigarette was similar to the standard cigarette condition, except the cigarette condition was associated with higher feelings of “exhilaration.” Many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette. The authors concluded the these data support the hypothesis that replacement of the sensory cues of smoking with “airway sensory replacement” may be useful for smoking cessation.

2.1.3.11. A Study to Dissociate the Nicotine and Nonnicotine Components of Cigarette Smoking Using the Next® Denicotinized Cigarette by Philip Morris

Rose *et al*[16] obtained denicotinized cigarettes manufactured by Phillip Morris to conduct this study to dissociate the sensorimotor aspects of cigarette smoking from the pharmacologic effects of nicotine. These cigarettes contained tobacco from which the nicotine had been selectively extracted by supercritical carbon dioxide, and had a taste and tar delivery similar to nicotine-containing cigarettes. In the study, smokers rated the subjective effects of nicotine - containing or denicotinized cigarettes, and IV nicotine or saline infusions. Three groups of participants (n = 20 per group) received either: (1) continuous nicotine, (2) pulsed nicotine, or (3) saline. Each group was exposed to an IV condition once while smoking a denicotinized cigarette and once while not smoking, in a 3_2 mixed design. A fourth group (n = 20) received saline while smoking their usual brand of cigarette. Denicotinized cigarette smoke significantly reduced craving and was rated significantly more satisfying and rewarding than the no-smoking conditions. IV nicotine reduced craving for cigarettes, and increased ratings of lightheadedness and dizziness. However, no significant satisfaction or reward was reported after IV nicotine. The combination of IV nicotine and denicotinized cigarette smoke produced effects similar to those of smoking the usual brand of cigarette. The authors concluded that these data suggest that sensorimotor factors are critical in mediating the immediate subjective response to smoking, and that the immediate subjective effects of nicotine administered in doses obtained from cigarette smoking are subtle.

2.2. Clinical Efficacy of X-22 for Smoking Cessation

2.2.1. Overview

Although numerous studies of cigarettes containing VLN tobacco have been published (see Section 2.1), only a handful provide meaningful evaluations of the efficacy of these cigarettes as a smoking cessation tool. Data are available in a clinical study report from one phase II clinical study and in publication format from 5 others. Data from these studies is discussed below. Carbon Monoxide results are discussed in the summary of safety information (Section 2.3).

2.2.2. Efficacy Results from Vector-201 Phase II Clinical Trial

The efficacy of cigarettes manufactured with VLN tobacco was systematically evaluated in one IND clinical trial: Vector-201, A Prospective, Double-blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of Quest Alone and in Combination with Nicotine Replacement Therapy as a Smoking

Cessation Aid.[26,27] A clinical study report for this clinical trial was previously submitted to FDA as part of a Vector Tobacco, Inc. End-of-Phase II Meeting package on June 12, 2006 for IND 69,185.

As summarized in Sections 2.1.1.1 and 2.3.1.2, a total of 346 healthy smokers who were motivated to quit smoking were enrolled in this double-blind trial and followed over 8 months, and 85 subjects completed the study. Subjects were randomized to one of the following groups:

- Group 1: Quest 1®, Quest 2®, and Quest 3® plus NRT patch
- Group 2: Quest 1®, Quest 2®, and Quest 3® plus placebo patch
- Group 3: Conventional active control cigarettes plus NRT patch

A diagram showing the study design is provided in Figure 2-4. During the first 6 weeks (Week 1 to Week 6), subjects in Groups 1 and 2 smoked *ad libitum* for 2 weeks at each nicotine level beginning with Quest 1®, then proceeding to Quest 2®, and finally to Quest 3®. Subjects in Group 3 received a blinded control cigarette with a conventional nicotine content. At Week 5, Quest® use was supplemented in Group 1 with the addition of a transdermal nicotine patch (21 mg), while subjects in Groups 2 and 3 added a placebo patch for 1 week. Visit 5 (end of Week 6/beginning of Week 7) was the "quit date".

In Group 1, during weeks 7 to 10, subjects continued to receive a 21 mg transdermal nicotine patch for an additional 4 weeks, followed by a 14 mg nicotine patch for 2 weeks (Weeks 11 and 12), and 7 mg nicotine patch for 2 weeks (Weeks 13 and 14), and a placebo patch for 2 weeks (Weeks 15 and 16).

In Group 2, during Weeks 7 to 16, subjects continued to receive a placebo patch.

In Group 3, subjects continued to use NRT on the standard of care schedule: i.e., subjects received a 21 mg transdermal nicotine patch for 6 weeks (Weeks 7 to 12), followed by a 14 mg nicotine patch for 2 weeks (Weeks 13 and 14), and a 7 mg nicotine patch for 2 weeks (Weeks 15 and 16).

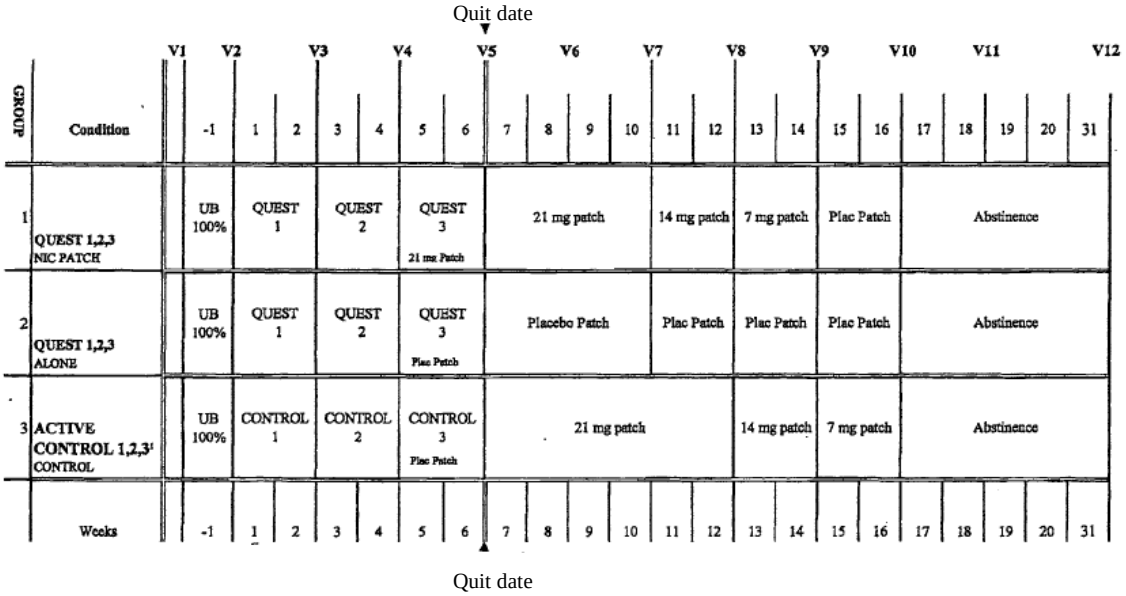


Figure 2-4 Design of Study Vector-201

2.2.2.1. Primary Efficacy Endpoint in Study Vector-201: 4 Week Abstinence Rates

The primary efficacy endpoint was 4 weeks of continuous abstinence from smoking. The protocol required that subjects quit smoking at Visit 7 (Week 7), and 4-week abstinence was determined at Visit 7 (Week 11). Abstinence was determined by self-report and verified by exhaled CO less than 10 ppm. If at least one of these 2 conditions was not met, the subject was classified as having failed to meet the primary endpoint.

The primary analysis was done on the intent-to-treat (ITT) population using all available data. Subsequently, the ITT population was analyzed using statistical methodology to impute missing values. All analysis methods and results are provided in the clinical study report;[27] a summary is provided in Table 2-3, below.

Table 2-3 Summary of Four Week Abstinence Results by Method of Imputation from Study Vector-201

Analysis/Imputation Method	Group 1 Proportion (p-value[a])	Group 2 Proportion (p-value[a])	Group 3 Proportion
Based on Available Data (ITT Population)[b]	43.2%	24.1%	26.3%
Primary Analysis: Using Treatment Failure (ITT Population)	32.8% (0.0499)	16.4% (0.8922)	21.9%
Using Treatment Failure for Subjects who Discontinued Due to Lack of Efficacy (Excluding Subjects Whose Abstinence Status Could Not be Determined)	41.8% (0.0169)	22.9% (0.7455)	26.0%
Using Multiple Imputation (ITT Population)	44.0% (0.0297)	29.3% (0.4567)	28.6%
Using Treatment Failure (Per Protocol Population)	45.5% (0.0213)	20.0% (0.9017)	27.8%

[a] One-sided Fisher's exact test for 4-week abstinence proportions compared with Group 3, at the 0.05 and 0.25 levels using Bonferroni adjustment.
[b] For the available population (ITT), statistical significance was not computed due to diminished sample size.
Source: CSR for Study Vector-201, in-text Table 12, Four-Week Abstinence Proportions by Method of Imputation

For the available population (ITT), statistical analysis was not computed due to the diminished sample size. Using all other statistical analysis methods, this study showed that Group 1 was statistically different from Group 3, under a 0.05 significance level. Using the Bonferroni adjusted value (i.e., 0.025), statistical significance was maintained in the ITT Treatment Failure analysis for subjects who discontinued due to lack of efficacy. Irrespective of the analysis, no significant differences were noted when comparing Group 2 to Group 3.

2.2.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints included quit rates at 3 and 6 months following treatment termination, corrected exhaled CO levels and change from baseline, Minnesota Nicotine Withdrawal Scale results, cigarette evaluation scale questionnaire results, sensory questionnaire results, and Fagerström Test of Nicotine Dependence results. Carbon Monoxide results are summarized below with safety data, in Section 2.3.1.2.5; other secondary efficacy variables are summarized below within this section.

2.2.2.2.1. Abstinence Rates at 3 and 6 Months Following Treatment Termination

Abstinence at 3 or 6 months was defined as no cigarettes smoked from Week 7 to Month 3 (or Month 6) and corrected exhaled CO < 10 ppm from Visit 6 to Visit 11 (or Visit 12). Abstinence rates were analyzed using several methods of imputation. A summary of results is provided in Table 2-4, below.

Table 2-4 3-Month and 6-Month Abstinence Proportions by Method of Imputation in Study Vector-201

Analysis/Imputation Method	Group 1 Proportion	Group 2 Proportion	Group 3 Proportion
3-Month Abstinence Rates			
Treatment Failure (ITT Population)[b]	20/116 (17.2%)	12/116 (10.3%)	17/114 (14.9%)
Treatment Failure Due to Lack of Efficacy (Excluding Subjects Whose Abstinence Status Could Not be Determined)	20/89 (22.5%)	12/81 (14.8%)	17/92 (18.5%)
Treatment Failure (Per Protocol Population)	17/65 (26/2%)	8/63 (12.7%)	16/76 (21.1%)
6-Month Abstinence Rates			
Treatment Failure (ITT Population)[b]	13/116 (11.2%)	9/116 (7.8%)	11/114 (9.6%)
Treatment Failure Due to Lack of Efficacy (Excluding Subjects Whose Abstinence Status Could Not be Determined)	13/88 (14.8%)	9/80 (11.3%)	11/90 (12.2%)
Treatment Failure (Per Protocol Population)	10/60 (16.7%)	5/62 (8.1%)	10/72 (13.9%)

Source: CSR for Study Vector-201, Appendix A, Tables S8, S13, and S16.

No significant differences in 3-month or 6-month abstinence rates were observed when comparing either Group 1 or Group 2 to Group 3 for any of the imputation methods.

2.2.2.2.2. Minnesota Nicotine Withdrawal Scale Results

In Study Vector-201, subjects completed the Minnesota Nicotine Withdrawal Scale at each visit. Subjects were asked to rate the test “for the period of today”:

Each question was analyzed individually for group differences (Group 1 or Group 2 compared to Group 3) by the two-sided Jonckheere-Terpstra test, and the change from baseline was analyzed using the Wilcoxon rank-sum test. All results are available in the

clinical study report for this study, Appendix A, Tables S22.1 to S22.8 and Tables S23.1 to S23.8.[27] Statistically significant results are summarized briefly by item below:

1. Depressed mood/sad:
   Group differences: Subjects in Group 1 selected slight or mild depressed mood/sad more frequently than subjects in Group 3 at Visit 5 ($p = 0.0223$).
   Change from Baseline: None
2. Insomnia/sleep problems, awakening at night:
   Group differences: A higher percentage of subjects in Group 1 indicated sleep problems compared to Group 3 at Visit 5 ($p = 0.0002$).
   Change from Baseline: At Visit 5, the mean change in Group 1 was 0.5 ± 1.4, while the mean change in Group 3 was -0.1 ± 1.1 ($p = 0.0004$).
3. Angry/irritable/frustrated:
   Group differences: At Visit 5, a higher proportion of subjects in Group 1 reported being angry/irritable/frustrated than in Group 3 ($p = 0.004$).
   Change from Baseline: At Visit 4, the mean change in Group 2 was 0.5 ± 1.2, while the mean change in Group 3 was 0.1 ± 1.2 ($p = 0.0214$).
4. Anxious/nervous:
   Group differences: At Visit 5, a higher proportion of subjects in Group 1 reported being anxious/nervous than in Group 3 ($p = 0.005$).
   Change from Baseline: None
5. Difficulty concentrating:
   Group differences: At Visits 4, 5, and 6, more subjects in Group 1 reported difficulty concentrating than subjects in Group 3 ($p = 0.0189$, $p = 0.0044$, $p = 0.0372$, respectively at Visits 4, 5, and 6).
   Change from Baseline: None
6. Restless/impatient:
   Group differences: None
   Change from Baseline: None
7. Increased appetite/hungry/weight problem:
   Group differences: At Visit 5, more subjects in Group 1 indicated increased appetite/hungry/weight problems than in Group 3 ($p = 0.0332$).
   Change from Baseline: At Visit 5, the mean change in Group 1 was 0.6 ± 1.1, while the mean change in Group 3 was 0.3 ± 1.2 ($p = 0.0472$).
   At Visit 9, the mean change in Group 2 was 0.4 ± 1.4, while the mean change in Group 3 was 1.0 ± 1.4 ($p = 0.0328$).
   At Visit 10, the mean change in Group 2 was 0.3 ± 1.5, while the mean change in Group 3 was 1.0 ± 1.2 ($p = 0.0176$).
8. Desire or craving to smoke
   Group differences: At Visit 3, more subjects in Groups 1 and 2 experienced a desire or craving to smoke or a more intense desire or craving to smoke than subjects in Group 3 (Group 1 vs Group 3 $p = 0.0428$; Group 2 vs Group 3 $p = 0.0105$).
   At Visit 12, subjects in Group 1 experienced a desire or craving to smoke or a more intense desire or craving to smoke than subjects in Group 3 ($p= 0.0466$).

Change from Baseline: At Visit 12, the mean change from Baseline in Group 1 was -1.3 ±1.3, while the mean change from Baseline in Group 3 was -0.5 ± 1.5 ($p = 0.0279$).

2.2.2.2.3. Cigarette Evaluation Scale Questionnaire Results

Subjects completed the Cigarette Evaluation Scale at Visits 1 to 5. A total of 11 questions were asked, which were categorized into 5 component scales (satisfaction, psychological reward, nausea/dizziness, enjoy sensation, and reduced craving), and subjects were asked to rate the last cigarette smoked. Replies were tabulated and analyzed using the Jonckheere-Terpstra test and changes from baseline were calculated and analyzed using the Wilcoxon rank-sum test. All results are available in the clinical study report for this study, Appendix A, Tables S24.6 to S24.17 and Tables S25.6 to S25.17.[27]

In summary, satisfaction scores at Visit 5 (after Groups 1 and 2 smoked Quest 3® for 2 weeks) were lower in Groups 1 and 2 than in Group 3. Group 1 satisfaction scores were also lower than Group 3 at Visit 4 (after smoking Quest 2® for 2 weeks). There were no significant differences in psychological reward at any visit date. Results for scores of nausea/dizziness indicated that Groups 1 and 2 experienced less nausea/dizziness compared to Group 3 at Visit 3 (after smoking Quest 1®) and Group 2 also experience less nausea than Group 3 at Visit 4 (after smoking Quest 2®). Not surprisingly, both Groups 1 and 2 experienced less enjoyment of the cigarette sensation than Group 3 at Visit 5 (after smoking Quest 3®). Finally, Groups 1 and 2 reported greater reductions in craving than Group 3 at Visit 2 and lesser reductions in craving than Group 3 at Visit 5. In terms of change from baseline scores, Group 1 and Group 2 reported lower reductions in craving compared to Group 3 at Visits 3, 4, and 5.

2.2.2.2.4. Sensory Questionnaire Results

Subjects completed the Sensory Questionnaire at Visits 1 through 5. A total of 9 questions were asked regarding the sensations subjects experienced from puffs of the last study cigarette smoked. Replies were tabulated and analyzed using the Jonchkeere-Terpstra test and change from baseline differences were calculated and analyzed using the Wilcoxon rank-sum test. All results are available in the clinical study report for this study, Appendix A, Tables S26.1 to S26.9 and Tables S27.1 to S27.9.[27]

In summary, results showed that subjects liked smoking Quest 3® cigarettes considerably less and indicated that the puffs were significantly less satisfying than subjects smoking conventional cigarettes. Subjects rated all levels of Quest® cigarettes as having significantly

lower nicotine content than subjects smoking conventional cigarettes. Subject rated the puffs of Quest 2® and Quest 3® as considerably more different than their usual brand compared to subjects using conventional cigarettes at the same study visits.

2.2.2.2.5. Fagerström Test of Nicotine Dependence Results

The Fagerström Test for Nicotine Dependence was completed at Visits 1 to 5. Subjects answered 6 questions to calculate their level of nicotine dependence. Replies were tabulated and analyzed using the Jonchkeere-Terpstra test and change from baseline differences were calculated and analyzed using the Wilcoxon rank-sum test. All results are available in the clinical study report for this study, Appendix A, Tables S28 and S29.[27] No significant differences involving the individual questions were observed when comparing Group 1 with Group 3 or Group 2 with Group 3.

2.2.3. Efficacy Results from Other Published Clinical Trials

2.2.3.1. Efficacy Results from Smoking Cessation Trials

Most recently, Hatsukami *et al*[28] published a study comparing the effects of smoking Quest 3® (nicotine yield ≤0.05 mg) cigarettes or Quest 2® (nicotine yield 0.30 mg) cigarettes to the use of 4 mg nicotine lozenges for 6 weeks. Efficacy outcome measures included number of cigarettes smoked, results of the Minnesota Nicotine Withdrawal Scale, results of the Fagerström Test for Nicotine Dependence, and perceived health risk.

As shown in Figure 2-5, among subjects in the Quest 2® group, the number of cigarettes smoked per day increased significantly ($p=0.0127$ to $p<0.0001$) at each of the first 5 weeks of treatment compared to the number of usual brand cigarettes they were smoking at baseline. This is in contrast to the significantly decreased ($p=0.0043$ to $p<0.0001$) number of cigarettes smoked per day (relative to baseline) observed after Week 2 in those assigned the VLN Quest 3® cigarettes. At week 6, the mean number of 0.3 mg cigarettes smoked per day was significantly greater than that of Quest 3® cigarettes smoked ($t = 4.73$, $p<0.0001$).

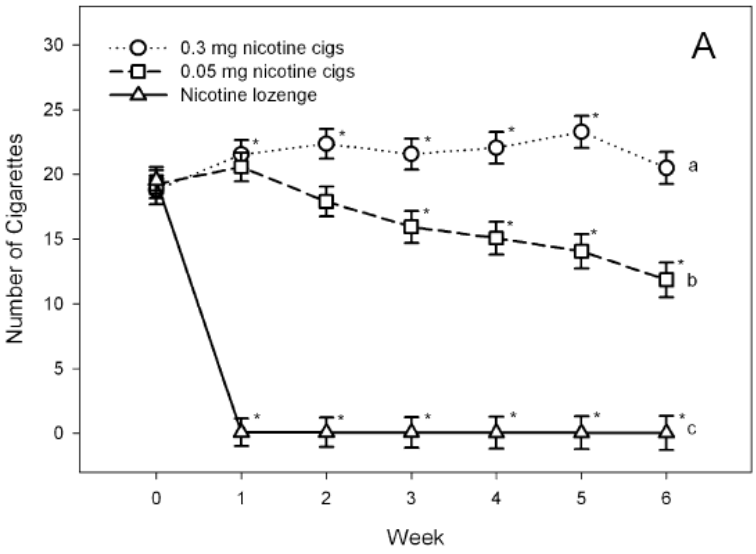


Figure 2-5 Number of Cigarettes Smoked During Treatment Period Published by Hatsukami *et al*, 2010

Four-week continuous abstinence rates and point abstinence rates for subjects who used nicotine lozenges but no cigarettes and for subjects who used no lozenges or cigarettes are presented in Table 2-5. In this analysis, dropouts were considered treatment failures. For abstinence from cigarettes, 4-week continuous abstinence rates were highest in those receiving VLN Quest 3® cigarettes and lowest in those receiving Quest 2® cigarettes with an intermediate nicotine content, with the difference across the three groups nearly significant. Point prevalence abstinence rates followed a similar pattern, with significant differences between groups observed in abstinence rates verified by both CO and urinary cotinine concentrations. CO verified point prevalence abstinence rates were statistically significant only at the week 6 posttreatment visit and nearly significant at the Week 2 and 4 post-treatment visits.

Table 2-5 Smoking Abstinence Rates Published by Hatsukami *et al*, 2010

	Treatments						
	0.3 mg nicotine cigarettes (n = 52)		*Nicotine lozenges (n = 60)*		*0.05 mg nicotine cigarettes (n = 53)*		
	# abstinent	*%*	*# abstinent*	*%*	*# abstinent*	*%*	*P-value*
Continuous abstinence							
[1]CO verified	11	21.2	21	35.0	23	43.4	0.0508
[2]CO and cotinine verified	7	13.5	11	18.3	16	30.2	0.0913
CO verified point prevalence abstinence							
Follow-up week							
1	18	34.6	25	41.7	22	41.5	0.6954
2	17	32.7	25	41.7	29	54.7	0.0719
4	12	23.1	22	36.7	23	43.4	0.0829
6	12	23.1[a]	22	36.7[a,b]	25	47.2[b]	0.0357
CO and cotinine verified point prevalence abstinence							
Follow-up week							
2	12	23.1[a]	16	26.7[a]	24	45.3[b]	0.0298
4	8	15.4[a]	13	21.7[a]	21	39.6[b]	0.0120
6	7	13.5[a]	12	20.0[a,b]	19	35.9[b]	0.0192

[1]Carbon monoxide (CO) verified abstinence represents abstinence from cigarettes but usage of nicotine lozenge is allowed. [2]CO and cotinine verified represents abstinence from all nicotine-containing products, including nicotine lozenge.

FTND score and perceived risk for addiction score during treatment in the Hatsukami study both showed significant treatment ($p = 0.0124$ and <0.0001, respectively), time (p-values <0.0001) and treatment x time interaction (p-values <0.0001) effects. Significant decreases in FTND and perceived risk of addiction scores were observed for the ≤0.05 mg cigarette and nicotine lozenge groups (all p-values < 0.001) at week 6 compared to baseline. For the Quest 2®cigarette group, perceived risk of addiction decreased significantly between baseline and week 6 ($p < 0.0001$); however, FTND score did not ($p = 0.4810$). At Week 6, significant differences between groups were found in FTND (p-values 0.0315–<0.0001) and perceived risk of addiction (p-values 0.0456–<0.0001), with the highest levels observed in those assigned to Quest 2® cigarettes and the lowest in those assigned to nicotine lozenge.

Upon cessation of usual brand cigarettes and switching to the study products, there was a significant increase in withdrawal symptoms (p-values 0.0188 to <0.0001) and no significant change in craving in all three treatment groups. Increase in nicotine withdrawal scores upon cessation of usual brand cigarettes (week 1 compared to baseline) was significantly smaller for the group assigned to VLN Quest 3® cigarettes compared to the group assigned nicotine lozenges ($p = 0.0253$) and nearly significantly smaller ($p = 0.0917$) than for those assigned to Quest 2® cigarettes. Upon cessation of the product (Week 7 compared to Week 6), significant increase in craving ($p = 0.0079$) and withdrawal symptoms ($p < 0.0001$) were observed for the Quest 2® cigarette group. In those discontinuing VLN Quest 3® cigarettes, craving increased significantly ($p = 0.0138$), but withdrawal symptoms did not ($p = 0.2297$). In those discontinuing nicotine lozenge, neither craving ($p = 0.0814$) nor withdrawal

symptoms (p = 0.4856) were increased significantly. Change in withdrawal symptoms was significantly lower in those discontinuing VLN Quest 3® cigarettes (p = 0.0006) or nicotine lozenges (p = 0.0002) compared to those discontinuing Quest 2® mg cigarettes, with no significant differences in craving observed between groups.

Rezaishiraz *et al*[32] measured smoking cessation efficacy in 98 adult smokers in an unblinded clinical study (see also Section 2.1.1.3). Before the quit date, half of the smokers received Quest 3® (nicotine yield ≤0.05 mg) and a 21 mg nicotine patch for 2 weeks and the other half received only Quest 1® (nicotine yield 0.6 mg) alone. After the quit date, all smokers received nicotine patch therapy for up to 8 weeks (4 weeks of 21-mg patches, 2 weeks of 14-mg patches, and 2 weeks of 7-mg patches). All subjects also participated in three 1-hour group cessation classes, plus individual counseling on subsequent clinic visits (each individual counseling session lasting about 20 minutes). Outcome measures included self-reported smoking abstinence rates at 3 and 6 months, self-reports of cigarette cravings, and nicotine withdrawal symptoms.

Self-reported smoking abstinence rates at 3 and 6 months are shown in Figure 2-6. The abstinence rate was higher in Group 1 at both 3 and 6 months (43% vs. 34% and 28% vs. 21%, respectively), although the differences between groups were not statistically significant. Subjects who reported quitting at 3 and 6 months had statistically lower average craving scores during the 2-week post cessation period (p=0.05 at both time points).

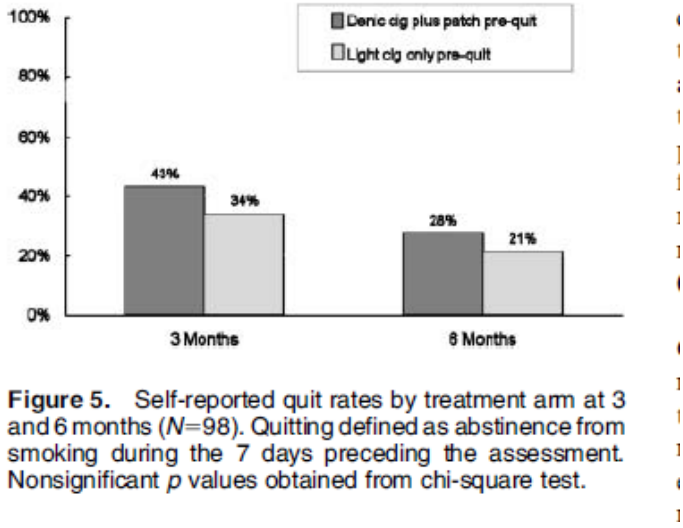
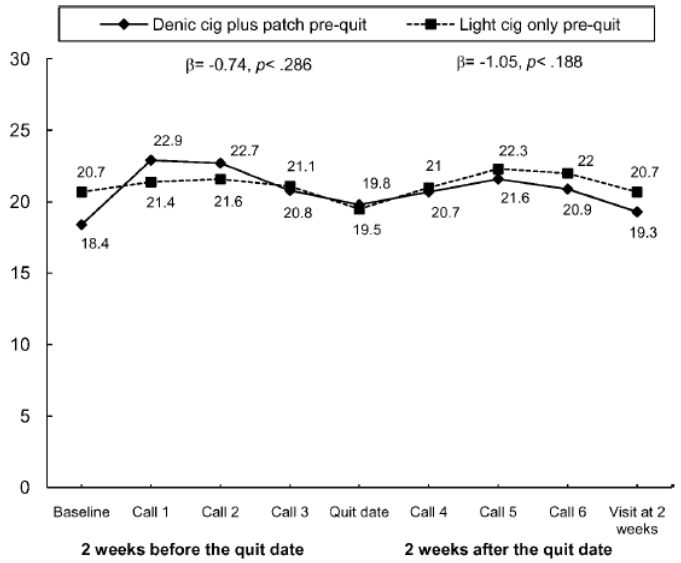


Figure 5. Self-reported quit rates by treatment arm at 3 and 6 months (*N*=98). Quitting defined as abstinence from smoking during the 7 days preceding the assessment. Nonsignificant *p* values obtained from chi-square test.

Figure 2-6 Smoking Abstinence Rates Published by Rezaishiraz *et al*, 2007.

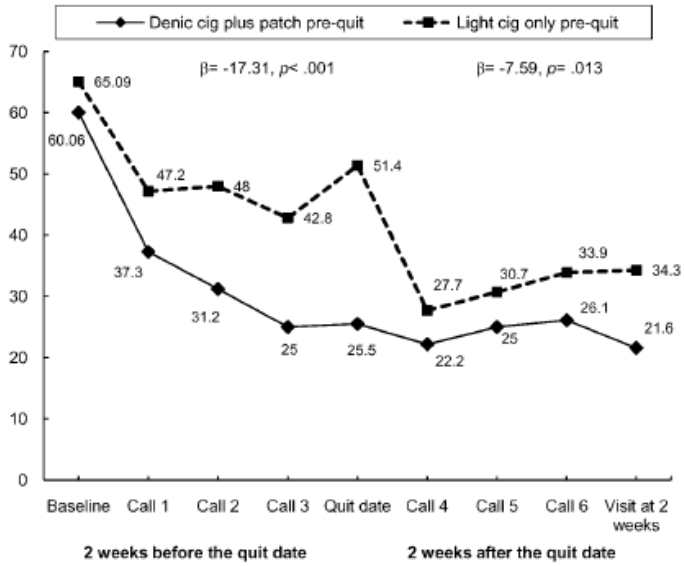
A comparison of the 2 study groups with regard to withdrawal symptoms is shown in Figure 2-7. The groups were similar in regard to the severity of withdrawal symptoms during the 2 weeks before and after the quit date.



Score (along vertical axis) = sum of scores for anger + nervousness+distractibility+impatience+appetite+insomnia+depression+desire to smoke. Beta and p values obtained from mixed-model analysis (adjusted for baseline values).

Figure 2-7 Withdrawal Symptoms Published by Rezaishiraz *et al*, 2007

Figure 2-8 shows the difference between the 2 study groups in regard to the combined craving score. Group 1, which used VLN cigarettes and nicotine patch before quitting, had lower combined craving score during the 2 weeks before ($p = 0.001$) and after ($p = 0.013$) the quit date.



Score (along vertical axis) = severity of craving x frequency of craving. Beta and p values obtained from mixed model analysis

Figure 2-8 Craving Scores Published by Rezaishiraz *et al*, 2007

Rose *et al*[33] conducted a small, unpublished study comparing Quest 3® with NRT, Quest® alone, and Quest 1®, Quest 2®, and Quest 3® in a step-down protocol. During the first week of the study, subjects smoked only their usual brand (UB) of cigarette. From Weeks 2 through 5, subjects gradually reduced the amount of UB and increased the amount of Quest 3® smoked (Groups 1 and 2), or smoked cigarettes with decreasing amounts of nicotine per cigarette (Group 3). During Weeks 6 through 11, subjects were to smoke Quest 3® exclusively. During Week 12 through Week 14, subjects were gradually weaned off Quest 3®, and subjects using NRT were weaned off of nicotine replacement. In Group 2, 33% of subjects achieved 4-week continuous abstinence. Group 3 attained a 13% abstinence rate. In Group 1 no subjects achieved abstinence. No further data are available from this study.

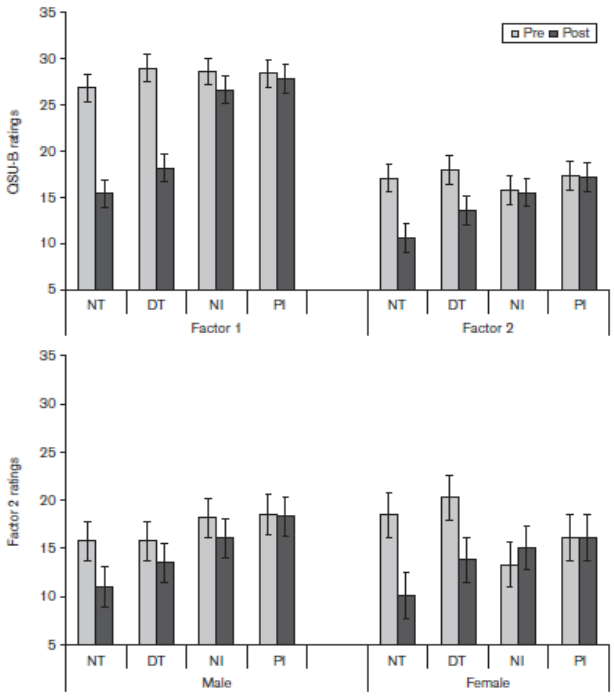
2.2.3.2. Efficacy Results from Human Studies Conducted in a Laboratory

Several studies examined the effect of Quest 3® cigarettes on withdrawal symptoms and craving in a laboratory setting.

As described in Section 2.1.2.1, Barrett[34] examined the effects of nicotine in the absence of tobacco (through nicotine inhalers and placebo inhalers), tobacco with very low nicotine (Quest 3® cigarettes, nicotine yield ≤0.05 mg), and nicotine-containing tobacco (Quest 1® cigarettes, nicotine yield 0.60 mg) on withdrawal symptoms and other subjective measures. Briefly, 22 smokers self-administered inhaled nicotine, inhaled placebo, Quest 1® cigarettes, or VLN Quest 3® cigarettes over 4 laboratory sessions. After smoking or inhaling nicotine or placebo, subjects completed The Questionnaire of Smoking Urges-Brief version; a 10-item,

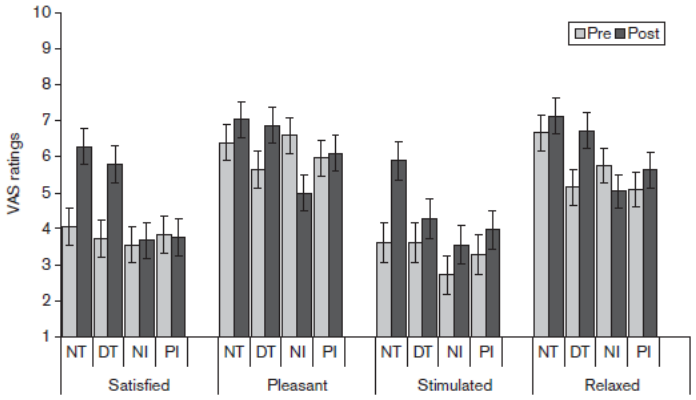
self-report measure that assesses cravings using two factors: Factor 1 – intention to smoke, and Factor 2 – withdrawal/negative affect relief. Results for men and women combined for both factors and results for men vs. women for Factor 2 only are provided in Figure 2-9, below. Results show that both Quest 1® and VLN Quest 3® cigarettes were effective at reducing intention to smoke and withdrawal/negative affect and that the effect of VLN tobacco was more pronounced in women than in men.

Figure 2-9 Effect of Nicotine on Withdrawal Symptoms Published by Barrett 2010



NT=nicotine tobacco, DT-denicotinized tobacco, NI-inhaled nicotine, PI-inhaled placebo, Factor 1= intention to smoke, Factor 2= withdrawal/negative affect relief

Barrett also evaluated the effects of nicotine on mood. Subjects rated themselves on scales for “satisfied”, “pleasant”, “stimulated” and “relaxed” after each experimental condition. Results are shown in Figure 2-10, below.



Mean (±SE) ratings of 'satisfied','pleasant','stimulated' and 'relaxed' before and after each experimental challenge. Nicotine-containing tobacco (NT) and denicotinized tobacco (DT) were rated as more satisfying than each of the inhalers; nicotine inhalers (NI) as being less pleasant than each of the other products, NT as producing more stimulation than each of the other products, and ratings of 'relaxed' were significantly greater after NT and DT administration relative to NI administration. PI, placebo inhalers; VAS, Visual Analog Scale.

Figure 2-10 Effect of Nicotine on Mood Published by Barrett 2010

As shown in this figure, smoking either VLN Quest 3® or Quest 1® tobacco was more satisfying and more relaxing than inhaling nicotine or placebo. In the figure, smoking VLN Quest 3® appears to have produced similar effects of satisfaction, pleasantness and relaxation, but not stimulation compared to Quest 1®, although this direct comparison was not presented in the Barrett 2010 publication.

As described in Section 2.1.2.2, Perkins *et al*[35] compared the effects of Quest 1® (nicotine yield 0.6 mg), Quest 3® (nicotine yield ≤0.05 mg), or no cigarettes on negative affect relief after imposing a variety of stress-induced situations on 104 adult smokers. Results of effects on mood and affect are shown graphically in Figure 2-11, below. Quest 1® or VLN Quest 3® cigarettes enhanced both measures of positive affect during abstinence, but had minimal effects during other mood-induction procedures. Analysis of variance results for a questionnaire on smoking urges and the Minnesota Nicotine Withdrawal Scale were similar to those for affect. Relief of craving by smoking was generally similar across mood induction procedures, and the nicotine content of the cigarettes had little influence on these responses to smoking.

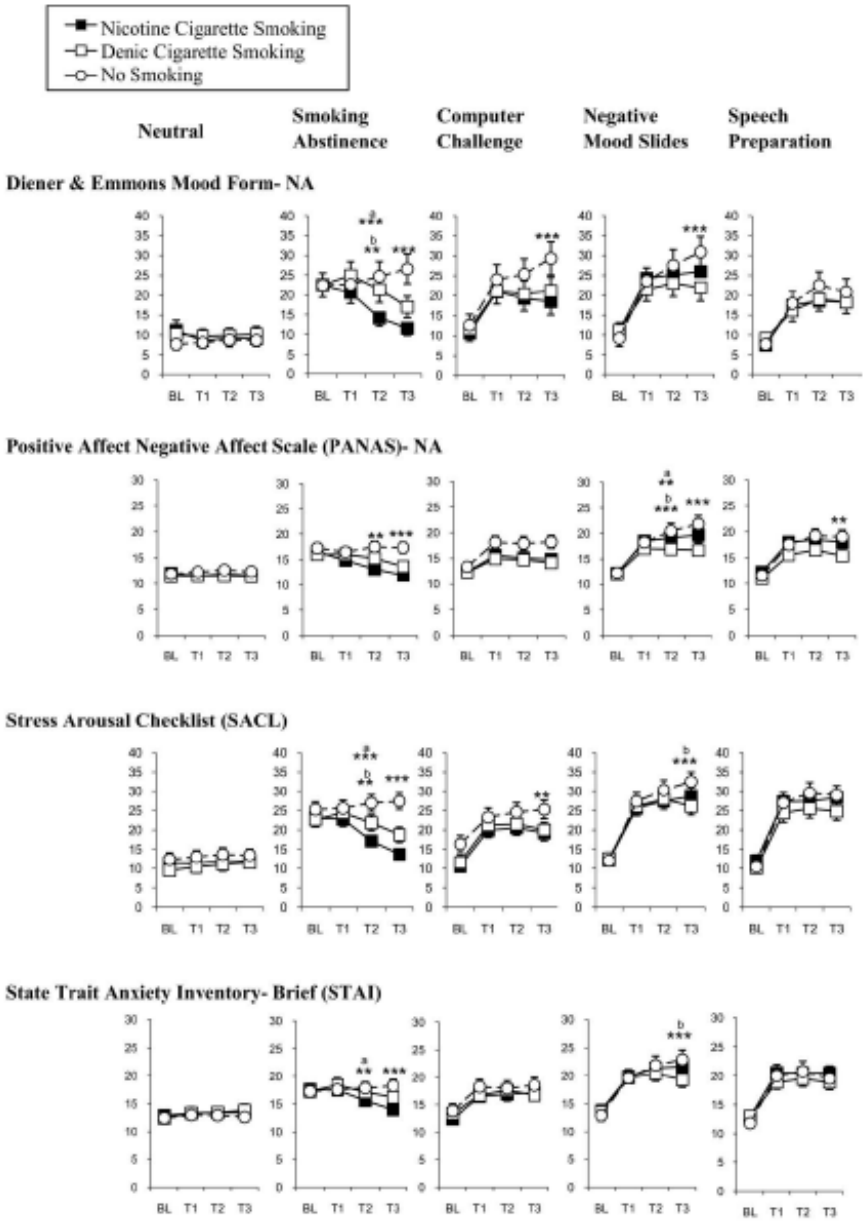


Figure 2-11 Effect of Smoking on Mood Published by Perkins *et al* 2010

2.2.4. Evaluations of Compensatory Smoking Behavior

One concern with using a nicotine reduction strategy for smoking cessation has been that smokers would compensate for reduced nicotine levels by smoking more cigarettes or smoking cigarettes more intensely. In addition to the work of Hatsukami *et al*[28] summarized in Section 2.2.3.1 above, which found no evidence of compensatory smoking when subjects smoked Quest 3® cigarettes, several other researchers have addressed the question of compensatory smoking when switching to Quest 3® or other VLN cigarettes.

Donny *et al*[39] (see also Section 2.1.2.6) evaluated the risk of compensatory smoking in an 11-day, controlled laboratory study. Thirty adult regular smokers were assigned randomly to either Quest 1® cigarettes (nicotine yield 0.6 mg), VLN Quest 3® cigarettes (nicotine yield ≤0.05 mg), or no smoking. The number of cigarettes smoked per day is shown in Figure 2-12. Subjects in the VLN Quest 3® group smoked fewer cigarettes (a decrease of 3.8 cigarettes/day compared to baseline vs. an increase of 2.1 cigarettes/day in the Quest 1® cigarette group), took fewer puffs per cigarette (8.8 vs. 11.5, p = 0.10), tended to leave larger butts (0.54 grams vs. 0.45 grams, p = 0.11), and had significantly lower expired CO levels. Subjects smoking VLN Quest 3® cigarettes also demonstrated a 31% decline in the number of puffs earned on a progressive ratio, a measure of the motivation to smoke, during the study. The study saw no evidence of compensatory smoking in the VLN Quest 3® cigarette group.

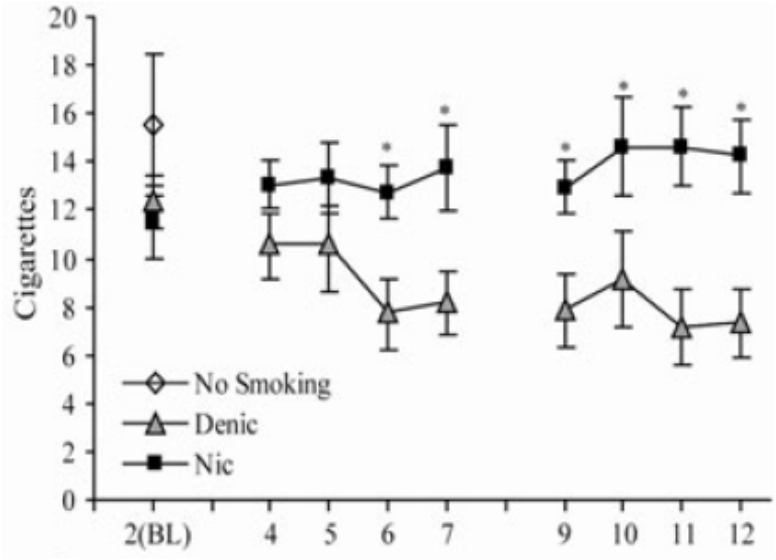


Figure 2-12 Mean (± SEM) Total Number of Cigarettes Smoked during Each Unrestricted Smoking Day Published by Donny *et al* 2007

Finally, Strasser *et al*[37,38] explored the concept of compensatory smoking in two publications (see also Sections 2.1.2.4 and 2.1.2.5). Fifty subjects participated in a single laboratory smoking session during which one cigarette of the subject's Own brand, one Quest 1® cigarette, one Quest 2® cigarette, and one Quest 3® cigarette were smoked using a smoking topography machine in random order at 30-minute intervals. Selected results, not including Own brand group data are shown in Figure 2-13. Mean total puff volumes were 832.0 ml, 540.3 ml, 518.1 ml, and 570.5 ml in the Own brand, Quest 1®, Quest 2®, and Quest 3® cigarette groups, respectively. Mean number of puffs per cigarette were 14.3, 9.8, 9.9, and 10.0 in the Own brand, Quest 1®, Quest 2®, and Quest 3® cigarette groups, respectively.

In summary, although the authors concluded that this study provides evidence for the potential of compensatory smoking with low nicotine cigarettes, all Quest® brand cigarette groups were associated with lower mean total puff volume and fewer mean number of puffs per cigarette than subject's Own brand. Within the Quest® groups, lower nicotine content was associated with higher total puff volume and mean number of puffs per cigarette.

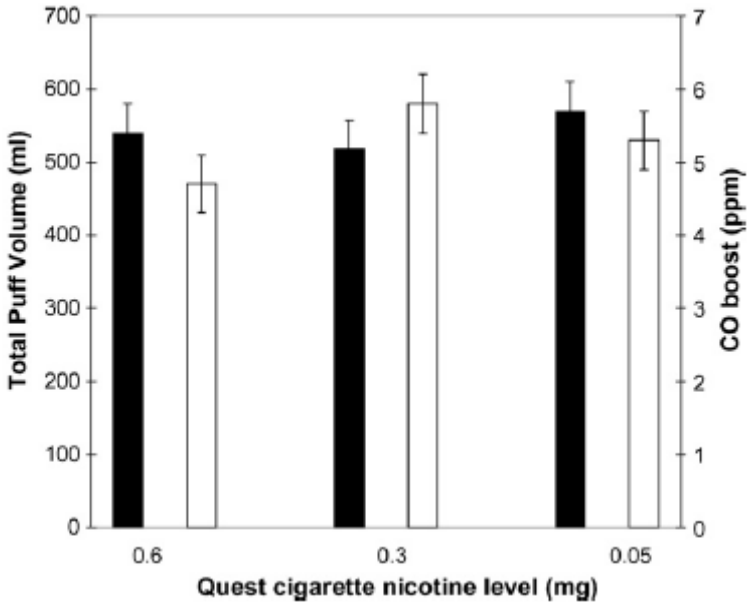


Figure 2-13 Smoking Topography Results for Quest® Cigarette Groups Published by Strasser *et al* 2007

In a separate publication, Strasser also measured tar staining of cigarette filters using digital imaging to estimate total puff volume after cigarette smoking. Again, 50 subjects participated in a single laboratory smoking cession total puff volume during which one cigarette of the subject's Own brand, one Quest 1® cigarette, one Quest 2® cigarette, and one Quest 3® cigarette were smoked in random order at 30-minute intervals. Mean total puff volumes were 827.1 ml, 540.6 ml, 518.1 ml, and 570.5 ml in the Own brand, Quest 1®, Quest 2®, and Quest 3® cigarette groups, respectively. Thus, results were similar to the first Strasser publication discussed above, i.e., all Quest® brand cigarette groups were associated with lower mean total puff volume than subject's Own brand, and within the Quest® groups, lower nicotine content was associated with higher total puff volume.

2.2.5. Gender Differences in Smoking Behaviors and Response to Nicotine

There is evidence that smoking behavior is influenced by the gender of the subject.[56] Previous research has found that the smoking behavior of women is influenced less by

nicotine and more by other factors. Although men and women do not differ in the physiological, cognitive, or psychomotor effects of nicotine, they may differ in their sensitivity to nicotine's reinforcing and rewarding effects.[57] This may be why women have more difficulty in quitting smoking in general.[56,58,59,60,61] Improving quit rates in women is an urgent public health need, as smoking consistently produces greater risk of the primary smoking-related illnesses in women than in men, including lung cancer[62], myocardial infarction[63], and deterioration of lung function due to smoking.[64] Furthermore, smoking in women induces health risks related to fetal development.

There is evidence that the use of NRT has less influence on long-term quit rates in women versus men.[56] West *et al*[65] found that women tended to do worse than men after use of NRT gum, patch, or nasal spray, but better than men when using an NRT inhaler as measured by 15-week abstinence rates in an uncontrolled open-label trial. Therefore, some formulations of NRT may be more effective in women than in men. There is also evidence that smoking cessation counseling may be more effective in women than in men.[59]

One approach in smoking cessation therapies is to provide substitutes that simulate the sensory effects of smoking. Standard counseling recommends strategies such as sucking on a straw or consuming carrot sticks or cinnamon sticks as substitutes for the motor effects of smoking.[56] However, these methods mimic only the motor effects of smoking, but not other sensory effects such as olfactory and taste stimuli and sensations to the throat. VLN cigarettes match almost all of the effects of smoking other than nicotine intake and therefore, may be particularly useful as a smoking cessation tool in women. This hypothesis is supported by Barrett *et al*[34] (see also Sections 2.1.2.1 and 2.2.3.2), who found that women experienced greater relief of withdrawal-related cravings than men after smoking Quest® cigarettes.

Because of possible gender differences in smoking cessation rates, the first clinical trial of X-22 Smoking Cessation Product will balance the gender of subjects across treatment groups. An exploratory objective of this study will be to compare the influence of gender on smoking cessation rates.

2.2.6. Efficacy Conclusions from Clinical Trials

Previous studies of VLN cigarettes for smoking cessation indicate that a product that delivers the sensory and behavioral cues associated with cigarette use but does not deliver a satisfying amount of nicotine breaks the association of those cues with the contingent delivery of nicotine reinforcement and promotes extinction of smoke cues. Studies described above in Sections 2.2.2.1 and 2.2.3.1 have evaluated the use of VLN cigarettes for periods of 2 to

6 weeks and used alone or in combination with NRT. It appears that short term use for 2 weeks was less effective than longer term use over 6 weeks.[32,28] Although some studies have found significant efficacy with concomitant use of NRT, especially when the NRT was begun at least 2 weeks before the quit date, other studies have found that VLN cigarettes alone are quite effective, with abstinence rates up to 43%.[28,26] Smoking VLN cigarettes for at least 6 weeks alone also seems to be more effective that using a step-down approach (e.g., 2 weeks of 0.6 mg nicotine yield cigarettes, followed by 2 weeks of 0.3 mg nicotine yield cigarettes, followed by 2 weeks of ≤0.05 mg nicotine yield cigarettes).[26,27,28]

Although there has been concern that when smokers switch from their usual brand to reduced nicotine cigarettes, compensatory increases in smoking may occur, when switching to Quest 3® ≤0.05 mg nicotine yield cigarettes compensatory smoking has not been substantiated. While short term studies have been inconclusive[37,38,39], several long-term studies have found that smokers who switch to VLN cigarettes voluntarily decrease the number of cigarettes they smoke over time.[28,21]

Finally, numerous studies have found that acute withdrawal effects and cravings after short term smoking abstinence, as evaluated in a laboratory setting, are decreased as effectively or nearly as effectively with VLN cigarettes as with regular cigarettes.[34,35,**Error! Reference source not found.**,15,14,19,12] Furthermore, smoking VLN cigarettes was more effective than inhaling nicotine at relieving cravings and other withdrawal symptoms.[34] During a longer term study of smoking cessation, smoking VLN cigarettes was also associated with less withdrawal effects as compared to nicotine lozenges.[28]

2.3. Safety

2.3.1. Clinical Safety of X-22

2.3.1.1. Overview

Like conventional cigarettes, X-22 cigarettes are toxic and pose health risks to subjects, namely cancer, cardiovascular disease, respiratory disease and reproductive effects[1]. Furthermore, it has been suggested that nicotine may mitigate some of the negative effects of other cigarette smoke components[55,40].

During clinical studies, X-22 cigarettes will be provided in a limited amount only to confirmed smokers. Previous clinical studies (see Section 2.1) have found that, when smoking VLN cigarettes, smokers generally consume fewer cigarettes per day than when they smoke their usual brand. It is therefore expected that the exposure of subjects to smoke

components in the proposed IND trial will be no greater than if they did not participate and continued to smoke their usual brand.

Because the purpose of X-22 Smoking Cessation Product is for smoking cessation, and not a substitute for other cigarettes, if approved its use will be short term and monitored by a physician as a prescription product. Therefore, it is anticipated that the long term benefits of smoking cessation that are provided by X-22 Cessation Product should out-weight its short term health risks to subjects.

Although numerous studies of cigarettes containing VLN tobacco have been published (see Section 2.1), most of these publications focused on efficacy or subjective effects and did not address safety. Studies that provided safety information are discussed in the following sections.

2.3.1.2. Safety Results from Vector-201 Phase II CSR

2.3.1.2.1. Summary

The safety of cigarettes manufactured with VLN tobacco was systematically evaluated in one IND clinical trial: Vector-201, A Prospective, Double-blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of Quest Alone and in Combination with Nicotine Replacement Therapy as a Smoking Cessation Aid.[26,27] A clinical study report for this clinical trial was previously submitted to FDA as part of a Vector Tobacco, Inc. End-of-Phase II Meeting package on October 13, 2006 for IND 69,185.

As summarized in Sections 2.1.1.1 and 2.2.2, a total of 346 healthy smokers who were motivated to quit smoking were enrolled in the trial and followed over 8 months. Subjects were randomized to one of the following groups:

- Group 1: Quest 1®, Quest 2®, and Quest 3® plus NRT patch
- Group 2: Quest 1®, Quest 2®, and Quest 3® plus placebo patch
- Group 3: Conventional active control cigarettes plus NRT patch

A total of 85 subjects completed the study. The median time to drop out was 12.8 weeks for Group 1, 10.5 groups for Group 2, and 14.2 weeks for Group 3. The most common reasons for drop out were failure to quit smoking (38.4%), lost to follow-up (17.1%), and subject's request/withdrawal of consent (13.3%).

Safety was evaluated by monitoring concomitant medications, adverse events, vital signs, and physical examinations. Exhaled carbon dioxide levels were also measured.

2.3.1.2.2. Adverse Events

A summary of AEs reported during study Vector-201 is presented below in Table 2-6. The number of subjects reported treatment emergent AEs was lowest in Group 2 (Quest® cigarettes plus placebo patch). There were also fewer SAEs and AEs leading to discontinuation of the study in Group 2 compared to Group 1 or Group 3. A complete list of all AEs reported during the study is provided in Table 2-6.

Table 2-6 Summary of Adverse Events in Clinical Study Vector-201

Adverse Event Category	Group 1 (N=116)	Group 2 (N=116)	Group 3 (N=114)
Treatment-emergent AEs	71 (61.2%)	61 (52.6%)	69 (60.5%)
Treatment-related AEs	51 (44.0%)	32 (27.6%)	42 (36.8%)
SAEs	2 (1.7%)	0	1 (0.9%)
Treatment-related SAEs	0	0	0
AEs leading to study product stopped	4 (3.4%)	1 (0.9%)	4 (3.5%)
AEs leading to study discontinuation	3 (2.6%)	2 (1.7%)	3 (2.6%)

N=number of subjects who received treatment; %=n/N x 100; AE=adverse event; SAE=serious adverse event
Source: CSR for Study Vector-201, in-text Table 25, Summary of Adverse Events (Safety Population)

A summary of all AEs reported in 2 or more subjects in any treatment group by system organ class is provided in Table 2-7. The types and frequencies of most AEs were similar across the 3 treatment groups. However, administration site conditions were higher in the 2 groups receiving the nicotine patch and lowest in Group 2, which received Quest® cigarettes plus the placebo patch. Infections and infestations occurred in more subject receiving regular cigarettes plus nicotine patch (Group 3), although 4 subjects in Group 2 compared with 0 subjects in Groups 1 and 2 experienced bronchitis. More subjects in Group 2 also experienced headache (7, 12, and 4 subjects in Groups 1, 2, and 3, respectively). However, rates of insomnia were higher in the groups receiving the nicotine patch (15, 6, and 14 in Groups 1, 2, and 3, respectively), and more subjects in Group 1 experienced anxiety and irritability (anxiety: 8, 2, and 3 in Groups 1, 2, and 3, respectively, and irritability: 7, 2, and 2, in Groups 1, 2, and 3, respectively).

Table 2-7 Adverse Events Reported in Study Vector -201 in Two or More Subjects in Any Treatment Group

System Organ Class Preferred Term	Group 1 (N=116) n (%)	Group 2 (N=116) n (%)	Group 3 (N=114) n (%)
Subjects with any adverse events	71 (61%)	61 (53%)	69 (61%)
Gastrointestinal Disorders			
Nausea	8 (7%)	7 (6%)	5 (4%)
Diarrhea	2 (2%)	3 (3%)	2 (2%)
Dyspepsia	3 (3%)	1 (<1%)	2 (2%)
Stomach Discomfort	1 (<1%)	0	2 (2%)
Abdominal Pain	2 (2%)	1 (<1%)	1 (<1%)
Vomiting	2 (2%)	3 (3%)	0
General Disorders and Administration Site Conditions			
Application Site Pruritus	8 (7%)	1 (<1%)	5 (4%)
Fatigue	3 (3%)	3 (3%)	3 (3%)
Application Site Dermatitis	1 (<1%)	1 (<1%)	2 (2%)
Application Site Discomfort	0	0	2 (2%)
Chest Discomfort	1 (<1%)	0	2 (2%)
Oedema Peripheral	2 (2%)	1 (<1%)	1 (<1%)
Application Site Discoloration	2 (2%)	0	0
Application Site Erythema	4 (3%)	2 (2%)	0
Immune System Disorders			
Hypersensitivity	0	0	2 (2%)
Seasonal Allergy	0	0	2 (2%)
Infections and Infestations			
Nasopharyngitis	3 (3%)	2 (2%)	8 (7%)
Upper Respiratory Tract Infection	2 (2%)	2 (2%)	6 (5%)
Tooth Abscess	0	0	2 (2%)
Ear Infection	0	2 (2%)	1 (<1%)
Bronchitis	0	4 (3%)	0
Sinusitis	2 (2%)	1 (<1%)	0
Injury, Poisoning and Procedural Complications			
Post Procedural Pain	2 (2%)	1 (<1%)	1 (<1%)
Arthropod Bite	0	2 (2%)	0
Contusion	0	2 (2%)	0
Investigations			

System Organ Class **Preferred Term**	**Group 1 (N=116) n (%)**	**Group 2 (N=116) n (%)**	**Group 3 (N=114) n (%)**
Blood Cholesterol Increased	2 (2%)	0	0
Metabolism and Nutrition Disorders			
Increased Appetite	0	0	3 (3%)
Musculoskeletal and Connective Tissue Disorders			
Chest Wall Pain	0	1 (<1%)	2 (2%)
Muscle Spasms	0	1 (<1%)	2 (2%)
Pain in Extremity	1 (<1%)	0	2 (2%)
Shoulder Pain	0	1 (<1%)	2 (2%)
Myalgia	1 (<1%)	2 (2%)	1 (<1%)
Back Pain	4 (3%)	6 (5%)	0
Neck Pain	1 (<1%)	3 (3%)	0
Pain in Jaw	2 (2%)		
Nervous System Disorders			
Headache	7 (6%)	12 (10%)	4 (4%)
Dizziness	4 (3%)	2 (2%)	2 (2%)
Paraesthesia	1 (<1%)	0	2 (2%)
Disturbance in Attention	2 (2%)	1 (<1%)	1 (<1%)
Psychiatric Disorders			
Insomnia	15 (13%)	6 (5%)	14 (12%)
Abnormal Dreams	4 (3%)	1 (<1%)	4 (4%)
Anxiety	8 (7%)	2 (2%)	3 (3%)
Depression	1 (<1%)	3 (3%)	3 (3%)
Irritability	7 (6%)	2 (2%)	2 (2%)
Initial Insomnia	0	2 (2%)	0
Nervousness	4 (3%)	0	0
Nightmare	2 (2%)	1 (<1%)	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	4 (3%)	2 (2%)	7 (6%)
Pharyngolaryngeal Pain	5 (4%)	2 (2%)	3 (3%)
Dyspnea	3 (3%)	2 (2%)	2 (2%)
Sinus Congestion	0	0	2 (2%)
Productive Cough	2 (2%)	2 (2%)	1 (<1%)
Respiratory Track Congestion	0	2 (2%)	0
Skin and Subcutaneous Tissue Disorders			
Dermatitis Contact	1 (<1%)	1 (<1%)	2 (2%)

System Organ Class **Preferred Term**	**Group 1 (N=116) n (%)**	**Group 2 (N=116) n (%)**	**Group 3 (N=114) n (%)**
Rash	0	0	
Urticaria	2 (2%)	1 (<1%)	1 (<1%)
Vascular Disorders			
Hot Flush	0	0	2 (2%)
Hypertension	2 (2%)	0	1 (<1%)

Source: CSR for Study Vector-201, Appendix A, Table S33

A total of 11 subjects either stopped taking the study product due to an AE or were discontinued from the study due to an AE. These events are summarized in Table 2-8, below. As shown in this table, most of the AEs leading to discontinuation in Groups 1 and 3 appear to be related to use of the nicotine patch and 1 of the events in Group 2 appears to be related to the placebo patch, not the use of the study cigarettes.

Table 2-8 Summary of Adverse Events Leading to Stopping of Study Product or Study Discontinuation in Clinical Study Vector-201

Group # Subject #	Adverse Event(s)	Stopped Study Product Due to AE?	Discontinued from Study Due to AE?
Group 1 01295	Nausea	Yes	Yes
Group 1 03051	Nausea/ Vivid dreams	Yes	No
Group 1 03067	Rash, itchiness under patch site	Yes	Yes
Group 1 04015	Chest urticaria	Yes	No
Group 1 03064	Chest pressure	No	Yes
Group 2 03060	Itchiness on chest and legs/ redness under patch site	Yes	Yes
Group 2 04003	Shortness of breath/ Chest pain/ Insomnia	No	Yes
Group 3 01311	Headache and cough	Yes	Yes
Group 3 02043	Contact dermatitis	Yes	Yes
Group 3 05110	Localized muscle aches under patch	Yes	Yes
Group 3 05245	Rash under patch	Yes	No

AE=adverse event; SAE=serious adverse event

Source: CSR for Study Vector-201, in-text Table 26, Subjects Who Experienced Adverse Events Directly or Indirectly Leading to Study Discontinuation

SAEs were reported for 3 subjects: 2 subjects in Group 1 and 1 subject in Group 3. In Group 1, chest discomfort and increased blood pressure were reported for Subject 03064 and bladder carcinoma was reported for Subject 01084. In Group 3, fibula and tibia fractures were reported for Subject 05121. None of the SAEs were considered treatment related.

Safety narratives for subjects who experienced SAEs or who discontinued use of the study product or who discontinued from the study due to an AE are presented in Appendix B of the clinical study report.[27]

2.3.1.2.3. Vital Signs

Vital signs were measured at each study visit in Study Vector-201. Clinically significant changes in heart rate or blood pressure were reported as AEs. The clinical study report states that other than the reported adverse events, no other clinically significant changes in vital signs were reported. Vital signs are summarized by study visit and treatment group in Appendix A, Table S38 of the clinical study report.[27] Overall, mean differences in heart rate and blood pressure between treatment groups and over time were small and without pattern.

2.3.1.2.4. Physical Examination Results

Summaries of baseline and posttreatment physical examination results are provided in Appendix A, Tables S43.2 and S43.3 in the clinical study report for Vector-201.[27] A large percentage of posttreatment physical examination results were reported as "unknown" during this study. Therefore, results are difficult to interpret.

2.3.1.2.5. Carbon Monoxide Levels

The corrected mean CO levels for each treatment group at each study visit are presented in Figure 2-14, below. The quit smoking date was at Visit 5 and subsequent visits took place at 2-week intervals. There were significant differences ($p \leq 0.05$) when comparing Group 1 to Group 3 at Visit 3 and Visit 4, and when comparing Group 2 to Group 3 at Visit 3. There were no significant differences between groups at other time points. The study schedule dictated that subjects smoke Quest 1® during weeks 1 to 2 (between Visits 2 to 3), Quest 2® during weeks 3 to 4 (between Visits 3 to 4), and Quest 3® during Weeks 5 to 6 (between Visits 4 to 5). Therefore, during the period that subjects smoked Quest 3, it appears that Groups 1 and 2 had somewhat lower CO levels than the 'regular' cigarette group (Group 3); however differences were not significant. In their report of this study, Becker *et al*[84] noted that:

> While CO levels remained constant from Week 1 to Week 3 in the active control plus NRT group (M change 520.2 ppm, standard deviation [SD] 510.25), CO levels increased nonsignificantly by 1.5 ppm (SD 511.27) with Quest 1® cigarettes in the Quest® plus NRT group (F[1,220]51.46, p5.22) and by 2.5 ppm (SD510.69) in the Quest® plus placebo patch group (F[1,221]53.64, p5.06). By Week 5, CO levels remained constant in the active control plus NRT group (M change vs. Week 1 of 0.2 ppm, SD510.59). There was, however, a trend for CO levels to increase upon smoking Quest 2®

cigarettes, by 2.9 ppm (SD511.25) in the Quest® plus NRT group (F[1,213]53.26, p5.07) and by 2.9 ppm (SD510.82) in the Quest® plus placebo patch group (F[1,215]53.39, p5.07). No differential increase in CO levels was seen with Quest 3® cigarettes [see Week 7 data].

A summary of mean CO values at each study visit for each group is provided in Appendix A, Table S19 of the clinical study report for this study.

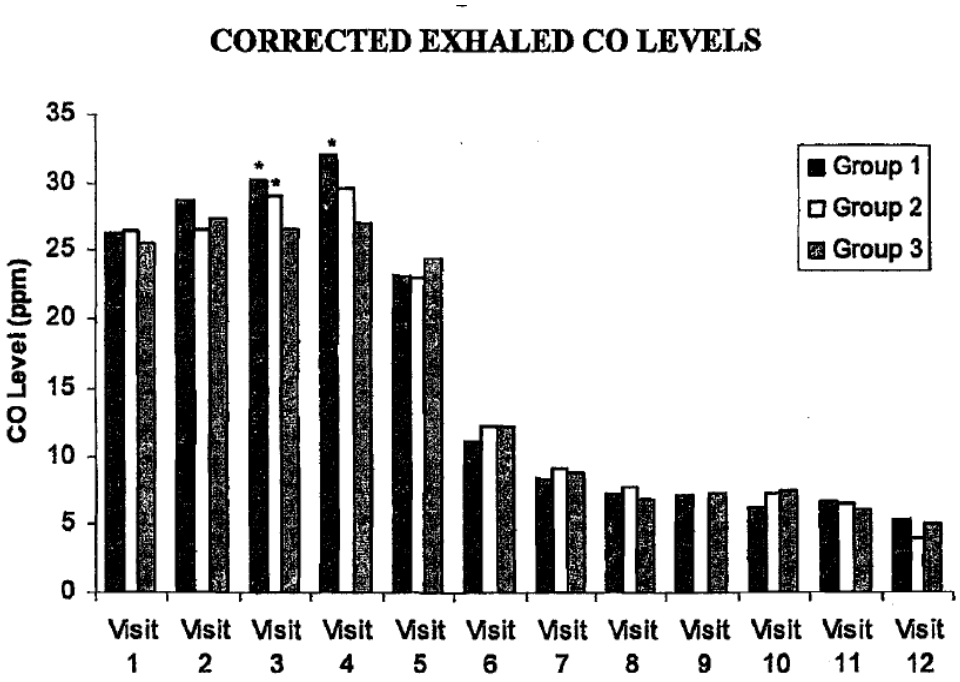


Figure 2-14 Exhaled Carbon Monoxide Data Reported in Study Vector-201

2.3.1.3. Safety Information from Other Published Clinical Studies

2.3.1.3.1. Adverse Events

Only one of the published studies of Quest® cigarettes summarized in Section 2.1 provided information regarding adverse events in study subjects. Rose *et al* reported that 24 hours after subjects completed 2 laboratory sessions involving smoking Quest 1® and Quest 3® cigarettes after rinsing the mouth with silver acetate or placebo solution, each participant was contacted via telephone and asked questions regarding any adverse events or signs of argyria (a bluish-tray discoloration of the skin). No occurrences were reported.

2.3.1.3.2. Vital Signs

A study by Cobb *et al*[36] (see section 2.1.2.3) evaluated the acute effects of various noncombustible PREPs (Ariva compressed tobacco tablet, Camel Snus, Marlboro Snus, and Commit® 2 mg Nicotine Lozenge) and combustible tobacco products (Subjects' OWN brand, SHAM [puffing on an unlit cigarette], and Quest 3® [nicotine yield ≤0.05 mg]) on heart rate in a laboratory setting.

This study found that mean heart rate increased in the Quest 3® group less than in a group of subjects smoking regular cigarettes and to a similar level to the group using Camel Snus, and that increase was not sustained after a second exposure to the Quest® product. For the OWN group, mean baseline heart rate was 67.8 bpm (SEM 1.9) and increased significantly to 82.3 bpm (SEM 2.3) 5 minutes after the first product administration and remained elevated at 15 and 30 minutes post administration; the same pattern was observed after a second administration of OWN cigarettes. For the Quest® group, mean baseline heart rate was 68.7 bpm (SEM 2.1), which increased significantly to 73.1 bpm (SEM 2.1) 5 minutes after the first, but not the second product administration. Mean changes in heart rate were small or did not occur in subjects assigned to SHAM (puffing on an unlit cigarette), ARIVA, COMMIT lozenge, or Marlboro Snus groups.

2.3.1.3.3. Carbon Monoxide Exposure

Carbon monoxide exposure from VLN cigarettes does not appear to be any greater than that from regular cigarettes. Strasser *et al*[37] reported CO levels in smokers after smoking 1 of their own brand cigarettes, 1 Quest 1® cigarette, 1 Quest 2® cigarette, and 1 Quest 3® cigarette with 30 minutes between cigarettes (see also Section 2.1.2.5). CO levels were obtained prior to and 4 minutes after smoking each cigarette. Results for the Quest® cigarettes, but not the Own brand cigarettes are presented with plasma nicotine levels in Figure 2-15, below. Mean CO boost measures were 5.3 ppm (S.D. = 2.5), 5.8 ppm (SD = 2.6), and 4.7 ppm (SD = 2.7) for the ≤0.05 mg nicotine, 0.3 mg nicotine and 0.6 mg nicotine cigarettes, respectively [$F(2,47) = 5.43$, $p = 0.01$]. These data show that smoking the VLN cigarette resulted in CO levels that were not significantly different from smoking cigarettes with higher nicotine contents.

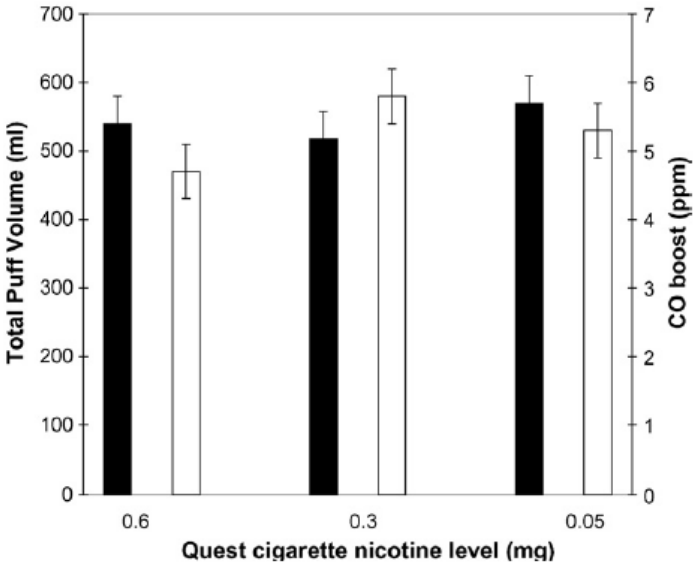


Fig. 1. The effect of cigarette nicotine level on total puff volume [(ml; solid bars; left *y*-axis); $F(2, 47) = 5.73$, $p = 0.006$, $N = 50$] and mean carbon monoxide boost [(ppm; open bars; right *y*-axis); $F(2, 47) = 5.43$, $p = 0.01$, $N = 50$]. Data presented as mean (±95% confidence interval).

Figure 2-15 Exhaled CO Levels Published by Strasser *et al*, 2007

Donny *et al*[39] compared groups who smoked Quest 1® (nicotine yield 0.6 mg) cigarettes, Quest 3® (nicotine yield ≤0.05 mg) cigarettes, or no cigarettes over a 2-week study period. They found lower CO levels in subjects who smoked Quest 3® cigarettes compared to Quest 2® cigarettes over a 2-week study period. Results are presented in Figure 2-16, below. The differences between the groups were statistically significant. Contrasts focused on the 2 smoking groups indicated that the Quest 2® cigarette group had higher CO levels than the VLN Quest 3® cigarette group overall ($p = 0.026$) and that the differences between smoking groups increased during the day ($p < 0.001$).

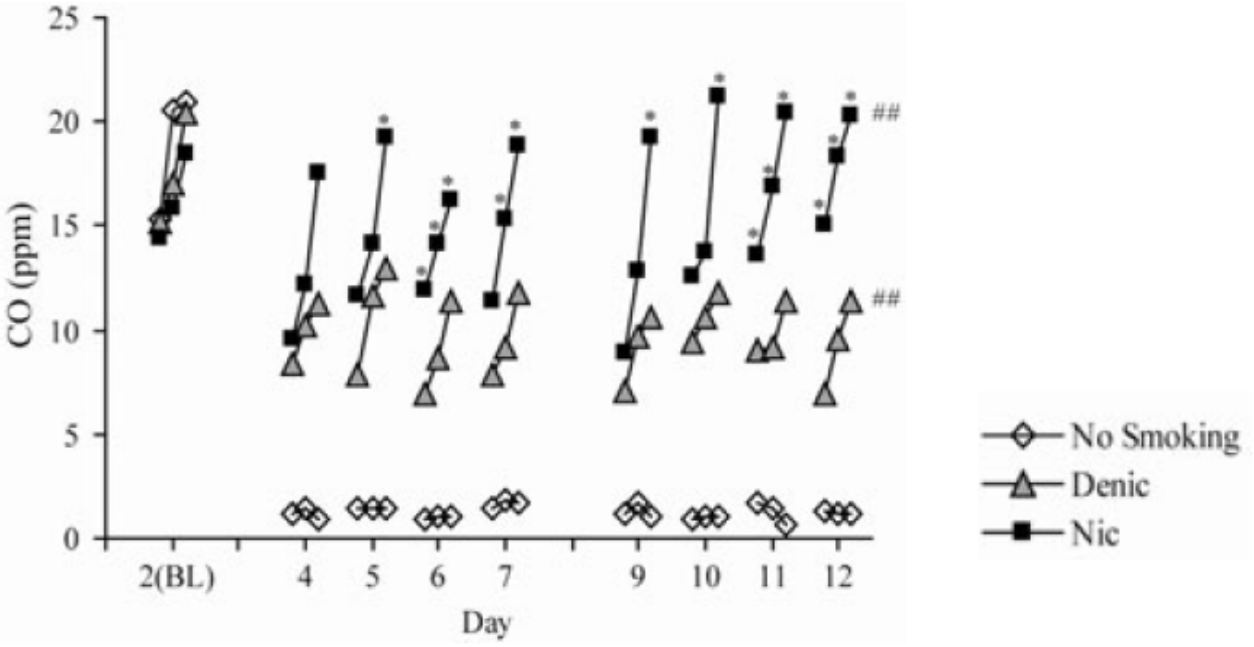


Figure 2-16 Carbon Monoxide Levels in Smokers Published in Donny *et al*, 2007

Cobb *et al*[36] (see section 2.1.2.3) evaluated the acute effects of various noncombustible PREPs (Ariva compressed tobacco tablet, Camel Snus, Marlboro Snus, and Commit® 2 mg Nicotine Lozenge) and combustible tobacco products (Subjects' OWN brand, SHAM [puffing on an unlit cigarette], and Quest 3® [nicotine yield ≤0.05 mg]) on expired CO in a laboratory setting. Each subject participated in each condition over 7 separate laboratory sessions. Mean CO values appeared to be slightly lower in the Quest 3® condition compared to the OWN brand condition. After the first product administration, the study found mean expired CO values in the OWN condition of 12.8 parts ppm (SEM 0.7) and mean expired CO values in the Quest 3® condition of 11.0 ppm (SEM 0.6) and after the second administration mean values were 17.5 ppm (SEM 1.0) in the OWN condition and 14.4 ppm (SEM 0.8) in the Quest 3® condition. There were no significant changes in any other condition.

2.3.1.3.4. Platelet Activation

Girdhar *et al*[66] conducted a study that evaluated platelet activation after cigarette smoking (see also Section 2.1.2.7). Chronic smoking is associated with increased risk of cardiovascular disease such as arterial venous thrombosis, stroke, and myocardial infarction. Platelets play an important role in both the initiation and propagation of clot formation and inflammatory response. The authors considered that baseline platelet activation state (PAS) is an important marker of cardiovascular risk and conducted this study to evaluate the effect of smoking different kinds of cigarettes on PAS.

Thirty-two smokers smoked 3 cigarettes with moderately reduced nicotine (Quest 1®, nicotine yield 0.6 mg) in 1 hour. Following this first smoking hour, 16 of the subjects continued smoking with 5 of the same cigarettes over the next 1.5 hours, while the other 16 subjects smoked 5 VLN cigarettes (Quest 3®, nicotine yield ≤0.05 mg). (Consuming 8 cigarettes over 2.5 hours equates to approximately 51 cigarettes/16-hour day and 5 VLN cigarettes over 1.5 hours equates to approximately 53 cigarettes/16-hour day.) Platelet surface expression of P-selectin, a marker for platelet activation, was determined by flow cytometry on samples drawn at the end of each period. The percentage of platelets scored as activated from baseline to posttreatment increased from 1.85% to 3.59% after smoking VLN cigarettes compared to an increase from 1.84% to 2.46% after smoking moderately reduced nicotine cigarettes. Statistical analyses showed this increase to be significantly different from baseline in both groups ($p < 0.01$) and the interaction between multiple measures of PAS with time and nicotine content of cigarettes was also significant ($p < 0.02$). The authors concluded that nicotine modulates platelet activation in vivo in smokers, and may significantly moderate the risk of cardiovascular disease caused by non-nicotine smoke components. No measure of smoke exposure was made, so it cannot be determined whether nicotine content of the cigarettes affected the intake of smoke under the rapid smoking schedule. Results are presented in Figure 2-17, below.

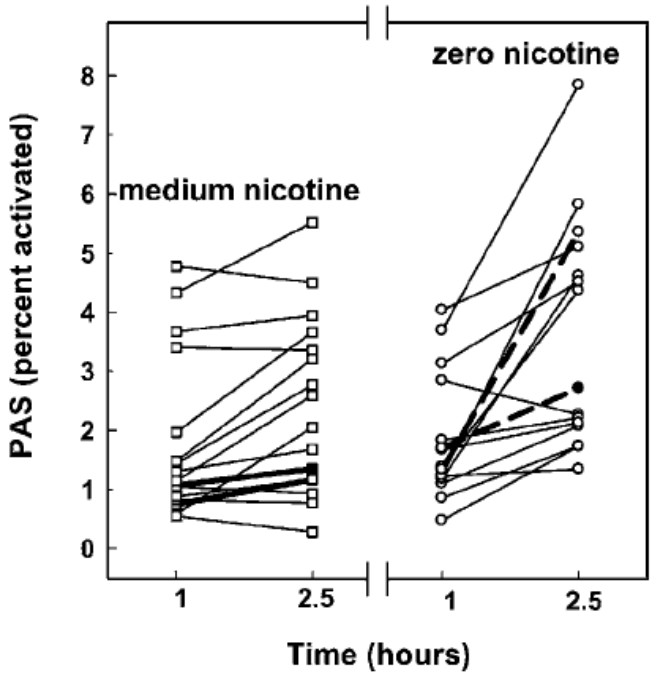


Figure 2-17 Platelet Activation Scores Published by Girdhar *et al*, 2008b

2.3.2. Clinical Safety Information about Menthol in Cigarettes

The 2011 Tobacco Products Scientific Advisory Committee's (TPSAC) "Draft Report and Recommendations on Menthol in Cigarettes"[69] found that the availability of menthol cigarettes increases initiation of smoking and reduces cessation, thereby increasing the number of people who are smoking. This increase in the number of smokers represents an adverse impact of the availability of menthol cigarettes on public health. However, they also concluded that the evidence does not indicate increased disease risks in smokers of menthol cigarettes compared to non-menthol cigarettes. This report summarizes several studies comparing the safety of menthol versus non-menthol cigarettes.

The TPSAC report[69] summarizes findings from a series of studies involving measurements of cardiovascular parameters after smoking menthol versus non-menthol cigarettes. They describe differing patterns of short-term response using echocardiography and measures of vascular response. The participants were healthy young volunteers. These findings have uncertain implications with regard to the comparative cardiovascular disease risks of smokers of menthol cigarettes versus non-menthol cigarettes. One study summarized investigated the effects of menthol in cigarettes by having volunteers smoke VLN cigarettes, with and without menthol. Using electroencephalogram and heart rate as outcome measures, they did not identify differences in response to the menthol-containing and non-menthol-containing cigarettes.

Another study summarized by the Tobacco Products Scientific Advisory Committee also examined biomarkers of potential harm, including markers of oxidative stress (i-epi-prostaglandin-F2 alpha, 8-isoprostaglandin F2 alpha-V1), inflammation (white blood cell count, fibrinogen, C-reactive protein, monocyte chemotactic adhesion molecule-1, soluble vascular cell adhesion molecule-1), coagulation (platelets, fibrinogen, von Willebrand factor, 11-dehydrothroboxane-B2), lipids (triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, oxidized LDL, lipoprotein-associated phospholipase A2) and metabolism (glucose, adiponectin, leptin). No significant effects of menthol smoking on these biomarkers were observed.

In summary, it is not expected that the addition of menthol to X-22 cigarettes will have an adverse effect on the safety of this product.

2.3.3. Exposure to Very Low Nicotine Cigarettes

Quest® 3 and Quest® 3 Menthol VLN cigarettes were sold commercially in the United States from 2002 to approximately 2008. According to filings by Vector Group Ltd. (parent company of Vector Tobacco Inc.) with the Securities and Exchange Commission, sales of Quest® by Vector Tobacco Inc. from 2002 to 2007 were approximately $60 million. This equates to approximately 26 million packs (520 million cigarettes) sold or 14,246 pack-a-day smokers using Quest® for 5 years.

Since Quest® was sold by Vector Tobacco in only 8 U.S. states (New York, New Jersey, Pennsylvania, Ohio, Indiana, Illinois, Michigan, and Arizona) representing 31% of U.S. smokers, approximately 1.4 million smokers tried Quest®. Assuming the trial rate was even among Quest® 1, Quest 2®, and Quest 3® (which was labelled “nicotine free” on the packaging), approximately 467,000 smokers used Quest 3® VLN cigarettes.

Subjects’ exposure to VLN cigarettes in published studies and one unpublished report is summarized in Table 2-9. Nearly 1000 subjects have received VLN cigarettes under controlled conditions. Most of these smoked VLN cigarettes in a laboratory setting during 1 to 7 sessions. Others smoked VLN cigarettes for periods of up to 13 weeks.

Table 2-9 Summary of Published Human Studies with Very Low Nicotine Tobacco

References	No. of Subjects In Study	No. of Subjects receiving Quest 3®/ completed treatment	Duration of Quest 3® Cigarette Exposure	Study Topics						
				Smoking Cessation	Craving/ Withdrawal	Response to Cues	Cigarette Perception	Smoking Behavior	Exposure/ Toxicology	Other
Becker *et al*. (2008); Drgon *et al* (2009); Vector-301 CSR	346	232/200	2 weeks (following 4 weeks of Quest 1 and Quest 2 cigarettes)	X	X					
Hatsukami *et al* (2010)	165, 1/3 smoked VLN cigarettes	49/32	6 weeks	X	X				X	
Rezaishiraz *et al* (2007)	98, 1/2 smoked VLN cigarette	51/32	2 weeks	X	X					
Personal communication from Jed Rose	45	45/?	Up to 13 weeks	X	X		X	X	X	
Barrett (2010)	22	20/20	1 laboratory session		X			X		
Perkins *et al* (2010)	104, 1/3 smoked VLN cigarettes	≈35/?	5 laboratory sessions		X					X
Cobb *et al* (2010)	28	28/28	1 laboratory session		X			X	X	
Strasser *et al* (2006); Strasser *et al* (2007)	50	50/50	1 laboratory session				X	X		
Donny *et al* (2007)	30, 1/3 smoked VLN cigarettes	≈10/?	11 days		X			X		
Girdhar *et al* (2008)	32, 1/2 smoked VLN cigarettes	16/16	1 laboratory session						X	
Perkins *et al* (2004)	96	≈48/48	1 laboratory session				X	X		
Naqvi and Bechara (2005)	20	20/20	1 laboratory session				X			

References	No. of Subjects In Study	No. of Subjects receiving Quest 3®/ completed treatment	Duration of Quest 3® Cigarette Exposure	Study Topics						
				Smoking Cessation	Craving/ Withdrawal	Response to Cues	Cigarette Perception	Smoking Behavior	Exposure/ Toxicology	Other
Rukstalis *et al* (2005)	26	≈26/26	1 laboratory sessions					X	X	
Perkins *et al* (2006)	120	≈60/60	1 laboratory session			X		X		
Ray *et al* (2006)	60	≈30/30	2 laboratory sessions					X		X
Kelemen and Kaighobadi (2007)	120	≈60/60	1 laboratory session			X				X
Lindsey *et al* (2007)	Not reported	Not reported	1 laboratory session							X
McClernon *et al* (2007)	20	20/16	4 weeks					X		X
Kelemen (2008)	103	52/52	1 laboratory session		X		X			X
Attwood *et al* (2009)	44	≈22/22	1 laboratory session							X
Brody *et al* (2009a)	15	≈10/10	1 or 2 laboratory sessions		X					X
Brody *et al* (2009b)	62	16/16	1 laboratory session							X
King *et al* (2009)	42	42/42	2 laboratory sessions					X		
Rose *et al* (2010)	20	20/20	2 laboratory sessions				X			X

2.3.4. Safety Conclusions from Clinical Trials

Like conventional cigarettes, X-22 cigarettes are toxic and pose health risks to subjects, namely cancer, cardiovascular disease, respiratory disease and reproductive effects[1]. However, previous clinical studies (see Section 2.1) have found that, when smoking very low nicotine cigarettes, smokers generally consume fewer cigarettes per day than when they smoke their usual brand. It is therefore expected that the exposure of subjects to smoke components in the proposed IND trial will be no greater than if they did not participate and continued to smoke their usual brand.

Previous clinical studies have not found evidence that VLN cigarettes are any less safe than regular cigarettes. The above literature review indicates that adverse events, vital signs measurements, and CO exposure are similar after smoking regular versus VLN cigarettes. It has been suggested that nicotine may mitigate some of the negative effects of other cigarette smoke components based on *in vivo* and *in vitro* laboratory studies[55,40]; however, it is expected that this theoretical risk will be mitigated by the planned short term exposure to the product with confirmed smokers and offset by the long-term benefits of increased smoking cessation rates.

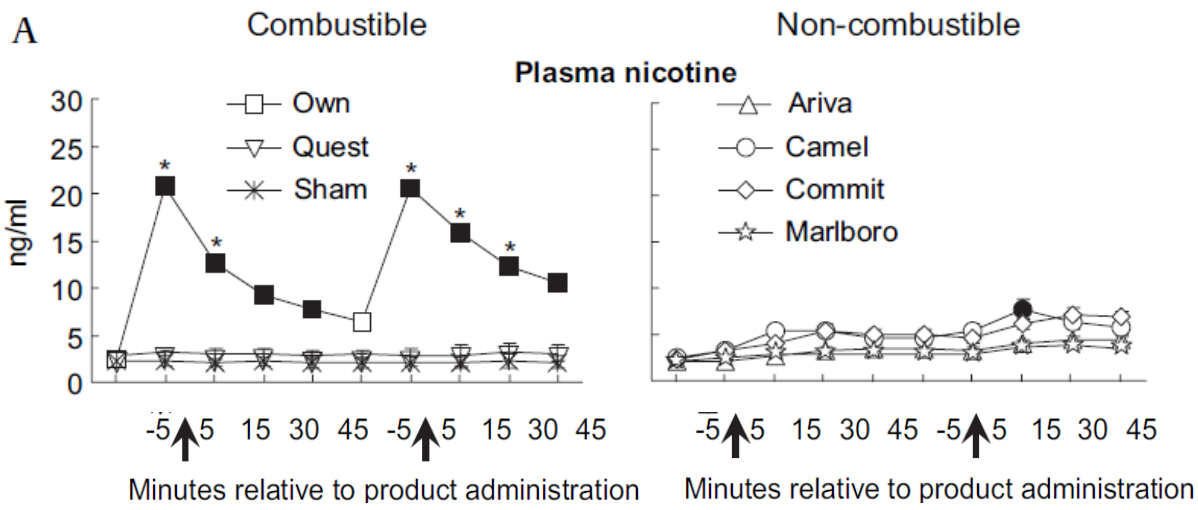
It is not expected that the addition of menthol to X-22 cigarettes will have an adverse effect on the safety of this product.

2.4. Clinical Pharmacokinetics

The clinical pharmacokinetics of the components of smoke from X-22 cigarettes have not yet been systematically evaluated. However, at least 2 studies have evaluated exposure to components of Quest 3® cigarettes and information is available regarding the pharmacology and pharmacokinetics of menthol. These data are provided in the subsections below.

2.4.1. Quest 3® Cigarettes

A study conducted by Cobb *et al*[36] compared blood nicotine values after the use of 7 different noncombustible PREPs (Ariva compressed tobacco tablet, Camel Snus, Marlboro Snus, and Commit® 2 mg Nicotine Lozenge) and combustible tobacco products (Subjects' OWN brand, SHAM [puffing on an unlit cigarette], and Quest 3® [nicotine yield ≤0.05 mg]). Nicotine levels reported from this study are provided in Figure 2-18, below. These data confirm that smoking cigarettes made with the VLN tobacco used in X-22 cigarettes does not result in appreciable increases in plasma nicotine.



Mean data (±SEM) for plasma nicotine. Arrows indicate product administration. Filled symbols indicate a significant difference relative to baseline, and asterisks (*) indicate a significant difference of OWN brand mean relative to all non-combustible product means at that time point (<0.05, Tukey's Honestly Significant Difference)

Figure 2-18 Plasma Nicotine Levels Reported by Cobb *et al*, 2010

Hatsukami *et al*[28] (see also Section 2.1.1.2) measured levels of various biomarkers of smoking exposure in subjects who smoked Quest 2® (nicotine yield 0.30 mg) or Quest 3® (nicotine yield ≤0.05 mg) cigarettes, or who did not smoke but used 4 mg nicotine lozenges. Biomarkers of tobacco toxicant exposure measures included:

- Urinary cotinine plus cotinine–glucuronide (total cotinine), a direct measure of nicotine exposure.
- Urinary 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanol and its glucuronides (total NNAL), metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
- Urinary N_-nitrosonornicotine and its glucuronide (total NNN), metabolites of the tobacco-specific carcinogen N_-nitrosonornicotine.
- Urinary 1-hydroxypyrene and its glucuronide and sulfate (total 1-HOP), a metabolite of pyrene which is an accepted biomarker for uptake of carcinogenic polycyclic aromatic hydrocarbons.
- Urinary 3- hydroxypropylmercapturic acid (3-HPMA), a metabolite of the toxicant, acrolein.
- Sphenylmercapturic acid (S-PMA), a metabolite of the human leukemogen, benzene.

These biomarkers reflect exposure to particulate or smoke constituents in cigarettes. 1-HOP, 3-HPMA, and S-PMA are influenced by factors other than tobacco, while total cotinine, total NNAL and total NNN are tobacco-specific. Results of these measures at baseline, Week 2, and Week 6 are shown in Table 2-10. Mean levels of all biomarkers measured decreased

relative to baseline in the Quest 3® VLN cigarette group and mean levels of nearly all biomarkers (all except S-PMA at 2 weeks) were lower in the Quest 3®, ≤0.05 mg cigarette, group than in the Quest 2®, 0.30 mg nicotine cigarette, group at Weeks 2 and 6.

Table 2-10 Geometric Means of Biomarkers After Exposure to 0.6 mg or ≤0.05 mg Nicotine Cigarettes or Nicotine Lozenges at Baseline and After 2 and 6 Weeks of Treatment Published by Hatsukami *et al* 2010

	Geometric mean (95% confidence interval)		
Biomarkers	*Baseline*	*Week 2*	*Week 6*
Total cotinine[1]			
0.3 mg cigarettes	4057 (3323, 4952)	2150 (1696, 2725)*	2093 (1611, 2719)*[a]
0.05 mg cigarettes	4216 (3492, 5090)	278 (174, 442)*	188 (111, 319)*[b]
Nicotine lozenge	3917 (3399, 4514)	2291 (1708, 3073)*	2154 (1312, 3536)*[a]
Total NNAL[2]			
0.3 mg cigarettes	0.96 (0.73, 1.26)	0.54 (0.41, 0.69)*	0.47 (0.30, 0.73)*[a]
0.05 mg cigarettes	0.92 (0.70, 1.21)	0.34 (0.20, 0.57)*	0.20 (0.11, 0.34)*[b]
Nicotine lozenge	1.06 (0.84, 1.35)	0.24 (0.18, 0.32)*	0.14 (0.07, 0.26)*[b]
Total NNN[2]			
0.3 mg cigarettes	0.10 (0.06, 0.16)	0.09 (0.06, 0.14)	0.06 (0.04, 0.10)[a]
0.05 mg cigarettes	0.09 (0.05, 0.15)	0.06 (0.04, 0.11)	0.03 (0.02, 0.07)*[ab]
Nicotine lozenge	0.08 (0.05, 0.12)	0.02 (0.01, 0.04)*	0.02 (0.01, 0.04)*[b]
Total 1-HOP[2]			
0.3 mg cigarettes	0.84 (0.70, 1.02)	0.95 (0.58, 1.53)	0.73 (0.59, 0.90)[a]
0.05 mg cigarettes	0.89 (0.71, 1.12)	0.75 (0.56, 1.01)	0.57 (0.42, 0.78)*[a]
Nicotine lozenge	0.94 (0.71, 1.24)	0.40 (0.29, 0.56)*	0.34 (0.21, 0.57)*[b]
3-HPMA[2]			
0.3 mg cigarettes	3662 (2868, 4674)	2838 (2226, 3619)	2732 (2110, 3537)[a]
0.05 mg cigarettes	3320 (2667, 4134)	1639 (1215, 2211)*	1453 (1039, 2032)*[b]
Nicotine lozenge	3445 (2539, 4673)	911 (670, 1239)*	1062 (749, 1508)*[b]
S-PMA[2]			
0.3 mg cigarettes	2.21 (1.54, 3.18)	1.30 (0.88, 1.92)*	1.35 (0.94, 1.93)*[a]
0.05 mg cigarettes	2.46 (1.68, 3.62)	1.54 (1.03, 2.31)*	0.76 (0.48, 1.20)*[b]
Nicotine lozenge	2.69 (1.95, 3.72)	0.33 (0.22, 0.49)*	0.48 (0.30, 0.78)*[b]

[1]ng/ml.
[2]pmol/mg creatinine.
**P* □□ 0.05 at that visit compared to baseline (within-group comparison). Groups with different letters were significantly different (*P* □□ 0.05) at the week 6 treatment visit (between-group comparison). For example, total cotinine is significantly different between the ≤0.05 mg cigarette group with 0.3 mg cigarette group and with nicotine lozenge group, but the 0.3 mg cigarette group is not significantly different from the nicotine lozenge group. Total NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides; total NNN: *N*_-nitrosonornicotine and its glucuronide; total 1-HOP: 1-hydroxypyrene and its glucuronide and sulfate; 3-HPMA: 3-hydroxypropylmercapturic acid; S-PMA: *S*-phenylmercapturic acid.

Data from the 2 studies presented above indicate that subjects who smoke cigarettes containing VLN tobacco are at no greater risk for exposure to nicotine (as measured in both plasma and urine) and several other substances than smokers of regular cigarettes, and smoking VLN tobacco may actual lessen exposure to these agents.

At the pre-IND meeting on January 27, 2009, FDA indicated that it should be demonstrated that the nicotine exposure from the X-22 cigarette is not more bioavailable than nicotine from other approved nicotine replacement products, or the sponsor would need to provide adequate safety data to support the difference. Specifically, a relative bioavailability comparison between X-22 cigarettes and a U.S. approved nicotine product such as a gum or lozenge was requested. FDA also requested information on the multiple dose pharmacokinetics of nicotine in the X-22 cigarette after a standard regimen and after the most intensive dosage regimen. 22nd Century is planning to obtain this information in advance of the phase III trials, so that the pharmacokinetic information on nicotine bioavailability in the X-22 cigarette can be used in the design of the phase III clinical trials.

It should be noted, however, that if a VLN cigarette contains less than 1 mg of nicotine in the filler, the upper limit on how much nicotine could be inhaled by any smoker would be a fraction of 1 mg. The bioavailability of nicotine from a cigarette varies widely with smoking behavior, but is typically about 12%, with a maximum of about 40%,[67,68] so a smoker would be expected to take in 0.4 mg or less nicotine per cigarette, even if the cigarette was smoked more intensely.

2.4.2. Menthol

The information in this section was obtained from the 2011 Tobacco Products Scientific Advisory Committee's (TPSAC) "Draft Report and Recommendations on Menthol in Cigarettes"[69].

Pharmacology of Menthol in Cigarettes

With repeated or prolonged administration, menthol is known to cause desensitization to its own cooling and irritant effects. Menthol is also reported to reduce sensitivity to noxious chemicals, including nicotine. The irritating effects of nicotine on the airway are mediated by activation of nicotinic cholinergic receptors and TRPA1. Menthol did however reduce burning pain both in baseline and nicotine conditions. Higher levels of nicotine reduced the subjects' ability to discriminate dose-related odor and cooling effects of menthol compared to lower nicotine levels. While both menthol and nicotine have the potential to desensitize responses with repeated exposure, a study comparing olfactory thresholds for menthol and nicotine in smokers and non-smokers found the smokers had a much higher olfactory threshold for nicotine but no difference in threshold for menthol. The same was seen in both menthol and non-menthol smokers. Thus the effects of menthol are persistent in smokers.

Pharmacokinetics of Menthol in Cigarettes

Menthol moves from cigarette smoke into the lungs and then into the bloodstream. Smokers systemically absorb an average of 5–20 percent of the menthol in a menthol cigarette, depending on the extent of ventilation. For a cigarette containing 3 mg of menthol (0.3 percent), a smoker of 20 cigarettes per day is exposed to an average systemic dose of 12.5 mg menthol per day.

Once it enters the general circulation, menthol is rapidly metabolized, making it difficult to measure free menthol in the blood or urine. Menthol is metabolized primarily through glucuronidation, a process that takes place in the liver to detoxify substances, and through oxidation, which also takes place in the liver. Glucuronidation primarily is driven by the liver enzyme UDP-glucuronosyl transferase 1A4. The result of this process is a compound called menthol glucuronide. Oxidation of menthol to hydroxylated metabolites has been observed in studies in rats. In humans, approximately 50% of an oral dose of menthol is excreted in the urine as menthol glucuronide. The half-life of menthol glucuronide after oral menthol dosing is about 50 minutes in plasma and 74 minutes in urine, although there appears to be a longer terminal half-life, most likely due to the slow release of the highly lipid-soluble menthol from body tissues and/or due to enterohepatic recirculation. It is difficult to do pharmacokinetic studies with inhaled menthol because the dose absorbed cannot be known with certainty. Urine menthol glucuronide concentrations have been measured in a cross-sectional study of smokers of menthol and non-menthol cigarettes. On average, menthol levels are higher in menthol smokers, but many non-menthol smokers also have high menthol levels due to consumption of menthol-containing foods.

While free menthol concentrations are quite low in blood, they are high in tobacco smoke. As a result, menthol concentrations will be high in the mouth, throat and lungs. Estimating concentrations in smoke is important to assess the plausibility that menthol has effects on sensory nerves and possible drug metabolism in the upper and lower airways in relation to concentrations that have effects in animals or cell preparations. Assuming that a menthol cigarette delivers 0.8 mg of menthol in smoke and that a smoker takes 8 puffs on a cigarette, the menthol per puff is 0.1 mg. Assuming that all of the menthol in a puff is absorbed and that the inhalation volume associated with one puff (puff volume plus air) is 800 ml, the concentration of menthol would be 1250 mcg/L, which would be 8.0 uM/L. There is uncertainty about the partition of menthol between smoke and lung tissue, but this gives some rough approximation about what levels might act in the lungs, where there are drug metabolizing enzymes. Concentrations could be considerably higher in the mouth and throat, before the inhaled smoke is fully diluted with the fresh air inhaled with the smoke.

Particulate Matter in the Smoke of Mentholated Cigarettes

Several studies have shown that menthol increases the amount of tar and fine particles in cigarette smoke. The mechanism of increased particle formation was speculated to be greater transfer of the additive materials to the particle phase of the smoke compared to tobacco constituents. Increased particulate matter in smoke is of concern because particulates are associated with greater morbidity and mortality from cardiovascular disease and are suspected to increase the risk of sudden cardiac death. The smoke generated from cigarettes to which menthol was added also delivered higher levels of formaldehyde, and lead, both tobacco smoke toxicants, compared to smoke from the control cigarettes.

2.5. Proposed IND Clinical Trial

Title:

A Prospective, Double-blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of X-22 as a Smoking Cessation Aid

Objectives:

The primary objective of the first proposed IND clinical trial is to evaluate the efficacy of X-22 as a smoking cessation aid.

Secondary objectives of the study will include:

- To assess the effect of X-22 on abstinence at 2 and 3 months after the quit date.
- To assess of the severity of withdrawal symptoms.
- To evaluate the effect of X-22 on cigarette consumption prior to the quit date.
- To evaluate the tolerability of X-22 as a smoking cessation aid.

Exploratory objectives will include:

- To evaluate other factors that may have an influence on the efficacy of X-22 as a smoking cessation aid, including subject gender, results of a Sensory Questionnaire prior to the quit date, and results of the FTND prior to the quit date.
- To compare nicotine use between groups over time.

Study Design:

This will be a prospective, randomized, multicenter, double blind, parallel, active controlled, Phase II clinical trial in which a total of 216 healthy smokers will be enrolled and followed

over approximately 19 weeks at a maximum of 3 sites.

Healthy smokers who plan to quit smoking will be screened for eligibility at Visit 1 (Screening Phase). Screening will include documentation of medical/smoking history, physical examination, clinical laboratory tests, electrocardiogram (ECG), urine pregnancy test (in women of child-bearing potential), drug screen, exhaled CO, saliva cotinine level, and the completion of 3 questionnaires (Sensory Questionnaire, Minnesota Nicotine Withdrawal Scale, and the FTND). All subjects will receive behavioral support through approximately 15-minute individual counseling sessions at Visits 4, 5, 6, and 9, including distribution of printed materials. Subjects will continue to smoke their usual brand *ad libitum* during Week 1.

One week following Screening, at Visit 2 (beginning of the Treatment Phase), eligible subjects will be randomized in a 1:1 ratio to 1 of the 2 treatment arms:

- Group 1: X-22 Smoking Cessation Product
- Group 2: Active Control Cigarettes

The randomization will be stratified by gender.

At Visit 2, subjects will switch from their usual brand cigarettes to X-22 cigarettes (Group 1) or blinded active control cigarettes (Group 2) and will smoke the assigned study cigarettes *ad libitum* for 6 weeks prior to the target quit date. Visit 5/Week 6 is considered the "quit date" (quit all smoking) for all study subjects.

After randomization, during the Treatment and Abstinence Phases, subjects will return to the study center at 2-week intervals for 10 weeks (Visits 2 to 7), and will receive a telephone call from the site between visits at Weeks 1, 3, 5, 7, and 9.

During the Follow-up Phase, subjects will receive follow-up telephone calls to determine smoking status at 4-week intervals for the following 8 weeks. At the Week 14 follow-up telephone call, subjects who report that they have not smoked in the past 7 days will be asked to return to the study site within 1 week for Visit 8. At Week 18, all subjects will return to the site for Visit 9, regardless of smoking status. Subjects will receive information regarding the use of approved smoking cessation pharmacotherapies during their Visit 9 counseling session.

Cigarette consumption will be evaluated using self-report diaries and measurement of exhaled CO and cotinine concentration. Withdrawal symptoms will be assessed using The Minnesota Nicotine Withdrawal Scale at each study visit. The Sensory Questionnaire and the

FTND will be administered at study Visits 1 to 7. Safety will be assessed by evaluation of AEs, physical examinations, clinical laboratory studies, concomitant medications, and measurement of heart rate, blood pressure, and body weight at each study visit.

2.6. Dose Selection

X-22 cigarettes may be consumed by subjects *ad libitum* during the first IND clinical trial. At the beginning of the Treatment Phase, the number of cigarettes dispensed will be approximately equal to the number of cigarettes the subject has reported smoking in a 2-week period plus an overage of 30%. The number of cigarettes dispensed may be adjusted at the next 2 visits as necessary up to a total of 10 cartons over the 6-week Treatment Phase. Subjects will be instructed to telephone the site to request additional study cigarettes during the treatment period, if necessary. Investigators and study staff will be instructed not to distribute study materials to any subject not enrolled in the study. Subjects will be instructed not to distribute study product to any other person.

2.7. Clinical Development Plan

- 22nd Century will conduct a study to evaluate the relative bioavailability of nicotine from X-22 cigarettes compared to other sources of NRT.
- Phase III studies will be conducted to further evaluate the safety and efficacy of X-22 cigarettes as an aid to smoking cessation. Any dose response with X-22 cigarettes will be evaluated in phase IIb and/or phase III studies.
- The relative safety and efficacy of X-22 cigarettes compared to approved NRT will be investigated.
- The benefit of X-22 cigarettes in combination with other approved smoking cessation aids will be evaluated.
- Other populations such as elderly subjects and subjects with renal or kidney disease may be evaluated.

3. SUMMARY AND CONCLUSIONS

- Previous studies have found no clinical evidence that VLN cigarettes are any less safe than regular cigarettes.

- Previous clinical studies have found that, when smoking VLN cigarettes, smokers generally consume fewer cigarettes per day than when they smoke their usual brand.

- Although there has been concern that when smokers switch from their usual brand to VLN nicotine cigarettes, compensatory increases in smoking may occur, when switching to VLN cigarettes compensatory smoking has not been substantiated.

- Short term use of VLN cigarettes for 2 weeks is less effective than longer term use over 6 weeks.

- Although some studies have found significant efficacy with concomitant use of NRT, especially when the NRT was begun at least 2 weeks before the quit date, another study has found that VLN cigarettes alone are quite effective, resulting in a 4-week continuous abstinence rate of 43% and a 6-week post-treatment point prevalence rate of 47%.

- Smoking VLN cigarettes for at least 6 weeks alone also seems to be more effective that using a step-down approach (e.g., 2 weeks of 0.6 mg nicotine cigarettes, followed by 2 weeks of 0.3 mg nicotine cigarettes, followed by 2 weeks of 0.06 mg nicotine cigarettes).

- Numerous studies have found that acute withdrawal effects and cravings after short term smoking abstinence, as evaluated in a laboratory setting, are decreased as effectively or nearly as effectively with VLN cigarettes as with regular cigarettes.

- Smoking VLN cigarettes was more effective than inhaled nicotine at relieving cravings and other smoking withdrawal symptoms.

- During a longer term study of smoking cessation, smoking VLN cigarettes were associated with less withdrawal effects compared to 4-mg nicotine lozenges.

4. REFERENCES

1. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004. http://www.cdc.gov/tobacco/data_statistics/sgr/2004/complete_report/index.htm Accessed on 16 February 2011.
2. Vital signs: Current cigarette smoking among adults aged ≥18 years – United States, 2009. *MMWR*. 2010; 59(35):1135-1140.
3. *Healthy People 2010* Tobacco use objectives. http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=41 Accessed 22 February 2011.
4. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009; 49:57-71.
5. Rose JE. Disrupting nicotine reinforcement: from cigarette to brain. *Ann NY Acad Sci*. 2008; 1141:233-256.
6. Rose JE, Westman EC, Behm FM, Johnson MP, Gold berg JS. Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. *Pharmacol Biochem Behav*. 1999; 62(1):165-172.
7. Rose JE, Behm FM. Extinguishing the reward value of smoking cues: Pharmacological and behavioral treatments. *Nicotine Tob Res*. 2004; 6(3):523-532.
8. Stead L, Perera R, Bulen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*. 2008, issue 1. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub3.
9. Fiore M, Jaen CR, Baker TB, *et al*. Clinical practice guideline treating tobacco use and dependence: 2008 update. A U.S. Public Health Service Report. *Am J Prev Med*. 2008; 35(2):158-176. Full guidance available at http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf
10. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. *JAMA.* 1994; 271(24):1940-1947.
11. Hajek P, West R, Foulds J, Milsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med*. 1999; 159(17):2033-2038.
12. Butschky MF, Bailey D, Henningfield JE, Pickworth WB. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacol Biochem Behav*. 1995; 50(1):91-96.
13. Westman EC, Behm FM, Rose JE. Dissociating the nicotine and airway sensory effects of smoking. *Pharmacol Biochem Behav*. 1996; 53:309-315.

14. Gross J, Lee J, Stitzer ML. Nicotine-containing versus denicotinized cigarettes: effects on craving and withdrawal. *Pharmacol Biochem Behav*. 1997; 57:159-165.

15. Pickworth WB, Fant RV, Nelson RA, Rohrer MS, Henningfield JE. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine Tob Res*. 1999; 1:357-364.

16. Rose JE, Behm FM, Westman EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacol Biochem Behav*. 2000; 67:71-81.

17. Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine Tob Res*. 2001; 3:101-109.

18. Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine Tob Res*. 2001; 3(2):111-118.

19. Dallery J, Houtsmuller EJ, Pickworth WB, Stitzer ML. Effect of cigarette nicotine content and smoking pace on subsequent craving and smoking. *Psychopharmacol* (Berlin). 2003; 165:172-180.

20. Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenber T. Tobacco abstinence symptoms suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction*. 2005; 100:550-559.

21. Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers*. 2007; 16:2479-2478.

22. Filtrona Technology Centre for 22nd Century Limited. Testing for Mainstream Smoke Yields. April 1, 2011.

23. Data on file (Alkaloid Reduced Tobacco [ART] Program).

24. Xie J, Song W, Maksymowicz W, Jin W, Cheah K, Chen W, Carnes C, Ke J, Conkling MA. Biotechnology: A tool for reduced risk tobacco products – the nicotine experience from test tube to cigarette pack. *Recent Advances in Tobacco Science*. 2004; 30:17-37.

25. US Department of Agriculture, Animal and Plant Health Inspection Service. Vector Tobacco; availability of determination of nonregulated status for tobacco genetically engineered for reduced nicotine. Federal Register Notices. December 3, 2002; 67(232).

26. Becker KM, Rose JE, Albino AP. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine Tob Res*. 2008; 10(7):1139-1148.

27. Vector Tobacco, Inc. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of Quest alone and in combination with nicotine replacement therapy as a smoking cessation aid, protocol number Vector-201, IND Number 69,185. Clinical Study Report dated October 13, 2006.

28. Hatsukami DK, Kotlyar M, Hertsgaar LA, *et al*. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction*. 2010; 105:343-355.

29. Drgon T, Johnson C, Walther D, Albino AP, Rose JE, Uhl GR. Genome-wide association for smoking cessation success: participants in a trial with adjunctive denicotinized cigarettes. *Mol Med*. 2009; 15(7-8):268-274.

30. Broms U, Silventoinen K, Madden PA, Heath AC, Kaprio J. Genetic architecture of smoking behavior: a study of Finnish adult twins. *Twin Res Hum Genet*. 2006; 9:64-72.

31. Lessov CN, Martin NG, Statham DJ, *et al*. Defining nicotine dependence for genetic research: evidence from Australian twins. *Psychol Med*. 2004; 34(5):865-879.

32. Rezaishiraz H, Hyland A, Mahoney MC, O'Connor RJ, Cummings KM. Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine Tob Res*. 2007; 9:1139-1146.

33. Personal communication from Jed Rose: Summary of Quest Smoking-cessation study, conducted at Duke University. September 16, 2003.

34. Barrett SP. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behav Pharmacol*. 2010; 21(2):144-152.

35. Perkins K, Karelitz JL, Conklin CA, Sayette MA, Giedgowd GE. Acute negative affect relief from smoking depends on the affect situation and measure but not nicotine. *Biol Psychiatry*. 2010; 67:707-714.

36. Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tobacco Control*. 2010; 19:367-373.

37. Strasser AA, O'Connor RJ, Mooney ME, Wileyto EP. Digital image analysis of cigarette filter stains as an indicator of compensatory smoking. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(12):2565-2569.

38. Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug Alcohol Depend*. 2007; 86:294-300.

39. Donny EC, Houtsmuler E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction*. 2007; 102:324-334.

40. Girdhar G, Xu S, Jesty J, Bluestein D. In vitro model of platelet-endothelial activation due to cigarette smoke under cardiovascular circulation conditions. *Ann Biomed Eng*. 2008; 36(7):1142-51.

41. Perkins KA, Jacobs, L, Ciccocioppo M, Conklin C, Sayette M, Caggiula A. The influence of instructions and nicotine dose on the subjective and reinforcing effects of smoking. *Exp Clin Psychopharmacol*. 2004; 12(2):91-101.

42. Naqvi NH, Bechara A. The airway sensory impact of nicotine contributes to the conditioned reinforcing effects of individual puffs from cigarettes. *Pharmacol Biochem Behav*. 2005; 81(4):821-829.

43. Rukstalis M, Jepson C, Strasser A, *et al*. Natlrexone reduces the relative reinforcing value of nicotine in a cigarette smoking choice paradigm. *Psychopharmacology*. 2005; 180:41-81.

44. Perkins KA, Doyle T, Ciccocioppo M, Conklin C, Sayette M, Caggiula A. Sex differences in the influence of nicotine dose instructions on the reinforcing and self-reported rewarding effects of smoking. *Psychopharmacology*. 2006; 184:600-607.

45. Ray R, Jepson C, Patterson F. Association of *OPRM1* A118G variant with the relative reinforcing value of nicotine. *Psychopharmacology*. 2006; 188:355-363.

46. Kelemen WL, Kaighobadi F. Expectancy and Pharmacology Influence the Subjective Effects of Nicotine in a Balanced-Placebo Design. I. 2007; 15(1):93-101.

47. Lindsey KP, Frederick BB, Ryan ET, Nickerson LD, Lukas SE. fMRI imaging of the effects of smoked tobacco and placebo tobacco. *J EEG Clin Neurosci* Abstracts. Oct 2007.

48. McClernon FJ, Hiott FB, Liu J, Salley AN, Behm FM, Rose JE. Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: results of a preliminary functional magnetic resonance imaging study. *Addict Biol*. 2007; 12(3-4):503-512.

49. Kelemen WL. Stimulus and Response Expectancies Influence the Cognitive Effects of Cigarettes. *Journal of Smoking Cessation*. 2008; 3(2):136-143.

50. Attwood AS, Penton-Voak IS, Munafo MR. Effects of acute nicotine administration on ratings of attractiveness of facial cues. *Nicotine and Tob Res*. 2009; 11(1):44-48.

51. Brody AL, Mandelkern MA, Olmstead RE, *et al*. Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology*. 2009a; 34:282-289.

52. Brody AL, Mandelkern MA, Costello MR, *et al*. Brain nicotinic acetylcholine receptor occupancy: effect of smoking a denicotinized cigarette. *Inter J Neuropsychopharmacol*. 2009b; 12(3):305-316.

53. King A, McNamara P, Conrad M, Cao D. Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women. *Psychopharmacol*. 2009; 207:107-117.

54. Rose JE, Behm FM, Murugesan T, McClernon FJ. Silver acetate interactions with nicotine and non-nicotine smoke components. *Exp Clin Psychopharmacol*. 2010; 18(6):462-469.

55. Chen J, Higby R, Tian D, et al. Toxicological Analysis of Low-Nicotine and Nicotine-Free Cigarettes. *Toxicology*. 2008; 249(2-3):194-203.

56. Perkins KA. Sex differences in nicotine reinforcement and reward: influences on the persistence of tobacco smoking. In: Bevins R, Caggiula AR, eds. *The Motivational Impact of Nicotine and its Role in Tobacco Use*. New York: Springer-Verlag; 2009:143-169.

57. Benowitz NL, Hatsukami DL. Gender differences in the pharmacology of nicotine addiction. *Addiction Biology*. 1998; 3:383-404.

58. Borrelli B, Papandonatos G, Spring B, Hitsman B, Niaura R. Experimenter-defined quit rates for smoking cessation: adherence improves outcomes for women but not for men. *Addiction*. 2004; 99:378-385.

59. Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women. *J Consult Clin Psychol*. 2004; 72:712-722.

60. Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of bupropion SR. *Addiction*. 2004; 99:1462-1469.

61. Wetter D, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Bater TB. Gender differences in smoking cessation. *J Consult Clin Psychol*. 1999; 67:555-562.

62. International Early Lung Cancer Action Program Investigators. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. *JAMA*. 2006; 296:180-184.

63. Prescott E, Hippe M, Schnohr P, Ole Hein H, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *Br Med J*. 1998; 316:1043-1047.

64. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptivility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respiratory Med*. 2006; 100:1110-1116.

65. West R, Hajek P, Nisson F, Foulds J, May S, Meadows A. Individual differences in preferences for and response to four nicotine replacement products. *Psychopharmacology*. 2001; 153:225-230.

66. Girdhar G, Xu S, Bluestein D, Jesty J. Reduced nicotine cigarettes increase platelet activation in smokers in vivo: A dilemma in harm reduction. *Nicotine Tob Res*. 2008b; 10(12):1737-1744.

67. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction, the implications for tobacco regulation. *New Engl J Med*. 1994; 331(2):123-125.

68. Benowitz NL, Jacob P III, Kozlowski LT, Yu L. Influence of smoking fewer cigarettes on exposure to tar, nicotine, and carbon monoxide. *New Engl J Med*. 1986; 315:1310-1313.

69. Tobacco Products Scientific Advisory Committee. Draft Report and Recommendations on Menthol in Cigarettes. May 2011.

Reference #1

U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

The full report is available online at:

http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm.

Vital Signs: Current Cigarette Smoking Among Adults Aged ≥18 Years — United States, 2009

On September 7, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

ABSTRACT

Background: Cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States, causing approximately 443,000 premature deaths annually.

Methods: The 2009 National Health Interview Survey and the 2009 Behavioral Risk Factor Surveillance System were used to estimate national and state adult smoking prevalence, respectively. Cigarette smokers were defined as adults aged ≥18 years who reported having smoked ≥100 cigarettes in their lifetime and now smoke every day or some days.

Results: In 2009, 20.6% of U.S. adults aged ≥18 years were current cigarette smokers. Men (23.5%) were more likely than women (17.9%) to be current smokers. The prevalence of smoking was 31.1% among persons below the federal poverty level. For adults aged ≥25 years, the prevalence of smoking was 28.5% among persons with less than a high school diploma, compared with 5.6% among those with a graduate degree. Regional differences were observed, with the West having the lowest prevalence (16.4%) and higher prevalences being observed in the South (21.8%) and Midwest (23.1%). From 2005 to 2009, the proportion of U.S. adults who were current cigarette smokers did not change (20.9% in 2005 and 20.6% in 2009).

Conclusions: Previous declines in smoking prevalence in the United States have stalled during the past 5 years; the burden of cigarette smoking continues to be high, especially in persons living below the federal poverty level and with low educational attainment. Sustained, adequately funded, comprehensive tobacco control programs could reduce adult smoking.

Implications for Public Health Practice: To further reduce disease and death from cigarette smoking, declines in cigarette smoking among adults must accelerate. The Patient Protection and Affordable Care Act is expected to expand access to evidence-based smoking-cessation services and treatments; this likely will result in additional use of these services and reductions of current smoking and its adverse effects among U.S. adults. Population-based prevention strategies such as tobacco taxes, media campaigns, and smoke-free policies, in concert with clinical cessation interventions, can help adults quit and prevent the uptake of tobacco use, furthering the reduction in the current prevalence of tobacco use in the United States across age groups.

Cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States. The negative health consequences of cigarette smoking have been well-documented and include cardiovascular disease, multiple cancers, pulmonary disease, adverse reproductive outcomes, and exacerbation of other chronic health conditions (*1*). Cigarette smoking causes approximately 443,000 premature deaths in the United States annually and $193 billion in direct health-care expenditures and productivity losses because of premature mortality each year.*

Despite significant declines during the past 30 years, cigarette smoking in the United States continues

*Additional information available at http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm.

to be widespread; in 2008, one in five U.S. adults (20.6%) were current smokers (*2*). Year-to-year decreases in smoking prevalence have been observed only sporadically in recent years. For example, a slight decrease occurred from 2006 to 2007 but not from 2007 to 2008 (*2*). Monitoring tobacco use is essential in the effort to curb the epidemic of tobacco use.† To assess progress toward the *Healthy People 2010* objective of reducing the prevalence of cigarette smoking among adults to ≤12% (objective 27-1a),§ this report provides the most recent national estimates of smoking prevalence among adults aged ≥18 years, based on data from the 2009 National Health Interview Survey (NHIS), and provides state-level estimates based on data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) survey.

Methods

The 2009 NHIS adult core questionnaire collects national health information on illness and disability. The questionnaire was administered by in-person interview and included a random probability sample of 27,731 noninstitutionalized civilian adults aged ≥18 years; the overall response rate was 65.4%. Of the 27,731, a total of 128 were excluded because of unknown smoking status; thus, the final sample size used in the analyses was 27,603. The BRFSS survey is a state-based, random-digit–dialed telephone survey of the noninstitutionalized civilian adult population and collects information on preventive health practices, health-risk behaviors, and health-care access in the United States. The core questionnaire includes questions on current cigarette smoking; the Council of American Survey and Research Organizations (CASRO) median response rate was 52.5% (from 38.0% in Oregon to 66.9% in Nebraska), and the median cooperation rate was 75.0% (55.5% in California to 88.0% in Kentucky).¶

Smoking status was defined identically for both surveillance systems by using two questions, "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes every day, some days, or not at all?" Respondents who had smoked at least 100 cigarettes during their lifetime and, at the time of interview, reported smoking every day or some days were classified as current smokers. Smoking status was examined by race/ethnicity, age group, education (among persons aged ≥25 years), poverty status, and region (overall and by sex). Starting in 2007, income-related follow-up questions were added to NHIS to reduce the number of responses with unknown values.** For this report, poverty status was defined using 2008 poverty thresholds published by the U.S. Census Bureau in 2009; family income was reported by the family respondent, who might or might not have been the same as the sample adult respondent from whom smoking information was collected.

Data from the 2009 NHIS were adjusted for nonresponse and weighted to provide national estimates of cigarette smoking prevalence; 95% confidence intervals were calculated to account for the survey's multistage probability sample design. Data from the 2009 BRFSS were weighted to adjust for differences in probability of selection and nonresponse, as well as noncoverage (e.g., households lacking landlines), and these sampling weights were used to calculate all estimates. Using NHIS data, the Wald test from logistic regression analysis was used to analyze temporal changes in current smoking prevalence during 2005–2009, overall and by region. For this 5-year trend analysis, results were adjusted for sex, age, and race/ethnicity; a p-value of <0.05 was used to determine statistical significance. NHIS results with relative standard error of ≥30% are not reported.

Results

In 2009, an estimated 20.6% (46.6 million) of U.S. adults were current cigarette smokers; of these, 78.1% (36.4 million) smoked every day, and 21.9% (10.2 million) smoked on some days. Prevalence of current smoking was higher among men (23.5%) than women (17.9%) (Table). Among racial/ethnic groups, Asians had the lowest prevalence (12.0%), and Hispanics had a lower prevalence of smoking (14.5%) than non-Hispanic blacks (21.3%) and non-Hispanic whites (22.1%). Adults reporting multiple races had the highest prevalence (29.5%), followed by American Indians/Alaska Natives (23.2%).

† Additional information available at http://www.who.int/tobacco/mpower/mpower_report_full_2008.pdf.

§ Additional information available at http://www.healthypeople.gov/document/html/objectives/27-01.htm.

¶ Based on Council of American Survey and Research Organizations (CASRO) definitions. The response rate is the percentage of persons who completed interviews among all eligible persons, including those who were not successfully contacted. The cooperation rate is the percentage of persons who completed interviews among all eligible persons who were contacted.

** Additional information available at ftp://ftp.cdc.gov/pub/health_statistics/nchs/dataset_documentation/nhis/1997/srvydesc.pdf.

TABLE. Percentage of persons aged ≥18 years who were current cigarette smokers,* by selected characteristics — National Health Interview Survey, United States, 2009

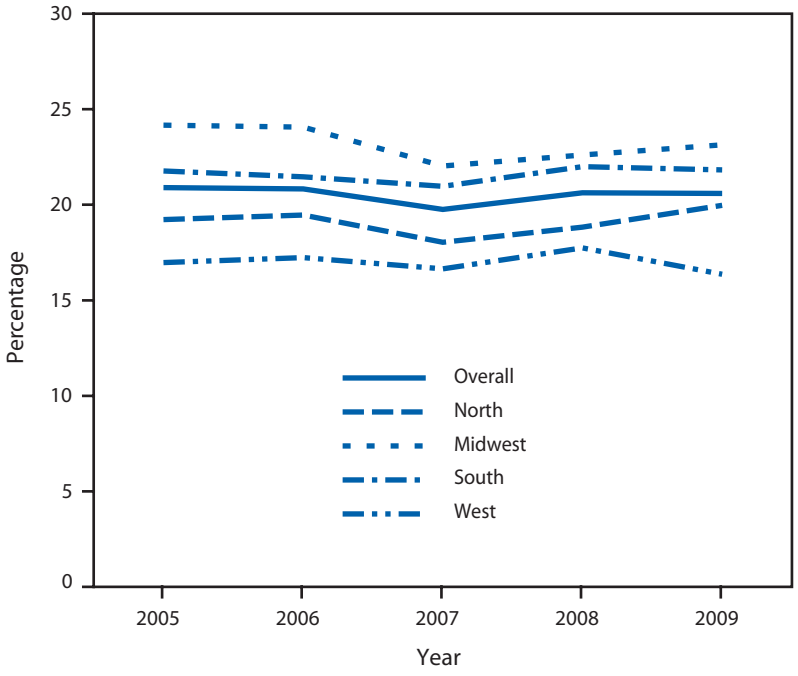
Characteristic	Total (N = 27,603) %	Total (N = 27,603) (95% CI)	Men (n = 12,193) %	Men (n = 12,193) (95% CI†)	Women (n = 15,410) %	Women (n = 15,410) (95% CI)
Age group (yrs)						
18–24	**21.8**	**(19.4–24.2)**	28.0	(24.5–31.5)	15.6	(12.9–18.3)
25–44	**24.0**	**(22.8–25.1)**	26.5	(24.7–28.2)	21.5	(20.1–22.9)
45–64	**21.9**	**(20.7–23.2)**	24.5	(22.8–26.2)	19.5	(17.9–21.1)
≥65	**9.5**	**(8.5–10.5)**	9.5	(8.1–10.9)	9.5	(8.2–10.8)
Race/Ethnicity§						
White, non-Hispanic	**22.1**	**(21.2–23.1)**	24.5	(23.2–25.9)	19.8	(18.8–20.8)
Black, non-Hispanic	**21.3**	**(19.6–22.9)**	23.9	(21.5–26.2)	19.2	(17.1–21.3)
Hispanic	**14.5**	**(13.2–15.8)**	19.0	(16.9–21.1)	9.8	(8.5–11.0)
American Indian/Alaska Native	**23.2**	**(12.9–33.5)**	29.7	(15.4–44.0)	—¶	—
Asian, non-Hispanic**	**12.0**	**(10.0–14.0)**	16.9	(14.0–19.9)	7.5	(4.8–10.3)
Multiple race, non-Hispanic	**29.5**	**(22.9–36.1)**	33.7	(24.4–43.0)	24.8	(16.6–33.0)
Education††						
0–12 yrs (no diploma)	**26.4**	**(24.5–28.3)**	30.5	(27.6–33.5)	22.2	(19.9–24.5)
≤8 yrs	**17.1**	**(14.5–19.6)**	22.2	(18.0–26.4)	11.9	(9.2–14.7)
9–11 yrs	**33.6**	**(30.7–36.5)**	36.5	(32.2–40.9)	30.5	(26.6–34.4)
12 yrs (no diploma)	**28.5**	**(23.2–33.9)**	34.1	(26.0–42.1)	23.3	(17.0–29.6)
GED§§	**49.1**	**(44.5–53.8)**	53.2	(46.6–59.8)	44.7	(38.2–51.2)
High school graduate	**25.1**	**(23.6–26.5)**	29.0	(26.9–31.2)	21.5	(19.8–23.3)
Some college (no degree)	**23.3**	**(21.7–24.9)**	26.1	(23.4–28.8)	21.0	(19.0–22.9)
Associate degree	**19.7**	**(17.9–21.5)**	20.6	(17.5–23.6)	19.1	(16.5–21.6)
Undergraduate degree	**11.1**	**(10.0–12.3)**	12.4	(10.7–14.2)	9.9	(8.3–11.4)
Graduate degree	**5.6**	**(4.6–6.6)**	4.9	(3.6–6.3)	6.3	(4.7–7.9)
Poverty status¶¶						
At or above poverty level	**19.4**	**(18.6–20.2)**	22.2	(21.1–23.3)	16.7	(15.7–17.6)
Below poverty level	**31.1**	**(29.1–32.9)**	34.2	(31.0–37.5)	28.7	(26.5–30.9)
Unspecified	**17.3**	**(15.3–19.3)**	22.3	(18.6–26.1)	13.2	(11.0–15.4)
Region***						
Northeast	**20.0**	**(18.0–22.0)**	23.4	(20.5–26.3)	16.9	(14.8–19.0)
New England	**19.4**	**(15.2–23.6)**	21.5	(14.4–28.6)	17.5	(14.6–20.4)
Mid-Atlantic	**20.2**	**(18.0–22.4)**	24.1	(21.1–27.1)	16.7	(14.1–19.3)
Midwest	**23.1**	**(21.6–24.7)**	25.7	(23.3–28.1)	20.8	(19.2–22.3)
East North Central	**23.8**	**(22.1–25.5)**	26.7	(23.8–29.6)	21.1	(19.5–22.6)
West North Central	**21.8**	**(18.8–24.8)**	23.6	(19.7–27.5)	20.1	(16.5–23.7)
South	**21.8**	**(20.7–22.9)**	24.5	(22.8–26.2)	19.3	(18.1–20.5)
South Atlantic	**20.1**	**(18.7–21.5)**	22.3	(20.1–24.5)	18.0	(16.4–19.6)
East South Central	**25.8**	**(22.7–28.9)**	30.1	(25.0–35.2)	22.3	(20.0–24.6)
West South Central	**22.5**	**(20.5–24.5)**	25.5	(22.6–28.4)	19.8	(17.4–22.2)
West	**16.4**	**(14.9–17.9)**	19.5	(17.6–21.4)	13.3	(11.3–15.2)
Mountain	**18.8**	**(16.0–21.6)**	21.7	(18.1–25.3)	16.0	(13.0–19.0)
Pacific	**15.3**	**(13.6–17.0)**	18.6	(16.4–20.8)	12.1	(9.7–14.5)
Total	**20.6**	**(19.9–21.3)**	**23.5**	**(22.4–24.5)**	**17.9**	**(17.1–18.7)**

* Persons who reported smoking at least 100 cigarettes during their lifetimes and who, at the time of interview, reported smoking every day or some days. Excludes 128 respondents whose smoking status was unknown.
† 95% confidence interval.
§ Excludes 53 respondents of unknown race.
¶ Data not reported because of unstable percentages; relative standard error ≥30%.
** Does not include Native Hawaiians or Other Pacific Islanders.
†† Among persons aged ≥25 years. Excludes 137 persons whose educational level was unknown.
§§ General Educational Development certificate.
¶¶ Family income is reported by the family respondent who might or might not be the same as the sample adult respondent from whom smoking information is collected; 2009 estimates are based on reported family income and 2008 poverty thresholds published by the U.S. Census Bureau.
*** *New England:* Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut. *Mid-Atlantic:* New York, Pennsylvania, and New Jersey. *East North Central:* Wisconsin, Michigan, Illinois, Indiana, and Ohio. *West North Central:* Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, and Iowa. *South Atlantic:* Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, and Florida. *East South Central:* Kentucky, Tennessee, Mississippi, and Alabama. *West South Central:* Oklahoma, Texas, Arkansas, and Louisiana. *Mountain:* Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, and New Mexico. *Pacific:* Alaska, Washington, Oregon, California, and Hawaii.

Key Points

- Smoking causes approximately 443,000 premature deaths, accounts for up to 30% of cancer deaths, and is the single most preventable cause of disease and death in the United States.
- Despite the adverse health effects of smoking cigarettes, one in five U.S. adults (46.6 million men and women) currently smoke.
- The prevalence of adult smoking is not decreasing. Effective population-based strategies to encourage cessation (e.g., tobacco taxes, smoke-free policies, and media campaigns) are essential to accelerate the reduction in tobacco use among adults in the United States and prevent smoking initiation in young persons.
- Effective cessation methods should be made available to increase success rates when tobacco users make quit attempts.
- Additional information is available at http://www.cdc.gov/tobacco and http://www.cdc.gov/vitalsigns.

FIGURE 1. Percentage of adults aged ≥18 years who were current smokers,* by geographic region — National Health Interview Survey, United States, 2005–2009



* Persons who reported smoking at least 100 cigarettes during their lifetimes and who, at the time of the survey, reported smoking every day or some days.

Variations in smoking prevalence in 2009 were observed by education level (Table). Smoking prevalence was highest among adults who had obtained a General Education Development certificate (GED) (49.1%) and generally declined with increasing education, being lowest among adults with a graduate degree (5.6%). The prevalence of current smoking was higher among adults living below the federal poverty level (31.1%) than among those at or above this level (19.4%). Smoking prevalence did not vary significantly for adults aged 18–24 years (21.8%), 25–44 years (24.0%), and 45–64 years (21.9%); however, it was lowest for adults aged ≥65 years (9.5%). Regionally, smoking prevalence was higher in the Midwest (23.1%) and South (21.8%), and lowest prevalence for adult current smoking was observed for the West (16.4%).

During 2005–2009, the proportion of U.S. adults who were current cigarette smokers was 20.9% in 2005†† and 20.6% in 2009, with no significant difference (Figure 1). No significant changes in current smoking prevalence for U.S. adults were observed during the 5-year period overall and for each of the four regions: Northeast, Midwest, South, or West ($p \geq 0.05$).

By state, the prevalence of current smoking ranged from 9.8% (Utah) to 25.6% (Kentucky and West Virginia) (Figure 2). States with the highest prevalence of adult current smoking were clustered in the Midwest and Southeast regions.

Conclusions and Comment

The results of these analyses indicate that the national estimates for the prevalence of current cigarette smoking among adults aged ≥18 years did not decline from 2008 (20.6%) (*2*) to 2009, and during the past 5 years (2005–2009) virtually no change has been observed, even by region. In 2009, certain population subgroups (e.g., Hispanic and Asian women, persons with higher levels of education, and older adults) continue to meet the *Healthy People 2010* target of ≤12% prevalence of smoking. Although smoking prevalence was found to be lowest among Asian and Hispanic women, the findings in this report cannot assess specific Asian and Hispanic subgroups. In a previous report, variations in smoking

†† Additional information available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5542a1.htm.

prevalence were observed within specific Asian and Hispanic subgroups and between the sexes within these subgroups, suggesting that overall prevalence for Asians and Hispanics do not accurately represent the wide variability across subgroups (*3*).

Differences in understanding the health hazards of smoking and receptivity to antismoking messages might be related to the prevalence variations observed by education level (*4*). For example, persons with higher levels of education might have a better understanding of the health hazards of smoking and might be more receptive to health messaging about the dangers of smoking (*4*). Nonetheless, most population subgroups, particularly those with low education and income levels, will not meet the *Healthy People 2010* target.

Differences also were noted by state and region. In 2009, the lowest prevalence was observed in the West, with lowest prevalence in Utah, followed by California. California traditionally has been cited for its success in tobacco control because of its long-running comprehensive tobacco control program (*5*). California's adult smoking prevalence declined approximately 40% during 1998–2006, and consequently lung cancer incidence in California has been declining four times faster than in the rest of the nation (*5*). Similarly, Maine, New York, and Washington have seen 45%–60% reductions in youth smoking with sustained comprehensive statewide programs (*5*).

Youth smoking is an important indicator to monitor because most adult established smokers (>80%) begin before the age of 18 years.[§§] In 2009, one in five U.S. high school students (19.5%) reported smoking cigarettes in the preceding 30 days (*6*). Moreover, declines in current smoking among high school students have slowed, with an 11% decline from 21.9% in 2003 to 19.5% in 2009 compared with a 40% decline observed from 1997 (36.4%) to 2003 (21.9%) (*7*). The slowing in the decline observed for youth cigarette smoking indicates that cigarette smoking among adults and the associated morbidity and mortality will continue to be important public health issues for the foreseeable future.

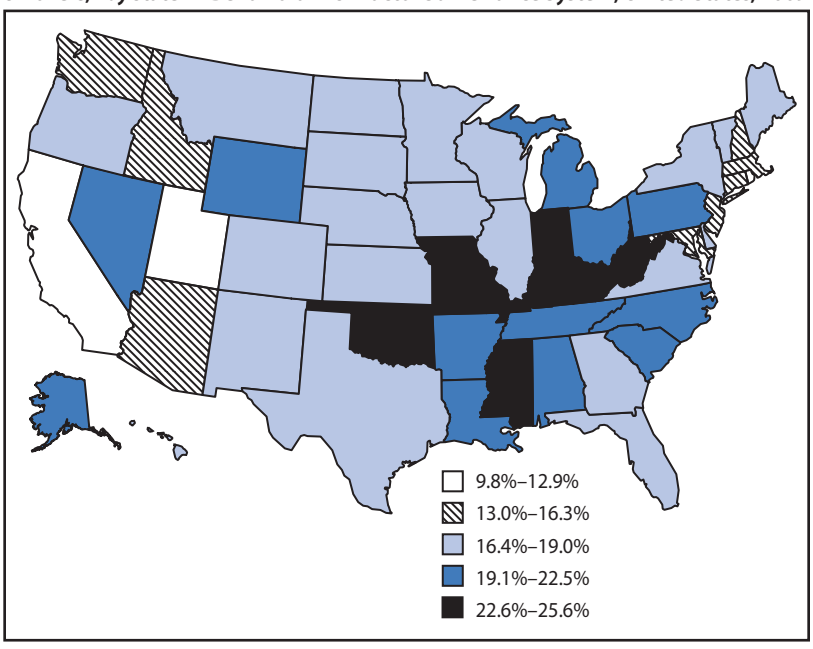
The findings in this report are subject to at least six limitations. First, the estimates of cigarette smoking were self-reported and were not validated by biochemical tests. However, other studies using levels of serum cotinine (a breakdown product of nicotine), yield similar prevalence estimates as those obtained from self-reports (*8*). Second, questionnaires are administered only in English and Spanish; therefore, smoking prevalence for certain racial/ethnic populations might be overestimated or underestimated if English and Spanish are not the primary languages spoken. Third, race/ethnicity was not adjusted for socioeconomic status. Fourth, because NHIS and BRFSS do not include institutionalized populations and persons in the military, the results are not generalizable to these groups. Fifth, BRFSS does not currently include adults without telephone service (1.9%) or with wireless-only service (13.6%).[¶¶] Because adults with wireless-only service are more likely to smoke cigarettes than the rest of the U.S. population and wireless-only service varies by state, state smoking prevalence might be underestimated.[***] Finally, small samples sizes for certain population groups resulted in some imprecise estimates. This might explain why

[§§] Additional information available at http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8results.cfm.

[¶¶] Additional information available at http://www.cdc.gov/nchs/data/nhsr/nhsr014.pdf.

[***] Additional information available at http://www.cdc.gov/nchs/nhis.htm.

FIGURE 2. Percentage of persons aged ≥18 years who were current cigarette smokers,* by state — Behavioral Risk Factor Surveillance System, United States, 2009



* Persons who reported smoking at least 100 cigarettes during their lifetimes and who, at the time of the survey, reported smoking every day or some days.

the 2009 prevalence estimate for American Indian/Alaska Native women is lower than prevalence estimates from recent years.

The *Healthy People 2010* objective of reducing the overall prevalence of cigarette smoking among U.S. adults to ≤12% (objective 27-1a) will not be met in 2010. However, for some subpopulations and states, this goal has been reached, demonstrating that the national target is achievable. To meet this goal for the entire population in the future, evidence-based strategies focused on populations such as persons with lower education are needed (*5*). Effective strategies including price increases, comprehensive smoke-free policies, and media campaigns to counter pro-tobacco industry influences need to be implemented aggressively in coordination with providing access to affordable and effective cessation treatments and services (*5,9*). If each state sustained comprehensive tobacco control programs for 5 years with CDC-recommended levels of funding, an estimated 5 million fewer persons in the country would smoke, resulting in prevention of premature tobacco-related deaths (*5*).

As this analysis shows, some populations have a higher prevalence of cigarette use; thus, a focus on reducing tobacco-related disparities also is necessary (*5*). The Patient Protection and Affordable Care Act[†††] is expected to expand access to evidence-based smoking-cessation services and treatments. Given the decline in smoking prevalence that was observed after the implementation of a mandated tobacco cessation coverage for the Massachusetts Medicaid program (*10*), expanded access to cessation services and treatments might result in reductions in current smoking and its adverse effects among U.S. adults. For this to occur, health professionals need to better identify, educate, and offer appropriate cessation services to persons who use tobacco.

The enactment of the 2009 Family Smoking Prevention and Tobacco Control Act[§§§] has provided new opportunities for reductions in tobacco use (*7,9*). The Act gives the Food and Drug Administration authority to regulate the manufacturing, marketing, and distribution of tobacco products. Full implementation of comprehensive tobacco control policies and programs at CDC-recommended levels of funding (*5*) would resume progress toward reducing the prevalence of smoking in the population.

[†††] Additional information available at http://www.dol.gov/ebsa/healthreform.

[§§§] Family Smoking Prevention and Tobacco Control Act, Pub. L. 111-31, 123 Stat1776 (2009). Additional information available at http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/content-detail.html.

Reported by

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References

1. US Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, CDC; 2004. Available at http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm.
2. CDC. Cigarette smoking among adults and trends in smoking cessation—United States, 2008. MMWR 2009;58:1227–32.
3. Caraballo RS, Yee SL, Gfroerer J, Mizra SA. Adult tobacco use among racial and ethnic groups living in the United States, 2002–2005. Prev Chronic Dis 2008;5:1–9.
4. Siahpush M, McNeill A, Hammond D, Fong GT. Socioeconomic and country variations in knowledge of health risks of tobacco smoking and toxic constituents of smoke: results from the 2002 International Tobacco Control (ITC) Four Country Survey. Tob Control 2006;15(Suppl III):65–70.
5. CDC. Best practices for comprehensive tobacco control programs—2007. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. Available at http://www.cdc.gov/tobacco/tobacco_control_programs/stateandcommunity/best_practices.
6. CDC. Youth Risk Behavior Surveillance—United States, 2009. MMWR 2010;59(No. SS-5).
7. CDC. Cigarette use among high school students—United States, 1991–2009 MMWR 2010;59:797–801.
8. Caraballo RS, Giovino GA, Pechacek TF, Mowery PD. Factors associated with discrepancies between self-reports on cigarette smoking and measured serum cotinine levels among person aged 17 years or older: third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol 2001;153:807–14.
9. CDC. CDC Grand Rounds: current opportunities in tobacco control. MMWR 2010;59:487–92.
10. Land T, Warner D, Paskowsky M, et al. Medicaid coverage for tobacco dependence treatments in Massachusetts and associated decreases in smoking prevalence. PLoS One 2010;5:e9770.

Reference #3

Healthy People 2010 Tobacco use objectives.

The full report is available online at:

http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=41



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Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics

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Key Words

Nicotine, addiction, smoking, pharmacogenetics, varenicline, bupropion

Abstract

Nicotine sustains tobacco addiction, a major cause of disability and premature death. Nicotine binds to nicotinic cholinergic receptors, facilitating neurotransmitter release and thereby mediating the complex actions of nicotine in tobacco users. Dopamine, glutamate, and gamma aminobutyric acid release are particularly important in the development of nicotine dependence, and corticotropin-releasing factor appears to contribute to nicotine withdrawal. Nicotine dependence is highly heritable. Genetic studies indicate roles for nicotinic receptor subtypes, as well as genes involved in neuroplasticity and learning, in development of dependence. Nicotine is primarily metabolized by CYP 2A6, and variability in rate of metabolism contributes to vulnerability to tobacco dependence, response to smoking cessation treatment, and lung cancer risk. Tobacco addiction is much more common in persons with mental illness and substance abuse disorders, representing a high proportion of current smokers. Pharmacotherapeutic approaches to tobacco addiction include nicotine replacement, bupropion, and varenicline, the latter a selective nicotine receptor partial agonist.

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INTRODUCTION

Use of nicotine sustains tobacco addiction, which in turn causes devastating health problems, including heart disease, lung disease, and cancer, and increased susceptibility to a variety of infectious diseases. Smoking harms almost every organ of the body (1). Quitting smoking at any age leads to significant reductions in the risks associated with it, and the vast majority of smokers in the United States indicate an interest in quitting (2). Despite these facts, however, approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence, and only approximately 3% remain abstinent at six months. This illustrates the powerful force of tobacco addiction and the chronic nature of the disorder.

Although most of the toxicity of smoking is related to other components of cigarette smoke, it is primarily the pharmacologic effects of nicotine that produce the addiction to tobacco. An understanding of how nicotine produces addiction and influences smoking behavior provides a necessary basis for optimal smoking cessation intervention. This article reviews the neurobiology of nicotine addiction and withdrawal, as well as the implications for nicotine addiction therapy.

MECHANISMS OF ACTION

Neuropharmacology

Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring, (S)-nicotine, found in tobacco, binds stereoselectively to nicotinic cholinergic receptors (nAChRs). (R)-nicotine, found in small quantities in cigarette smoke owing to racemization during the pyrolysis process, is a weak agonist at nAChRs.

When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and is carried in smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation. It then enters the arterial circulation and moves quickly to the brain. Nicotine diffuses readily into brain tissue, where it binds to nAChRs, which are ligand-gated ion channels. When a cholinergic agonist binds to the outside of the channel, the channel opens, allowing the entry of cations, including sodium and calcium. These cations further activate voltage-dependent calcium channels, allowing further calcium entry.

The nAChR complex is composed of five subunits and is found in both the peripheral and central nervous systems (3). In the mammalian brain, there are as many as nine α subunits (α_2 to α_{10}) and three βsubunits (β_2 to β_4). The most abundant receptor subtypes in the brains of humans are $\alpha_4\beta_2$, $\alpha_3\beta_4$, and α_7 (homomeric). The $\alpha_4\beta_2{}^*$ (asterisk indicates possible presence of other subunits in the receptor) receptor subtype is predominant in the human brain and is believed to be the main receptor mediating nicotine dependence. In mice, knocking out the β_2 subunit gene eliminates the behavioral effects of nicotine, such that nicotine no longer releases dopamine in the brain or maintains self-administration (4). Reinserting the β_2 subunit gene into the ventral tegmental area of a β_2 knockout mouse restores behavioral responses to nicotine (5). The α_4 subunit appears to be an important determinant of sensitivity to nicotine. In mice, a single nucleotide point mutation in the pore-forming region results in a receptor that is hypersensitive to the effects of nicotine (6). This mutation makes mice much more sensitive to nicotine-induced reward behaviors, as well as to effects on tolerance and sensitization. The $\alpha_3\beta_4$ nAChR is believed to mediate the cardiovascular effects of nicotine (7). The homomeric α_7 nAChR is thought to be involved in rapid synaptic transmission and may play a role in learning (8) and sensory gating (9). The $\alpha4\,\beta2^*$ receptor may include $\alpha5$, $\alpha6$, and/or $\beta3$ subunits, which may modulate the sensitivity and function of the receptor. For example, $\alpha5$ knockout mice are less sensitive to nicotine-induced seizures and hypolocomotion (10).

REVIEWS IN ADVANCE

Brain imaging studies demonstrate that nicotine acutely increases activity in the prefrontal cortex, thalamus, and visual system, consistent with activation of corticobasal ganglia-thalamic brain circuits (11). Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, most importantly dopamine. Nicotine causes the release of dopamine in the mesolimbic area, the corpus striatum, and the frontal cortex. Of particular importance are the dopaminergic neurons in the ventral tegmental area of the midbrain, and the release of dopamine in the shell of the nucleus accumbens, as this pathway appears to be critical in drug-induced reward (12, 13). Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid (GABA), glutamate, and endorphins, are released as well, mediating various behaviors of nicotine.

Most of the nicotine-mediated release of neurotransmitters occurs via modulation by presynaptic nAChRs, although direct release of neurotransmitters also occurs (14). Dopamine release is facilitated by nicotine-mediated augmentation of glutamate release and, with long-term treatment, by inhibition of GABA release (15). In addition to direct and indirect stimulation of neurotransmitter release, chronic cigarette smoking (but not nicotine administration) reduces brain monoamine oxidase A and B (MAOA and MAOB) activity, which would be expected to increase monoaminergic neurotransmitter levels such as dopamine and norepinephrine in synapses, thus augmenting the effects of nicotine and contributing to addiction (16). Inhibition of MAO facilitates acquisition of nicotine self-administration in rats, supporting the idea that MAO inhibition interacts with nicotine to reinforce tobacco dependence (17).

Dopamine release signals a pleasurable experience, and is critical to the reinforcing effects of nicotine and other drugs of abuse (13). Chemically or anatomically lesioning dopamine neurons in the brain prevents nicotine self-administration in rats. When intracranial self-stimulation is used as a model for brain reward in rats, nicotine acutely lowers the threshold for self-stimulation (18). Thus, through its effects on dopamine release, acute nicotine administration increases brain reward function. Likewise, nicotine withdrawal is associated with significant increases in intracranial self-stimulation reward threshold, consistent with deficient dopamine release and reduced reward (19). The decrease in brain reward function experienced during nicotine withdrawal is an essential component of nicotine addiction and a key barrier to abstinence.

With repeated exposure to nicotine, tolerance (neuroadaptation) develops to some, but not all, of the effects of nicotine (20). Concurrent with this neuroadaptation is an increase in the number of nAChR binding sites in the brain. This increase is believed to represent upregulation in response to nicotine-mediated desensitization of receptors. This desensitization may play a role in nicotine tolerance and dependence. It has been suggested that craving and withdrawal symptoms begin in chronic smokers when previously desensitized $\alpha_4\beta_2{}^*$ nAChRs become unoccupied and recover to a responsive state during periods of abstinence such as during nighttime sleep (21). Thus, nicotine binding and desensitization of these receptors during smoking may alleviate craving and withdrawal. The idea that desensitization of nAChRs occurs in the usual smoker is supported by a brain imaging study showing that cigarette smoking in amounts used by typical daily smokers maintains near-complete saturation—and thus desensitization—of brain nAChRs (22). It is speculated that smokers maintain $\alpha_4\beta_2{}^*$ nAChRs in a desensitized state to avoid withdrawal. Another theory is that conditioned smoking cues maintain smoking behavior during periods of saturation and desensitization of brain nAChRs (23, 24). In actuality, these two theories may be complementary: Smokers may continue to smoke throughout the day to maintain plasma nicotine levels that prevent the occurrence of withdrawal symptoms, and may also continue to derive some rewarding effects from the conditioned reinforcers associated with smoking such as the taste and feel of the smoke (23). Conditioning as a component of addiction is discussed in more detail below.

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REVIEWS IN ADVANCE

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Nicotine withdrawal is associated with a negative emotional state, including anxiety and the perception of increased stress, which may represent powerful stimuli to relapse to tobacco use. There is evidence that the activation of the extrahypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor system contributes to negative affect during nicotine withdrawal. During precipitated nicotine withdrawal in rats, which is associated with anxiety-like behavior, CRF is released in the central nucleus of the amygdala (25). CRF activation produces anxiety behavior, and pharmacologic blockade of CRF1 receptors inhibits the anxiogenic effects of nicotine withdrawal. Blocking the CRF1 nicotine receptor also has been shown to prevent the increase in nicotine self-administration that occurs during abstinence from forced nicotine administration in rats.

Withdrawal from other drugs of abuse such as alcohol, cocaine, opiates, and cannabinoids is also associated with activation of the extrahypothalamic CRF system, suggesting that this is a common mechanism of affective manifestations of drug withdrawal. Thus, both the hypoactivity of the dopaminergic system and the activation of the CRF system appear to mediate nicotine withdrawal symptoms that often precipitate relapse to smoking.

Psychoactive Effects of Nicotine and Nicotine Withdrawal

In humans, nicotine from tobacco induces stimulation and pleasure, and reduces stress and anxiety. Smokers come to use nicotine to modulate their level of arousal and for mood control in daily life. Smoking may improve concentration, reaction time, and performance of certain tasks. When a person stops smoking, nicotine withdrawal symptoms emerge. These include irritability, depressed mood, restlessness, anxiety, problems getting along with friends and family, difficulty concentrating, increased hunger and eating, insomnia, and craving for tobacco (26). Nicotine withdrawal in untreated smokers produces mood disturbances comparable in intensity to those seen in psychiatric outpatients (27). Hedonic dysregulation, the feeling that there is little pleasure in life, and activities that were once rewarding are no longer enjoyable, is seen with withdrawal from nicotine and from other drugs of abuse (28). It is hypothesized that a relative deficiency in dopamine release following long-standing nicotine exposure accounts for many of the mood disorders and the anhedonia, as well as the tobacco craving, that may persist in smokers for a long time after they have quit.

Thus, the pharmacologic bases of nicotine addiction can be seen as a combination of positive reinforcements, such as enhancement of mood or functioning, as well as avoidance of the negative consequences of prior drug use—that is, the relief of withdrawal symptoms—in situations when nicotine is not available. In addition to these direct pharmacologic mechanisms, there is an important role for conditioning in the development of tobacco addiction.

Conditioned Behavior and Nicotine Addiction

All drug-taking behavior is learned, a result of conditioning. Drug-taking behavior is made more probable, or reinforced, by the consequences of the pharmacologic actions of the drug, as discussed for nicotine above. At the same time, the user begins to associate specific moods, situations, or environmental factors with the rewarding effects of the drug. Respiratory tract sensory cues associated with tobacco smoking represent a type of conditioned reinforcer that has been shown to play an important role in the regulation of smoke intake and the craving to smoke, as well as the rewarding effects of smoking (29, 30).

The association between such cues and anticipated drug effects, and the resulting urge to use the drug, is a type of conditioning. Animal studies find that nicotine exposure increases the behavioral control of conditioned stimuli, which may contribute to the compulsivity of smoking behavior (31).

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Furthermore, experimental studies in nicotine-dependent rats show that nicotine withdrawal–associated conditioned stimuli potentiate the magnitude of nicotine withdrawal, including an elevation of brain reward threshold (32). Thus, cues associated with nicotine withdrawal have the ability to decrease brain reward function.

Cigarette smoking is maintained, in part, by such conditioning. People habitually smoke cigarettes in specific situations such as after a meal, with a cup of coffee or an alcoholic drink, or with friends who smoke. The association between smoking and these other events repeated many times causes the environmental situations to become powerful cues for the urge to smoke. Likewise, aspects of the drug-taking process, such as the manipulation of smoking materials, or the taste, smell, or feel of smoke in the throat, become associated with the pleasurable effects of smoking. Even unpleasant moods can become conditioned cues for smoking. For example, a smoker may learn that not having a cigarette provokes irritability (a common symptom of the nicotine abstinence syndrome) and smoking a cigarette provides relief. After repeated experiences of this sort, a smoker may come to regard irritability from any source such as stress or frustration as a cue for smoking. Functioning imaging studies indicate that exposure to drug-associated cues activates cortical regions of the brain, including the insula. Smokers who acquire damage to the insula (for example, due to brain trauma) are more likely to quit smoking soon after the injury, are more like to remain abstinent, and are less likely to experience conscious urges to smoke compared with smokers with brain injury that does not affect the insula (33).

Although conditioning becomes an important element of drug addiction, conditioning develops only because of a pairing of the pharmacologic actions of the drug with behaviors. It has been suggested that conditioning serves to maintain nicotine use during periods of desensitization of $\alpha_4\beta_2^*$ nAChRs, in which there is a loss or decrease in the biologic response to nicotine (23). Therefore, conditioned reinforcers could be the primary motivation to smoke during periods when desensitization prevents the reinforcing effects of nicotine obtained from smoking. This relationship is renewed on a cyclic basis: After a period of abstinence, when $\alpha_4\beta_2^*$ nAChRs are once again sensitive, the rewarding effects of smoking are re-established and once again paired with the sensory stimuli of tobacco smoking, and the association of these two factors (stimuli and reward) is again strengthened. Conditioning is a major factor that causes relapse to drug use after a period of cessation. It must be addressed as a component of counseling and behavioral therapy for drug addiction.

NICOTINE PHARMACOKINETICS AND METABOLISM

Nicotine is a weak base ($pK_a = 8.0$). Absorption through mucous membranes depends on pH. Chewing tobacco, snuff, and nicotine gum are buffered with an alkaline pH to facilitate absorption through buccal mucosa. Smoking is a highly efficient form of drug administration, as the drug enters the circulation rapidly through the lungs and moves into the brain within seconds. Inhaled drugs escape first-pass intestinal and hepatic metabolism. The more rapid the rate of absorption and entry of a drug into the brain, the greater the rush, and the more reinforcing the drug. Smoking produces high concentrations of a drug in the brain that are comparable to those seen after intravenous administration. A number of substances of abuse, including marijuana, cocaine, opiates, phencyclidine, and organic solvents, are abused by the inhalational route because access to the brain is so rapid. The smoking process also allows precise dose titration, so a smoker may obtain desired affects.

Nicotine is rapidly and extensively metabolized by the liver, primarily by the liver enzyme CYP2A6 (and to a lesser extent by CYP2B6 and CYP2E1) to the cotinine (34). The metabolite cotinine is widely used as a quantitative marker for exposures to nicotine, and is useful as a

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diagnostic test for the use of tobacco and as a measure of compliance with treatments for smoking cessation. Cotinine is subsequently metabolized to trans-3′-hydroxycotinine (3HC) exclusively or nearly exclusively by CYP2A6. The ratio of 3HC to cotinine can be used as a phenotypic marker for CYP2A6 activity and for the rate of nicotine metabolism (35). The half-life of nicotine averages ~2 h, while the half-life of cotinine averages ~16 h. Cotinine levels are fairly stable throughout the day in smokers; because the levels of 3HC are formation-limited, the ratio of 3HC to cotinine is also fairly stable. This ratio can be measured in the blood, saliva, or urine of people while they are using tobacco, based on their intake of nicotine from tobacco. Nicotine and cotinine are also metabolized by glucuronidation, primarily, it is thought, via UGT 1A4, 1A9, and 2B10 (34). Although glucuronidation is usually a minor pathway of nicotine metabolism, in people who have low CYP2A6 activity, glucuronidation can be a major determinant of nicotine clearance.

Considerable genetic polymorphism in CYP2A6 and UGT activity is associated with wide individual variability and racial differences in the rate of nicotine metabolism (36, 37). Asians and African Americans metabolize nicotine on average more slowly than do Caucasians or Hispanics (38, 39). Sex hormones also substantially affect CYP2A6 activity. The rate of nicotine metabolism is faster in women than men (40). Among women, nicotine metabolism is faster in women taking estrogen-containing oral contraceptives, and is even faster during pregnancy, compared with other women.

There is considerable peak to trough oscillation in blood levels from cigarette to cigarette. However, consistent with the half-life of two hours, nicotine accumulates in the body over six to nine hours of regular smoking. Thus, smoking results not in intermittent and transient exposure to nicotine, but in an exposure that lasts 24 hours per day. Arterio-venous differences in nicotine concentration during cigarette smoking are substantial, with arterial levels exceeding venous levels up to tenfold (41). The persistence of nicotine in the brain throughout the day and night results in changes in the structure and function of nicotinic receptors and in intracellular processes of neuroadaptation, as mentioned previously.

NICOTINE METABOLISM AS A DETERMINANT OF TOBACCO USE AND DISEASE RISK

Insofar as smokers regulate their intake of nicotine to maintain particular levels of nicotine in the body throughout the day, people who metabolize nicotine more quickly would be expected to take in more cigarette smoke per day compared with slower metabolizers. This appears to be the case. Genetically poor metabolizers (e.g., people with variant CYP2A6 genes associated with substantially reduced enzyme activity) smoke on average fewer cigarettes per day and tend to have higher carbon monoxide levels than do normal metabolizers (37). In addition, genetically slow metabolizers appear to be less dependent, based on the observation that the fraction of slow metabolizers in the population of smokers decreases with increasing age of the smoker cohort, suggesting that slow metabolizers are more likely to quit. In a population of Asian and white smokers, the clearance of nicotine assessed by intravenous infusion of deuterium-labeled nicotine was positively correlated with the number of cigarettes smoked per day and the nicotine intake per cigarette, supporting the idea that clearance influences smoking behavior (39).

Genetic variation of *CYP2A6* may influence the risk of smoking-induced cancer by a mechanism in addition to its effects on smoking behavior. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is believed to contribute to lung and possibly pancreatic cancer. This nitrosamine is activated to a carcinogen in part by CYP2A6 (42). Therefore, a smoker who is a slow metabolizer would be expected to both take in less smoke per cigarette and to bioactivate less of the NNK taken in compared with a normal metabolizer. A few

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studies support this hypothesis, showing that slow metabolizers have a lower risk of lung cancer compared with normal metabolizers, although some studies do not confirm this association (43). Genetic variation of CYP2A6 activity may also explain some racial differences in lung cancer risk, such as the lower risk in Asians, who have lower CYP2A6 activity and slower nicotine clearance on average compared with whites (37, 39). However, this mechanism does not seem to hold for African-American smokers, who are also more likely to be CYP2A6 slow metabolizers, but who have a higher cancer risk compared with whites (38, 44).

GENETICS OF NICOTINE ADDICTION

Twin studies indicate a high degree of heritability (~50%) in the prevalence of cigarette smoking and the ability to quit smoking (dependence) and in the number of cigarettes smoked per day (45). Twin studies even demonstrate heritability in the nature of particular symptoms experienced when a smoker stopped smoking (46).

Numerous studies have attempted to identify genes underlying nicotine addiction, as summarized in a recent review (45). Studies of the genetics of nicotine dependence and smoking behavior are problematic because complex behaviors such as smoking are determined by multiple genes, as well as environmental factors, and because there are many different dependence phenotypes that may be examined, which may have different genetic underpinnings. Family linkage studies and candidate gene association studies have suggested a number of loci or particular genes that are associated with smoking behavior, although smoking phenotypes vary considerably from study to study. Candidate genes coding for nicotine receptor subtypes, dopamine receptors or transporters, GABA receptors, and others have been identified in various studies as being associated with different aspects of smoking behavior (47). However, subsequent research has not replicated many of these earlier findings.

Recent genome-wide association studies point to several genes that are promising signals for genetic determinants of nicotine dependence. Bierut, Saccone, and coworkers examined a phenotype that is thought to reflect a vulnerability to becoming dependent on nicotine (48, 49). All subjects had to have smoked 100 cigarettes lifetime, and the comparison groups were those who became dependent on nicotine versus those who did not become dependent. Genotype signals from the genome-wide association studies were used to guide a second-phase candidate gene association study, which resulted in several strong genetic associations. Most prominent were the α-5, α-3, and β-4 nicotinic receptor gene complex, neurexin 1, VPS13A (vacuolar sorting protein), KCNJ6 (a potassium channel), and the GABA A4 receptor gene. Of interest is that some of these genes, such as the neurexin 1 gene, are genes related to cell communication. Other genome-wide association studies have identified a number of genes affecting cell adhesion and extracellular matrix molecules that are common among various addictions, consistent with the idea that neural plasticity and learning are key determinants of individual differences in vulnerability to nicotine, as well as other drug addictions (50, 51).

NICOTINE ADDICTION AND PSYCHIATRIC COMORBIDITY

Tobacco addiction is much more prevalent with people with mental illness and substance abuse disorders. These individuals consume 44% of all cigarettes sold in the U.S., despite representing only 22% of the population (52). More than 40% of smokers report having a mental health disorder in the past month and 60% have experienced a mental health disorder in their lifetimes (52). The prevalence of smoking is higher in patients with a diagnosis of schizophrenia, major depression, bipolar disorder, anxiety disorder, panic attacks, attention deficit hyperactivity disorder,

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posttraumatic stress disorder, alcohol abuse, and illicit drug abuse than in the general population. Patients with more severe psychiatric symptoms are more likely to be smokers (53). Smokers with a history of major depression are at increased risk for experiencing depression after cessation of smoking (54).

Several mechanisms are believed to underlie comorbid nicotine addiction with mental health disorders. There appears to be a shared genetic susceptibility to tobacco addiction with alcohol abuse and major depression (55, 56). Nicotine may also serve to medicate some psychiatric symptoms. For example, the serotonin and norepinephrine released in the brain by nicotine are similar to the neurochemical effects of some antidepressant medications. Nicotine acting on alpha7 nAChRs may improve sensory gating, which is abnormal in schizophrenics (57). Improved sensory gating, secondary to nicotine intake, might be expected to enhance the ability to sort out extraneous stimuli and therefore to improve attention. As mentioned earlier, cigarette smoking inhibits MAOA and MAOB (16). MAO inhibitors are used to treat depression, suggesting that cigarette smoking might provide benefit to depressed patients in the same way. There is evidence that excessive cholinergic activity contributes to depression (58). As described earlier, regular nicotine exposure may result in desensitization of nAChRs. It is postulated that desensitization of these receptors results in stabilization of mood and amelioration of depression. Finally, nicotine, by its stimulant effects, may reduce unpleasant sedative side effects of psychiatric medications and sedation from alcohol, providing another motivation for tobacco use.

The adverse health consequences of tobacco use in people with mental illness and drug abuse are substantial. People with chronic mental illness die on average 25 years earlier than individuals without those disorders, primarily due to cardiovascular disease and diabetes (59). A substantial number of the premature deaths are undoubtedly caused by smoking. In chronic alcoholics, half of the premature deaths are attributable to cigarette smoking (60). Smoking cessation treatment is difficult in patients with psychiatric comorbidities; but given the high prevalence of smoking in this population and the enormous burden of disease due to smoking, developing effective treatments for this population is an important public health priority.

PHARMACODYNAMICS OF NICOTINE: CONTRIBUTIONS TO SMOKING-RELATED DISEASE

Because nicotine underlies addiction and sustains cigarette smoking, it is logical to consider nicotine maintenance as a potential alternative to tobacco use for smokers who cannot quit. The administration of nicotine replacement therapy in smokers has been shown to reduce smoking rates, and among those who reduce their smoking, to promote smoking cessation (61). However, the currently available nicotine delivery systems deliver nicotine into the blood stream much more slowly than does cigarette smoking, so for most smokers nicotine medications are not satisfactory substitutes for smoking. The development of a consumer-acceptable inhaled nicotine delivery system with absorption kinetics similar to those of a cigarette has been proposed and could be an important advancement in pursuing harm reduction through nicotine maintenance.

An important question in promoting nicotine maintenance is the safety of nicotine per se. Without doubt, nicotine medication is much safer than cigarette smoking, with the latter delivering not only as much or more nicotine but also thousands of toxic combustion products to the smoker. However, there are some concerns involving the safety of long-term exposure to nicotine, including cardiovascular disease, cancer, reproductive disorders, and delayed wound healing.

Nicotine is a sympathomimetic drug that releases catecholamines, increases heart rate and cardiac contractility, constricts cutaneous and coronary blood vessels, and transiently increases blood pressure (62). Nicotine also reduces sensitivity to insulin, and may aggravate or precipitate

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diabetes, and nicotine may contribute to endothelial dysfunction (63, 64). These various effects of nicotine on the cardiovascular system could, in theory, promote atherogenesis and precipitate acute ischemic events in people who have coronary artery disease. This has been of particular concern in smokers who use nicotine medication while they are still smoking. However, increased cardiovascular risk due to nicotine medication does not appear to be a problem. The dose-response curve for cardiovascular effects such as heart rate acceleration or the release of catecholamines is flat, such that adding nicotine medication to smoking produces no further effect (65). Clinical trials of nicotine patches in smokers with cardiovascular disease showed no increased risk of cardiovascular events compared with placebo (66). Furthermore, the experience of men in Sweden with a long history of snuff use, which delivers nicotine without combustion products, suggests little or no increase of cardiovascular risk (67).

Nicotine is not a direct carcinogen, but there are concerns that it may be a tumor promoter. In animal studies, nicotine can inhibit apoptosis, resulting in impaired killing of cancer cells (68). Nicotine also promotes angiogenesis in animals, an effect which could lead to greater tumor invasion and metastasis (69). Whether nicotine is a cancer promoter in people has not been established, but one report that suggests that smokers who switch to smokeless tobacco may have an increased risk of lung cancer compared with smokers who quit entirely raises concern about this possibility (70). Exposure to nitrosamines from smokeless tobacco could also explain or contribute to such an increase in lung cancer risk. Against the proposition that nicotine promotes cancer are data from Scandinavia, where the use of low nitrosamine oral snuff (snus) is very common among men. Epidemiology studies indicate that snus use is associated with an increased risk of only pancreatic cancer, which would be unlikely in a general population if nicotine exerted a general tumor-promoting action (71).

Suspected adverse reproductive effects of nicotine include most prominently fetal neuroteratogenic effects (72). In general, it is not desirable to use nicotine during pregnancy, but if the alternative is cigarette smoking, then nicotine medication is undoubtedly less hazardous. The use of snus by pregnant women in Scandanavia has been associated with an increased risk of pre-eclampsia (73). This is in contrast to a reduced risk of pre-eclampsia in smokers. The discrepancy between snus use and smoking might be due to carbon monoxide in cigarette smoke, which is expected to have vasodilatory effects that could counteract the vasoconstricting effects of nicotine. Nicotine is a potent cutaneous vasoconstrictor and can impair wound healing. However, clinical trials using nicotine replacement medication to aid cessation in surgical patients indicate that the overall outcome is much better in individuals using nicotine therapy who quit smoking compared with continued smoking (74).

PHARMACOTHERAPY TO AID SMOKING CESSATION

A complete review of the pharmacology of drugs used to treat tobacco dependence is beyond the scope of this article. The focus here is on mechanisms of action and the prospects for future therapies.

Currently, three classes of medications have been approved for smoking cessation: nicotine replacement products (patch, gum, spray, inhaler, and lozenge), bupropion. and most recently, varenicline. Although not approved by regulatory authorities for smoking cessation, clinical trials have also demonstrated the efficacy of nortriptyline and clonidine, which are considered to be second-line drugs (75). All of the drugs mentioned above have been shown in controlled clinical trials to be effective, with odds ratios ranging from two to four in comparison with placebo treatment. Absolute smoking cessation rates range from 5 to 35%, depending on the drug and the intensity of concomitant counseling.

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Nicotine Replacement Therapy

Nicotine medications act on nAChRs to mimic or replace the effects of nicotine from tobacco. Nicotine replacement medications are believed to facilitate smoking cessation in several ways. The principal action is the relief of withdrawal symptoms when a person stops tobacco use (76). Amelioration of these symptoms is observed with relatively low blood levels of nicotine. A second mechanism of benefit is positive reinforcement, particularly for the arousal and stress-relieving effects. The degree of positive reinforcement is related to the rapidity of absorption and the peak nicotine level achieved in arterial blood. Positive reinforcement is most relevant to rapid-delivery formulations such as nicotine nasal spray and, to a lesser extent, nicotine gum, inhaler, and lozenge. The use of these products allows smokers to dose themselves with nicotine when they have the urge to smoke cigarettes. Nicotine patches, on the other hand, deliver nicotine gradually and produce sustained nicotine levels throughout the day, thus not providing much positive reinforcement.

A third possible mechanism of benefit is related to the ability of nicotine medications to desensitize nicotinic receptors. This desensitization results in a reduced effect of nicotine from cigarettes, e.g., when a person lapses to smoking while on nicotine replacement therapy, the cigarette is less satisfying and the person is less likely to resume smoking.

Bupropion

Bupropion was marketed as an antidepressant medication before it was marketed for smoking cessation. The serendipitous observation of spontaneous smoking cessation among veterans treated with bupropion for depression led to the exploration of bupropion as a smoking cessation medication. Bupropion increases brain levels of dopamine and norepinephrine, simulating the effects of nicotine on these neurotransmitters (77). Bupropion also has some nicotine receptor–blocking activity, which could contribute to reduced reinforcement from a cigarette in the case of a lapse (78).

Varenicline

Varenicline was synthesized with the goal of developing a specific antagonist for the $\alpha 4\ \beta$-2 nAChR (79). Varenicline is an analog of cytisine, a plant alkaloid that has been reported to have some benefit in smoking cessation but is thought to have generally poor oral bioavailability. Varenicline was shown in in vitro receptor binding studies to have high affinity for the $\alpha 4\ \beta$-2 nAChR, and relatively little effect on other nAChR subtypes or neurotransmitter receptors. Varenicline is a partial agonist of the $\alpha 4\ \beta$-2 receptor in vivo, as demonstrated by studies of dopamine release, measured with microdialysis in the nucleus accumbens of conscious rats (79). Nicotine, a full agonist, causes substantial dopamine release. Varenicline, a partial agonist, produces less of a response than nicotine (~50%) but at the same time blocks the effects of any nicotine added to the system. Clinical trials have found that varenicline is superior to bupropion in promoting smoking cessation, and prolonged administration of varenicline has been shown to reduce relapse in smokers who were abstinent 12 weeks after initial therapy (80, 81).

Medications in Development

Rimonabant is a cannabinoid (CB-1) receptor antagonist developed for treatment of obesity and the metabolic syndrome. Clinical studies have also shown rimonabant to be effective as an aid for smoking cessation (82). Cannabinoid receptors are believed to contribute to the reinforcing effects of nicotine action. Rimonabant has not been approved by the U.S. FDA owing to concern about adverse neuropsychiatric effects.

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Nicotine vaccines are currently undergoing clinical trials (83). Acute immunization is performed so as to develop antibodies to nicotine. The antibody binds nicotine and slows its entry into the brain, thereby reducing the reinforcing effects of cigarette smoking. The nicotine vaccine is a logical approach to preventing relapse.

Other potential future medications for smoking cessation include monoamine oxidase inhibitors (MAOA and MAOB), which inhibit the metabolism of dopamine and therefore increase dopamine levels in brain, and dopamine D3 receptor antagonists and partial agonists, which modulate activity of receptors involved in drug-seeking behaviors (84). Inhibitors of CYP2A6 activity have also been proposed as smoking cessation aids that work by increasing nicotine levels from tobacco use and thereby reducing urges to smoke. Methoxsalen and tranylcypromine inhibit CYP2A6 activity and slow nicotine metabolism, but both have significant toxicity, making routine clinical use problematic. Finally, novel selective nicotinic cholinergic receptor agonists and antagonists, in addition to varenicline, are under development.

PERSONALIZING NICOTINE ADDICTION TREATMENT

Although a number of drugs are effective in enhancing smoking cessation, as discussed above, success rates are still relatively low, and most smokers require multiple quit attempts before they quit for good. Tobacco addiction differs in its manifestations from person to person. There are individual differences in the nature of reinforcement (that is, what benefit people say they get from smoking), in withdrawal symptoms, and in conditioned aspects of smoking. There has been much interest, therefore, in individualization of smoking cessation pharmacotherapy. The goal would be to select medications and doses based on individual characteristics of smokers. An area of much current research activity in this regard is pharmacogenetics of nicotine addiction treatment. A number of pharmacogenetic studies have been conducted, focusing primarily on candidate genes related to nicotine reward and nicotine metabolism pathways (47). For example, variants in the dopamine D2 receptor, dopamine transporter, dopamine β hydroxylase, and catechol-O-methyltranferase genes have been reported to affect response to transdermal nicotine and/or bupropion. Variation in the opiate mu 1 receptor gene has been reported to influence response to transdermal nicotine, and variants in the CYP2B6 gene have been found to predict response to placebo in bupropion clinical trials (85, 86). To date, few of these findings have been replicated, and the fraction of the total variance in smoking cessation response explained by single candidate genes appears to be small. Ongoing research is focusing on looking at multiple genes and looking at gene-gene interactions as predictors of treatment outcome.

Given the tendency of smokers to regulate their intake of nicotine, it is logical to consider nicotine metabolism genes, namely CYP2A6, as potential predictors of response to smoking cessation treatment. Unfortunately, the prevalence of CYP2A6 gene variants is too low, at least in Caucasians, to be able to detect significant genetic associations in most studies. An alternative to CYP2A6 genotyping is the use of the phenotype for the rate of nicotine metabolism. As mentioned previously, the 3HC to cotinine ratio is a phenotypic marker of the rate of nicotine metabolism (35), and this metabolite ratio has been studied as a predictor of response to pharmacotherapy. In one trial, comparing transdermal nicotine and nicotine nasal spray, the nicotine metabolite ratio was shown to be a strong predictor of smoking cessation both at the end of treatment and at six months in people treated with transdermal nicotine, but not with nicotine nasal spray (87). In smokers treated with transdermal nicotine, slow metabolizers had a better cessation response and a higher plasma nicotine concentration while using the patch compared with faster metabolizers, suggesting that higher nicotine levels might be responsible for better cessation outcome. In contrast, smokers treated with nicotine nasal spray showed no difference in plasma nicotine

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concentration as a function of rate of nicotine metabolism, consistent with the idea that nicotine from the spray is titrated by the smoker to the desired effect.

Another recent trial examined the association between a nicotine metabolite ratio and a response to bupropion treatment (88). Faster metabolism of nicotine was associated with a lower success rate in quitting in the placebo treated group, but among smokers receiving bupropion, the rate of nicotine metabolism had no differential effect. This finding is consistent with the idea that rapid metabolizers of nicotine are generally more dependent and have a harder time quitting compared with slow metabolizers. The mechanism of such a relationship has not been proven, but might be related to a faster elimination half-life in rapid metabolizers. Faster elimination would be expected to result in more severe withdrawal symptoms and therefore a greater compulsion for the next cigarette. In addition more rapid clearance of nicotine from the brain in rapid metabolizers would be expected to be associated with more rapid loss of tolerance between cigarettes and therefore a greater effect from the nicotine in next cigarette, which would also enhance dependence. Future studies are needed to potentially test the idea of tailoring the type or dose of pharmacotherapy using phenotypes or genotypes of the rate of nicotine metabolism.

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POTENTIAL CONFLICTS OF INTEREST

Dr Benowitz has served as a paid consultant to several pharmaceutical companies that market smoking cessation medications. He has also been a paid expert witness against tobacco companies in matters related to nicotine addiction.

LITERATURE CITED

1. U. S. Dep. Health Hum. Serv. Public Health Serv. 2004. *The Health Consequences of Smoking: A Report of the Surgeon General*. Washington, DC: GPO
2. Cent. Dis. Control Prev. 2002. Cigarette smoking among adults—United States, 2000. *MMWR* 51:637–60
3. Gotti C, Zoli M, Clementi F. 2006. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol. Sci.* 27:482–91
4. Picciotto MR, Zoli M, Rimondini R, Léna C, Marubio M, et al. 1998. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature* 391:173–77
5. Maskos U, Molles BE, Pons S, Besson M, Guiard BP, et al. 2005. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature* 436:103–7
6. Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, et al. 2004. Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. *Science* 306:1029–32
7. Aberger K, Chitravanshi VC, Sapru HN. 2001. Cardiovascular responses to microinjections of nicotine into the caudal ventrolateral medulla of the rat. *Brain Res.* 892:138–46
8. Levin ED, Bettegowda C, Blosser J, Gordon J. 1999. AR-R17779, and alpha7 nicotinic agonist, improves learning and memory in rats. *Behav. Pharmacol.* 10:675–80
9. Hajós M, Hurst RS, Hoffmann WE, Krause M, Wall TM, et al. 2005. The selective alpha7 nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J. Pharmacol. Exp. Ther.* 312:1213–22
10. Salas R, Orr-Urtreger A, Broide RS, Beaudet A, Paylor R, De Biasi M. 2003. The nicotinic acetylcholine receptor subunit alpha 5 mediates short-term effects of nicotine in vivo. *Mol. Pharmacol.* 63:1059–66

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11. Brody AL. 2006. Functional brain imaging of tobacco use and dependence. *J. Psychiatr. Res.* 40:404–18
12. Dani JA, De Biasi M. 2001. Cellular mechanisms of nicotine addiction. *Pharmacol. Biochem. Behav.* 70:439–46
13. Nestler EJ. 2005. Is there a common molecular pathway for addiction? *Nat. Neurosci.* 8:1445–49
14. Wonnacott S. 1997. Presynaptic nicotinic ACh receptors. *Trends Neurosci.* 20:92–98
15. Mansvelder HD, McGehee DS. 2002. Cellular and synaptic mechanisms of nicotine addiction. *J. Neurobiol.* 53:606–17
16. Lewis A, Miller JH, Lea RA. 2007. Monoamine oxidase and tobacco dependence. *Neurotoxicology* 28:182–95
17. Villégier AS, Lotfipour S, McQuown SC, Belluzzi JD, Leslie FM. 2007. Tranylcypromine enhancement of nicotine self-administration. *Neuropharmacology* 52:1415–25
18. Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. 2003. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. *Psychopharmacology* 168:347–58
19. Epping-Jordan MP, Watkins SS, Koob GF, Markou A. 1998. Dramatic decreases in brain reward function during nicotine withdrawal. *Nature* 393:76–79
20. Wang H, Sun X. 2005. Desensitized nicotinic receptors in brain. *Brain Res. Brain Res. Rev.* 48:420–37
21. Dani JA, Heinemann S. 1996. Molecular and cellular aspects of nicotine abuse. *Neuron* 16:905–8
22. Brody AL, Mandelkern MA, London ED, Olmstead RE, Farahi J, et al. 2006. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. *Arch. Gen. Psychiatry* 63:907–15
23. Balfour DJ. 2004. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. *Nicotine Tob. Res.* 6:899–912
24. Donny EC, Chaudhri N, Caggiula AR, Evans-Martin FF, Booth S, et al. 2003. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology* 169:68–76
25. George O, Ghozland S, Azar MR, Cottone P, Zorrilla EP, et al. 2007. CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. *Proc. Natl. Acad. Sci. USA* 104:17198–203
26. Hughes JR, Hatsukami D. 1986. Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry* 43:289–94
27. Hughes JR. 2006. Clinical significance of tobacco withdrawal. *Nicotine Tob. Res.* 8:153–56
28. Koob GF, LeMoal M. 1997. Drug abuse: Hedonic homeostatic dysregulation. *Science* 278:52–58
29. Rose JE, Behm FM, Levin ED. 1993. Role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacol. Biochem. Behav.* 44:891–900
30. Rose JE, Behm FM, Westman EC, Johnson M. 2000. Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacol. Biochem. Behav.* 67:71–81
31. Olausson P, Jentsch JD, Taylor JR. 2004. Repeated nicotine exposure enhances responding with conditioned reinforcement. *Psychopharmacology* 173:98–104
32. Kenny PJ, Markou A. 2005. Conditioned nicotine withdrawal profoundly decreases the activity of brain reward systems. *J. Neurosci.* 25:6208–12
33. Naqvi NH, Rudrauf D, Damasio H, Bechara A. 2007. Damage to the insula disrupts addiction to cigarette smoking. *Science* 315:531–34
34. Hukkanen J, Jacob P 3rd, Benowitz NL. 2005. Metabolism and disposition kinetics of nicotine. *Pharmacol. Rev.* 57:79–115
35. Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, et al. 2004. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. *Clin. Pharmacol. Ther.* 76:64–72
36. Benowitz NL, Swan GE, Jacob P 3rd, Lessov-Schlaggar CN, Tyndale RF. 2006. CYP2A6 genotype and the metabolism and disposition kinetics of nicotine. *Clin. Pharmacol. Ther.* 80:457–67
37. Malaiyandi V, Sellers EM, Tyndale RF. 2005. Implications of CYP2A6 genetic variation for smoking behaviors and nicotine dependence. *Clin. Pharmacol. Ther.* 77:145–58
38. Perez-Stable EJ, Herrera B, Jacob P 3rd, Benowitz NL. 1998. Nicotine metabolism and intake in black and white smokers. *JAMA* 280:152–56
39. Benowitz NL, Perez-Stable EJ, Herrera B, Jacob P 3rd. 2002. Slower metabolism and reduced intake of nicotine from cigarette smoking in Chinese-Americans. *J. Natl. Cancer Inst.* 94:108–15

REVIEWS IN ADVANCE

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40. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. 2006. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin. Pharmacol. Ther.* 79:480–88
41. Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. 1993. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend.* 33:23–29
42. Kamataki T, Fujita K, Nakayama K, Yamazaki Y, Miyamoto M, Ariyoshi N. 2002. Role of human cytochrome P450 (CYP) in the metabolic activation of nitrosamine derivatives: application of genetically engineered *Salmonella* expressing human CYP. *Drug Metab. Rev.* 34:667–76
43. Fujieda M, Yamazaki H, Saito T, Kiyotani K, Gyamfi MA, et al. 2004. Evaluation of CYP2A6 genetic polymorphisms as determinants of smoking behavior and tobacco-related lung cancer risk in male Japanese smokers. *Carcinogenesis* 25:2451–58
44. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, et al. 2006. Ethnic and racial differences in the smoking-related risk of lung cancer. *N. Engl. J. Med.* 354:333–42
45. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. 2008. Genetics of nicotine dependence and pharmacotherapy. *Biochem. Pharmacol.* 75:178–95
46. Pergadia ML, Heath AC, Martin NG, Madden PA. 2006. Genetic analyses of DSM-IV nicotine withdrawal in adult twins. *Psychol. Med.* 36:963–72
47. Ho MK, Tyndale RF. 2007. Overview of the pharmacogenomics of cigarette smoking. *Pharmacogenomics J.* 7:81–98
48. Bierut LJ, Madden PA, Breslau N, Johnson EO, Hatsukami D, et al. 2007. Novel genes identified in a high-density genome wide association study for nicotine dependence. *Hum. Mol. Genet.* 16:24–35
49. Saccone SF, Hinrichs AL, Saccone NL, Chase GA, Konvicka K, et al. 2007. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum. Mol. Genet.* 16:36–49
50. Uhl GR, Liu QR, Drgon T, Johnson C, Walther D, Rose JE. 2007. Molecular genetics of nicotine dependence and abstinence: whole genome association using 520,000 SNPs. *BMC Genet.* 8:10
51. Kauer JA, Malenka RC. 2007. Synaptic plasticity and addiction. *Nat. Rev. Neurosci.* 8:844–58
52. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. 2000. Smoking and mental illness: A population-based prevalence study. *JAMA* 284:2606–10
53. Kalman D, Morissette SB, George TP. 2005. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am. J. Addict.* 14:106–23
54. Covey LS, Glassman AH, Stetner F. 1997. Major depression following smoking cessation. *Am. J. Psychiatry* 154:263–65
55. Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. 1993. Smoking and major depression. A causal analysis. *Arch. Gen. Psychiatry* 50:36–43
56. Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, et al. 1998. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. *Arch. Gen. Psychiatry* 55:982–88
57. Martin LF, Freedman R. 2007. Schizophrenia and the alpha7 Nicotinic Acetylcholine Receptor. *Int. Rev. Neurobiol.* 78:225–46
58. Shytle RD, Silver AA, Lukas RJ, Newman MB, Sheehan DV, Sanberg PR. 2002. Nicotinic acetylcholine receptors as targets for antidepressants. *Mol. Psychiatry* 7:525–35
59. Colton CW, Manderscheid RW. 2006. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev. Chronic Dis.* 3:A42
60. Hurt RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, et al. 1996. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA* 275:1097–103
61. Batra A, Klingler K, Landfeldt B, Friederich HM, Westin A, Danielsson T. 2005. Smoking reduction treatment with 4-mg nicotine gum: a double-blind, randomized, placebo-controlled study. *Clin. Pharmacol. Ther.* 78:689–96
62. Benowitz NL. 2003. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Prog. Cardiovasc. Dis.* 46:91–111
63. Eliasson B. 2003. Cigarette smoking and diabetes. *Prog. Cardiovasc. Dis.* 45:405–13
64. Puranik R, Celermajer DS. 2003. Smoking and endothelial function. *Prog. Cardiovasc. Dis.* 45:443–58

REVIEWS IN ADVANCE

65. Benowitz NL, Gourlay SG. 1997. Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. *J. Am. Coll. Cardiol.* 29:1422–31
66. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, et al. 1996. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N. Engl. J. Med.* 335:1792–98
67. Wennberg P, Eliasson M, Hallmans G, Johansson L, Boman K, Jansson JH. 2007. The risk of myocardial infarction and sudden cardiac death amongst snuff users with or without a previous history of smoking. *J. Intern. Med.* 262:360–67
68. Zeidler R, Albermann K, Lang S. 2007. Nicotine and apoptosis. *Apoptosis* 12:1927–43
69. Cooke JP, Bitterman H. 2004. Nicotine and angiogenesis: a new paradigm for tobacco-related diseases. *Ann. Med.* 36:33–40
70. Henley SJ, Connell CJ, Richter P, Husten C, Pechacek T, et al. 2007. Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. *Tob. Control* 16:22–28
71. Luo J, Ye W, Zendehdel K, Adami J, Adami HO, et al. 2007. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 369:2015–20
72. Cohen G, Roux JC, Grailhe R, Malcolm G, Changeux JP, Lagercrantz H. 2005. Perinatal exposure to nicotine causes deficits associated with a loss of nicotinic receptor function. *Proc. Natl. Acad. Sci. USA* 102:3817–21
73. England LJ, Levine RJ, Mills JL, Klebanoff MA, Yu KF, Cnattingius S. 2003. Adverse pregnancy outcomes in snuff users. *Am. J. Obstet. Gynecol.* 189:939–43
74. Møller AM, Villebro N, Pedersen T, Tønnesen H. 2002. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 359:114–17
75. U.S. Dep. Health Hum. Serv. Public Health Serv. 2008. *Treating Tobacco Use and Dependence: 2008 Update. May*. Washington, DC: GPO
76. Henningfield JE. 1995. Nicotine medications for smoking cessation. *N. Engl. J. Med.* 333:1196–97
77. Paterson NE, Balfour DJ, Markou A. 2007. Chronic bupropion attenuated the anhedonic component of nicotine withdrawal in rats via inhibition of dopamine reuptake in the nucleus accumbens shell. *Eur. J. Neurosci.* 25:3099–108
78. Slemmer JE, Martin BR, Damaj MI. 2000. Bupropion is a nicotinic antagonist. *J. Pharmacol. Exp. Ther.* 295:321–27
79. Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, et al. 2005. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J. Med. Chem.* 48:3474–77
80. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, et al. 2006. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 296:47–55
81. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. 2006. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 296:64–71
82. Cahill K, Ussher M. 2007. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane Database Syst. Rev.* 2007(3):CD005353
83. Hatsukami DK, Rennard S, Jorenby D, Fiore M, Koopmeiners J, et al. 2005. Safety and immunogenicity of a nicotine conjugate vaccine in current smokers. *Clin. Pharmacol. Ther.* 78:456–67
84. Siu EC, Tyndale RF. 2007. Non-nicotinic therapies for smoking cessation. *Annu. Rev. Pharmacol. Toxicol.* 47:541–64
85. Lerman C, Kaufmann V, Rukstalis M, Patterson F, Perkins K, et al. 2004. Individualizing nicotine replacement therapy for the treatment of tobacco dependence: a randomized trial. *Ann. Intern. Med.* 140:426–33
86. Lee AM, Jepson C, Hoffmann E, Epstein L, Hawk LW, et al. 2007. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. *Biol. Psychiatry* 62:635–41
87. Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, et al. 2006. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clin. Pharmacol. Ther.* 79:600–8
88. Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, et al. 2008. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Clin. Pharmacol. Ther.* 84:320–325

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Disrupting Nicotine Reinforcement

From Cigarette to Brain

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Cigarette smoking is a tenacious addiction that is maintained to a significant extent by the reinforcing effects of nicotine. An emerging theme in smoking cessation treatment is the development of methods for interfering with these reinforcing effects. By attenuating nicotine reinforcement, treatments may enhance a smoker's chances of successfully remaining abstinent. Several treatment approaches will be described, including the use of denicotinized cigarettes, nicotine vaccines, nicotinic receptor agonists and antagonists, and modulators of brain reinforcement processes. These techniques highlight the numerous sites along the path between the cigarette and the brain that can be targeted for intervention. In addition to unimodal therapies, treatment combinations will be discussed that might more effectively block cigarette reward and thereby further enhance smoking abstinence.

Key words: **addiction; tobacco; nicotine; cigarette; reinforcement; reward; antagonist; agonist**

Cigarette smoking remains a leading cause of morbidity and mortality worldwide. It is estimated that approximately 5 million premature deaths annually are attributable to cigarette smoking.[1] For many smokers, continuing to smoke reflects a psychological and physical dependence on tobacco. This dependence is maintained in large part by the pharmacologic effects of nicotine.[2] Nicotine and tobacco dependence, like dependence on other drugs, is increasingly viewed as a disorder of the brain's reward[a] system.[3] Indeed, cigarette smokers choose to experience the immediate rewarding effects of smoking despite the threat of delayed cancer and heart and lung disease. Moreover, criteria based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (*DSM-IV*) for tobacco dependence stress the involvement of reward systems: a preference for the activity of cigarette smoking over other rewarding activities.[4] Smoking behavior is maintained not only by positive reinforcement, indicated by enjoyment of the sensory and motoric aspects of the habit[5] as well as by the euphoric effects of nicotine,[6–8] but also by negative reinforcement through the relief of craving and withdrawal symptoms, including irritability, depression, restlessness, insomnia, anxiety, hunger, and poor concentration.[9]

An emerging theme in the treatment of tobacco dependence consists of interfering with the rewarding effects of smoking, thereby helping smokers to resist the temptation to smoke a cigarette and thus be more successful at maintaining long-term abstinence. To the extent that the rewarding effects of tobacco can be attenuated, while not affecting (or perhaps enhancing) other pleasurable aspects of living, a treatment may successfully yield higher abstinence rates. This article will review several pharmacologic approaches for attenuating nicotine reinforcement. To organize the discussion, we will follow the path of the smoke as it is generated by the cigarette, enters the body through the mouth, is inhaled into the lungs, is absorbed into the circulatory system, and ultimately reaches the

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[a]The term *reward* will be used to refer to a stimulus capable of positively reinforcing behavior.

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brain. At each point we will see that different strategies can be brought to bear to interfere with nicotine reinforcement. In so doing, we will discuss the mechanisms of action of current treatments and will also consider novel therapeutic approaches and combination treatments that hold promise for greater efficacy in aiding smoking cessation.

The treatment approaches to be considered will be limited to those that have progressed beyond *in vitro* or animal behavioral models to human investigations. These include U.S. Food and Drug Administration (FDA)-approved treatments such as bupropion, varenicline, and nicotine replacement therapy (NRT) in several forms: polacrilex (gum), transdermal patches, lozenge, inhaler, and nasal spray. Also discussed will be pharmacologic agents recommended as second-line therapies in the Agency for Health Care Policy and Research (AHCPR) treatment guidelines,[10] clonidine and nortriptyline. In addition, treatments will be discussed that, although not yet generally recommended, are supported by clinical data (e.g., mecamylamine and rimonabant). These treatments will be introduced as we follow the course of nicotine from the cigarette to the brain.

Figure 1 depicts the path followed by nicotine as it is self-administered during cigarette smoking and indicates critical points where the reinforcement process can be disrupted. These include the following sites (with corresponding treatment approaches):

1) the cigarette (reduced nicotine content cigarettes);
2) the respiratory system (airway sensory replacement or blockade);
3) the circulatory system (nicotine vaccines);
4) central nervous system (CNS) nicotinic receptors (substitution or blockade with nicotine, mecamylamine, or varenicline); and
5) brain reinforcement pathways (a variety of agents that disrupt postnicotinic receptor reinforcement processes, including treatments based on γ-aminobutyric acid [GABA]-ergic, glutamatergic, opioid, cannabinoid, noradrenergic, and dopaminergic systems).

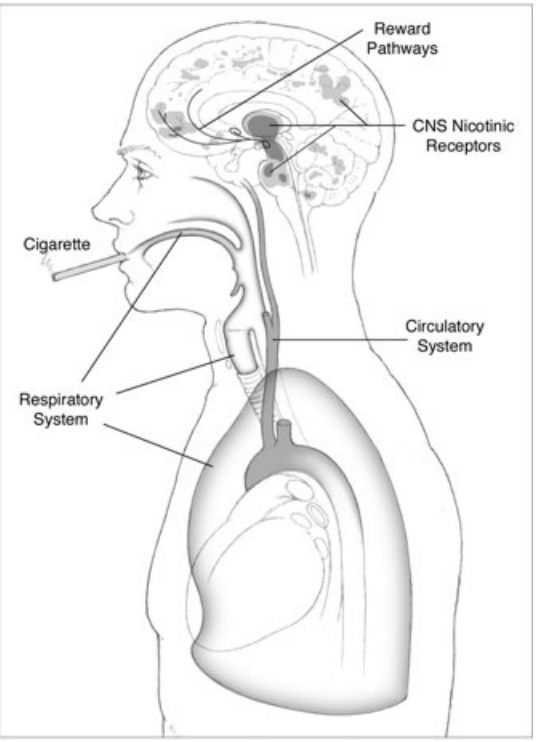


Figure 1. Depiction of the path followed by nicotine from the cigarette to the brain, showing possible sites for disrupting the reinforcement process.

The Cigarette

Reduced Nicotine Content Cigarettes for Attenuating Reinforcement of Smoking Behavior

When viewed from the broad framework considered here, an obvious approach to attenuating the nicotine reinforcement of smoking behavior is to remove nicotine from tobacco. Reducing the nicotine content of tobacco has been proposed by Drs. Neal Benowitz and Jack Henningfield as a method of preventing the development of addiction.[11–13] The reasoning

behind this approach is the potential for a threshold for the nicotine intake required to sustain dependence. If cigarettes' nicotine content can be reduced so that smokers' intake is below this threshold, dependence will be avoided. It was also proposed that a national tobacco control policy or regulation should include mandated reductions in tobacco nicotine content. Although the merits of such a policy are being debated, this approach has already been tested in smoking cessation trials with some degree of success.

Before reviewing these clinical results, it is important to recognize that a selective reduction in cigarette nicotine content is a very different approach from that taken in the manufacture of "ultralight" or "low tar and nicotine" cigarettes. Cigarettes of the latter type actually have a concentration of nicotine as high as that of other cigarettes, but incorporate filtration and air dilution. When smoked by machines using a standard Federal Trade Commission protocol, they will achieve a low (e.g., 0.1-mg) nicotine yield.[14] By covering the ventilation holes in the filter or puffing more intensively, however, a smoker can defeat the filtration and dilution mechanisms and extract as much nicotine as from a cigarette with a high (e.g., 1.0-mg) nicotine yield.[15]

In contrast to ventilated filter low tar and nicotine cigarettes, selectively reduced nicotine content cigarettes are manufactured either by extracting nicotine from the tobacco or by using genetically modified tobacco plants that lack an enzyme necessary for the synthesis of nicotine.[16] These cigarettes maintain the usual smoke (e.g., "tar") delivery while selectively lowering nicotine yield. Because nonnicotine tobacco smoke constituents provide many of the sensory effects to which smokers are accustomed, cigarettes with high smoke yield but low nicotine content can relieve craving and possibly other smoking withdrawal symptoms.[17–19]

Selective reductions in nicotine yield can reduce the nicotine delivery to extremely low (e.g., 0.05-mg) levels; these cigarettes are often referred to as *denicotinized* cigarettes. Smokers generally prefer nicotine-containing cigarettes over denicotinized cigarettes, which lack some of the desired sensory characteristics and CNS effects of nicotine. They nevertheless comply with using these cigarettes in the context of a cessation program.[20,21] Moreover, compensatory increases in smoking are usually limited and insufficient to maintain the habitual level of nicotine intake. The finding that smokers do not completely compensate for the reduced cigarette nicotine yield is critical for the success of the strategy to attenuate nicotine reinforcement. If smokers were to increase their smoking dramatically, then nicotine reinforcement would not be attenuated. The results of several studies, however, suggest that substantial compensation does not occur: reduction of nicotine at the source, the tobacco, will indeed reduce the reinforcing effects of cigarette smoking.

In this regard, both laboratory and field studies have shown, somewhat surprisingly, that denicotinized cigarettes are smoked in much the same way as high-nicotine cigarettes. For example, most investigations have found that smoke intake—as measured by smoking topography or expired air carbon monoxide (CO), an index of smoke inhalation—are similar when participants smoke denicotinized cigarettes and when they smoke cigarettes that deliver the usual amounts of nicotine.[18,19,22–26] Importantly, substantial compensatory increases in smoking have not been found when smokers are studied over several days or weeks while using denicotinized cigarettes. In fact, a decrease in smoking may occur over time, as would be expected during behavioral extinction. Donny *et al.*[27] conducted a study in which subjects were exposed for 11 days to either nicotine-containing cigarettes, denicotinized cigarettes, or no smoking. Compared to the nicotine-containing cigarette condition, subjects exposed to denicotinized cigarettes showed a reduction in *ad lib* smoking and a reduction in the reinforcing effects of smoking, as assessed by using a progressive ratio schedule of reinforcement.

Similarly, in a field study, Benowitz[22] exposed 20 smoking participants to five successive stages of weekly reductions in cigarette nicotine content, while attempting to hold the overall smoke yield relatively constant. Measures of nicotine exposure showed progressive reductions throughout the 5 weeks, with little evidence of compensatory increases in smoking, assessed by measuring CO in expired air. At a 4-week follow-up, subjects showed a decline in nicotine dependence as indexed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire[28] and an increase in reports of self-efficacy for quitting smoking. Interestingly, five participants (25%) quit smoking spontaneously after the nicotine tapering regimen, even though they had not expressed an interest in doing so when entering the study.

A controlled cessation trial comparing reduced-nicotine cigarettes to standard NRT was conducted by Hatsukami *et al.*[29] The study presented three groups of smokers with either (1) denicotinized cigarettes having a yield of approximately 0.05 mg nicotine ($n = 54$), (2) cigarettes with moderately reduced nicotine having a 0.3-mg yield ($n = 53$), or (3) 4-mg nicotine lozenges ($n = 60$). All treatments were administered for 6 weeks. The point abstinence results at 12 weeks were 47% for the denicotinized cigarette group, 23% for the moderately reduced nicotine group, and 32% for the group receiving the nicotine lozenge ($P = 0.03$). In addition, the denicotinized cigarette treatment reduced toxicant exposure as assessed by total *N*′-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, the acrolein metabolite hydroxypropylmercapturic acid, and the benzene metabolite S-phenylmercapturic acid. Moreover, as with the previously cited study,[22] the denicotinized cigarettes reduced dependence levels as assessed by FTND scores.

Denicotinized Cigarettes in Combination with NRT

A promising strategy for employing denicotinized cigarettes in a smoking cessation treatment is to combine their use with NRT. The rationale for the concurrent use of NRT with denicotinized cigarettes is twofold. First, the use of NRT prevents nicotine withdrawal symptoms and enhances compliance with the use of denicotinized cigarettes. Rose *et al.*,[20] for example, reported that compliance with the use of denicotinized cigarettes to the exclusion of nicotine-containing cigarettes was higher in a group receiving concurrent nicotine skin patch (21 mg/24 h) treatment than in a group receiving placebo patches. Second, from a behavioral conditioning perspective, administering nicotine from a source other than smoking, while reducing the nicotine delivery in smoke, more effectively dissociates the behavior of smoking from the reinforcing effects of nicotine. Theoretically, this strategy should facilitate extinction of the conditioned reinforcing properties of cigarette smoking compared with the use of denicotinized cigarettes alone.

Recently, a randomized double-blind, active controlled, parallel group, multicenter Phase II clinical trial was conducted to evaluate the efficacy of reduced-nicotine cigarettes as a smoking cessation treatment.[30] Treatment consisted of cigarettes with progressively reduced nicotine content that delivered 0.6 mg, 0.3 mg, or less than 0.05 mg nicotine, either alone or in combination with NRT. The primary endpoint was 4 weeks of continuous abstinence. Three hundred forty-six adult male and female smokers who expressed a motivation to quit were randomized to one of three treatment groups: (1) reduced nicotine content cigarettes plus NRT (21 mg/24 h nicotine skin patch treatment 2 weeks before the quit date and a 10-week course of standard nicotine patch treatment after the quit date); (2) reduced nicotine content cigarettes plus placebo patch; or (3) conventional cigarettes, followed by NRT after the quit date. Results showed the highest continuous abstinence rate for the reduced-nicotine cigarettes plus NRT treatment (32.8%), with the conventional cigarettes plus NRT treatment yielding 21.9% abstinence and the reduced nicotine content cigarettes plus

placebo patch treatment yielding an abstinence rate of 16.4%.

Rezaishiraz *et al.*[31] conducted a study to investigate whether treatment with the combination of denicotinized cigarettes and a 21-mg nicotine patch for 2 weeks before a designated quit date could lessen the craving for cigarettes and help smokers abstain from smoking. Participants included 98 adult heavy smokers who smoked 20 or more cigarettes per day. For 2 weeks before the quit date, half of the subjects received the combination of denicotinized cigarettes and a 21-mg nicotine patch. The remaining smokers were switched to cigarettes with a nicotine yield of 0.3 mg during the 2 weeks before the quit date. After the quit date, all subjects received 8 weeks of nicotine skin patch treatment. Although the rates of abstinence did not differ significantly between groups, a trend for greater abstinence was reported in the group that used denicotinized cigarettes and a nicotine patch before quitting (43% versus 34% at 12 weeks). In the 2 weeks before and after the designated quit date, subjects in the denicotinized cigarette plus patch condition reported a significantly lower frequency and intensity of craving for cigarettes.

Cue-elicited craving was examined in a study that investigated brain mechanisms involved in the effects of treatment using denicotinized cigarettes plus NRT.[32] Smokers received 2–4 weeks of treatment with denicotinized cigarettes plus 21 mg/24 h nicotine patches. They were subjected to functional magnetic resonance imaging while they viewed smoking-related pictures or neutral pictures. Scanning sessions occurred at baseline and again after exposure to the extinction-based treatment. After treatment, responses to smoking cues were significantly attenuated in the amygdala, a brain region involved in the evaluation of reinforcing stimuli. Exploratory analysis revealed a similar reduction of smoking cue response in the thalamus and ventral striatum of smokers who went on to achieve abstinence, but not in those who went on to relapse. Thus, critical brain regions involved in stimulus processing and reward evaluation appear to be affected by extinction-based therapy.

A final point to consider is the duration of exposure to cigarettes with reduced nicotine content in a cessation program. The exposure period should be limited inasmuch as these cigarettes still deliver numerous toxic smoke components. Nonetheless, for a 20-year smoker, an additional 6 weeks of smoke exposure would appear to provide acceptable risk if it significantly increased the chances of reduced nicotine dependence and long-term smoking abstinence.

The Respiratory System

The Role of Airway-Mediated Sensations

Upon inhaling each puff of cigarette smoke, the smoker perceives sensory cues that provide an immediate reinforcing effect. The importance of peripheral airway sensations associated with cigarette smoking has been demonstrated by several lines of evidence.

(1) Smokers prefer cigarette smoke to alternative, rapid forms of nicotine administration, such as intravenous nicotine administration or nicotine nasal spray.[33,34]
(2) The positive subjective effects of cigarette smoking are substantially reduced by the blockade of smoking-related sensory cues (e.g., with lidocaine local anesthetic).[35,36]
(3) Craving and other smoking withdrawal symptoms can be alleviated by the inhalation of agents that simulate some of the sensory effects of cigarette smoke, such as citric or ascorbic acids delivered in fine particulate aerosols. In one study, the addition of a citric acid dry powder inhaler to nicotine patch treatment yielded significantly higher continuous abstinence rates at 10 weeks (19.5%) than the addition of a placebo (lactose) inhaler (6.8%).[37] Subjects reporting stronger-than-average airway sensations had a higher abstinence rate (33%). Moreover, abstinence was

predicted by a baseline questionnaire asking participants to rate the importance of airway sensations to their enjoyment of smoking. Those who rated airway sensations as being more important had a higher success rate with the citric acid inhaler plus NRT treatment.

Interestingly, the sensory effects of smoking include both a nicotinic receptor–mediated component and a nonnicotine component. Nicotine itself has sensory effects. Inhalation of nicotine aerosols or vapor has a discernible sensory impact that is mediated by trigeminal, glossopharyngeal, and vagal nerve stimulation.[38] Moreover, airway sensations produced by inhalation of nicotine-containing, but not denicotinized, cigarette smoke can be blocked by administration of the peripheral nicotinic receptor antagonists hexamethonium or trimethaphan.[38,39] Indeed, in the Rose *et al.* study,[39] trimethaphan administration completely abolished the higher ratings of smoking satisfaction for the subject's usual brand of nicotine-containing cigarette. These findings, along with studies showing that lung sensory neurons respond to nicotinic agonists and antagonists,[40,41] support the view that the sensory effects of cigarette smoke are mediated in part by nicotinic receptors. Thus, nicotine, acting upon sensory nerve terminals in the lung, contributes substantially to the immediate sensory and reinforcing effects of cigarette smoking.

The reinforcing potency of peripheral nicotine-related airway sensations may reflect their conditioned reinforcing value, maintained by the pairing with nicotine's actions in the CNS. It is also possible, however, that stimulation of airway nicotinic receptors provides an unconditioned reinforcing effect. This possibility was suggested by a series of studies conducted by Ginzel *et al.*,[42] in which nicotinic agonists were injected into the right ventricle of the heart in cats. Within 1–3 s, a skeletal muscle relaxation response was elicited, mediated through vagal afferent nerve fibers. This relaxation response preceded the arrival of nicotine at the brain, thus suggesting that an innate vagal reflex could provide a potentially reinforcing effect of cigarette smoking. Indeed, smokers commonly report that a key motivation to smoke is to experience "relaxation," therefore, nicotine's actions on airway receptors must be kept in mind as a possible underlying mechanism. If so, therapeutic approaches might target this peripheral site by either substituting for or antagonizing the reinforcing sensory effects of nicotine.

Therapeutic Approaches Based on Airway Sensory Substitution or Blockade

Providing nicotine via inhalation is a strategy to activate (and to desensitize) peripheral airway nicotinic receptors to substitute for the reinforcing sensory effects of cigarettes. Indeed, one of the current modalities of NRT is based on gas-phase nicotine vapor inhalation. Puffing on the nicotine inhaler elicits noticeable upper airway sensations.[43,44] Interestingly, placebo-controlled efficacy trials for nicotine inhalers showed that the placebo formulation (containing menthol) did not produce sensory effects as intense as those produced by the active nicotine-containing formulation.[45] Thus, roles for a peripheral component of clinical efficacy cannot be ruled out in these studies. To some extent, other NRT modalities may also elicit respiratory tract sensations (i.e., pharyngeal stimulation) in ways that might help relieve craving.

Most of the nicotine vapor that is inhaled does not reach the lung, but rather is absorbed buccally and in the upper airways.[46] Buccal and upper airway absorption result from both the high diffusivity of nicotine gas molecules and their high water solubility. Nicotine absorption is therefore relatively slow compared with pulmonary delivery and is comparable to that after administration of nicotine gum or lozenge.[44] Nicotine vapor inhalation thus does not fully replace either the lung sensations elicited by cigarette smoke or the rapid nicotine delivery of cigarette smoke. This suggests that it may be

a fruitful strategy to go beyond the nicotine vapor inhalation system by developing an inhaler that delivers fine nicotine-containing particles (or droplets) to the lung. To effectively reach the lung, particles must have a small aerodynamic diameter (e.g., less than 5 μm[47]). A variety of approaches for generating nicotine-containing particles in this size range are being evaluated in Phase I human trials. A lung-delivery nicotine inhaler would probably provide a more effective NRT than current methods because it would not only substitute for the rapid pharmacokinetics of nicotine inhaled in cigarette smoke, but would also provide the lower respiratory tract with sensory stimulation from nicotine.

A lung-delivery nicotine inhaler that provided rapidly acting nicotine might also be more highly reinforcing and addictive and thus more difficult to relinquish than current forms of NRT. Because this prediction has not been tested, it is also possible that a lung-delivery nicotine inhaler might not be as addictive as cigarettes. It has been proposed, for example, that other components of cigarette smoke, such as monoamine oxidase (MAO) inhibitors, may interact with nicotine to augment its addictive potential.[48,49] If a lung-delivery nicotine inhaler were highly addictive and/or highly efficacious in relapse prevention, smokers might wish to continue using it for months or years. Whether prolonged use would be a serious drawback would depend on the extent of adverse health effects accompanying sustained exposure to nicotine. Many researchers attribute the bulk of smoking-related disease to smoke constituents other than nicotine, such as carbon monoxide, polycyclic aromatic hydrocarbons, nitrosamines, and so forth.[50,51] On the other hand, some findings point to roles for nicotine itself in disease.[51] Ultimately, a risk–benefit analysis will need to be conducted based on empirical findings regarding the disease risk associated with inhaled nicotine as well as data concerning the risk of its prolonged use. If prolonged use of a lung-delivery nicotine inhaler presents a significant risk of disease, then its use might be controlled by classifying it as a prescription product. Additionally, behavioral weaning programs might be devised to facilitate the transition from inhaled nicotine to other forms of NRT, such as gum, patch, or lozenge, because these forms are not difficult for most smokers to relinquish after a prescribed period of use.[52,53]

Other treatments besides NRT may work in part through their actions at airway nicotinic receptors. Two of these will be discussed more fully below (under CNS Nicotinic Receptors) but also merit attention here: the nicotinic receptor antagonist mecamylamine and the partial nicotinic receptor agonist varenicline. Mecamylamine is a noncompetitive antagonist of nicotinic receptors that acts peripherally as well as in the CNS. Mecamylamine can thus attenuate sensory effects of inhaled nicotine.[54,55] Similarly, the partial agonist varenicline also reduces subjective enjoyment of the airway sensory effects of cigarette smoking.[56] Thus, although the efficacy of these agents is usually assumed to be mediated by their actions in the CNS, it should be borne in mind that at least portions of their efficacies in aiding cessation might come from peripheral influences.

The Circulatory System

After nicotine is inhaled, it must be absorbed by the pulmonary circulation before entering the arterial blood that travels to the brain. The arterial blood thus provides another site for a treatment intervention that could reduce the reinforcing effects of nicotine. Nicotine vaccination is a treatment approach that seeks to do just that, by generating antibodies that selectively bind nicotine and prevent it from rapidly crossing the blood–brain barrier (also see Orson and colleagues, this volume). Before discussing specific vaccine approaches and clinical trial results, it will be helpful to review this underlying rationale in more depth. One critical parameter is the time required for the nicotine delivered in a puff of cigarette smoke to reach

the brain; in other words, how much time do antibodies have to interfere with the transit of nicotine from lung to brain? The shorter this time interval, the higher the antibody titer that may be required to produce significant blocking effects.

Pharmacokinetic Rationale for Nicotine Vaccines

The prevailing dogma suggests that antibodies would need to act very quickly to intercept nicotine on its way from the lung to the brain because it is generally believed that the nicotine in each puff of cigarette smoke is absorbed from the lung within seconds and reaches the brain in the form of a high-concentration "bolus." This view arose from a highly influential article published by Russell and Feyerabend,[57] which suggested that nicotine arrives at the brain approximately 7 s after absorption from the lungs. Although not explicitly stated in the article, this statement has been interpreted to mean that the entire dose of nicotine in each puff of smoke is absorbed and reaches the brain within 7 s. Recent findings, however, have contradicted this view. As discussed below, it actually takes substantially longer for the nicotine inhaled in each puff of smoke to travel from the lung to the arterial blood circulation to the brain.

Several types of evidence have led to this modification of the "nicotine bolus theory." First, direct measurements of arterial nicotine concentrations in smokers after inhalation of cigarette smoke have indicated that the concentrations of nicotine in arterial blood are lower, and last longer, than would be predicted if all of the nicotine were absorbed in a matter of seconds.[58] That is, if the nicotine content of a typical puff of cigarette smoke (0.1 mg) were absorbed in approximately 7 s, then it would be diluted in only about 0.7 L of blood (the volume passing through the lungs in 7 s), and the resulting peak arterial concentrations observed should be greater than 140 ng/mL (800 nM). In contrast, measurements of arterial blood samples have revealed nicotine concentrations after a single puff of smoke to be less than one-tenth as high, or 10 ng/mL (60 nM). Moreover, instead of observing that peaks in arterial nicotine concentration last only 7 s, investigators have found that the rise and fall in arterial nicotine concentration after each puff instead can last well over 60 s. It was hypothesized that this sustained rise in arterial nicotine concentrations resulted from the relatively slow release of nicotine from the lung. This prediction was initially confirmed in an animal (rat) model: nicotine injected into the right ventricle of the heart was retained in the lung for a longer duration than expected,[59] supporting the idea that the lung might serve as a short-term "depot."

Additional evidence contradicting the 7-s bolus hypothesis has been obtained from studies using radioimaging to track the course of nicotine from the cigarette to the lung to the brain. In a study of highly dependent smokers, the radiotracer [^{11}C]-nicotine was added to the tobacco rod of a cigarette. Positron emission tomography was used to track absorption in the lung and uptake by the brain. A substantial fraction of the inhaled nicotine dose was found to remain in the lung for several minutes, with a washout half-life ($t\frac{1}{2}$) averaging 89 s.[60] The rise in nicotine concentration in the brain showed a $t\frac{1}{2}$ of 33 s. Moreover, the rate of brain uptake was highly correlated with the rate of elimination from the lung.

The slower-than-expected kinetics of nicotine absorption in the lung bodes well for the potential efficacy of nicotine vaccines because it allows more time for nicotine-specific antibodies to bind a portion of the nicotine before it reaches the brain. It is possible that individual differences in lung retention of nicotine could be used to help predict which smokers would respond more favorably to vaccine therapy. Future research is needed to evaluate this hypothesis.

Clinical Trials of Nicotine Vaccines

The preceding discussion makes it clear that there may indeed be an opportunity for

interfering with the brain uptake of nicotine by inducing nicotine-specific antibodies with vaccination. Nicotine is not a good antigen by itself in that it is not thought to elicit an antibody reaction. However, by conjugating nicotine with various molecules that are recognized by the immune system as foreign, antinicotine antibody responses can be elicited.[61] Both active and passive immunization methods are currently being developed and evaluated.[62,63] The feasibility of nicotine vaccines has been supported by results from Phase II clinical trials.[64,65] In one trial,[66] 9-month continuous abstinence was 18% for a high-dose vaccine versus 4% for placebo.

Although the strategy behind a nicotine vaccine appears straightforward, a puzzle is posed by the fact that the amount of antibody likely to be present in the bloodstream is relatively small compared with the dose of nicotine inhaled from a cigarette. Thus, animal studies have reported antibody concentrations on the order of 440 nM.[67] Even if this relatively high antibody concentration could be achieved in a human smoker, it would be sufficient to bind only about 400 μg of nicotine (assuming two nicotine-binding sites per molecule and that the antibody is limited to a plasma volume of 2.75 L). This dose of nicotine is less than the amount delivered from five puffs of a typical cigarette. It is therefore challenging to understand how a nicotine antibody could be effective. If an antibody had a high affinity for nicotine (e.g., an equilibrium binding constant of less than 20 nM), then the available antibody would quickly become saturated with nicotine from the first few puffs of smoke. Nicotine inhaled from subsequent puffs of cigarette smoke could then simply bypass the saturated antibody; just as much nicotine might then reach the brain just as quickly as it would in the absence of vaccine treatment.

Nicotine antibodies with moderate affinities for nicotine might avoid saturation of antibody binding sites. In this case, there would be a partitioning of nicotine between an antibody-bound and an unbound (free) fraction. The consequent reduction in free nicotine concentration in arterial blood would lead to a reduction in the rate at which nicotine crosses the blood–brain barrier. As the remaining nicotine dissociated from the antibody and slowly entered the brain, antibody molecules would be freed to bind additional nicotine. The same process, whereby nicotine at first binds to the antibody, and then dissociates from it, could be repeated each time a cigarette is smoked. Ultimately, significant amounts of nicotine may reach the brain; however, by reducing the rate with which nicotine enters the brain, reinforcement from smoking might be attenuated.

According to this view, nicotine vaccine treatment might blunt the peak concentration of nicotine reaching the brain from inhaled cigarette smoke. Such vaccines might not necessarily prevent nicotine from sustained-release NRT products from reaching levels in the brain that are adequate to relieve withdrawal symptoms.[64] Thus, although nicotine vaccine treatment and NRT are usually assumed to be mutually exclusive approaches, they may turn out to be compatible or even synergistic.

CNS Nicotinic Receptors

Once nicotine is inhaled from the cigarette, has been absorbed into the arterial circulation, and crosses the blood–brain barrier, it acts on nicotinic receptors within the CNS. Neuronal nicotinic receptor subtypes in mammals consist of different combinations of eight alpha subunits (α2–α7, α9–α10) and three beta subunits (β2–β4), which are assembled into pentameric, ligand-gated ion channels.[68,69] When nicotine binds to a receptor, it may induce activation—a transient opening of the ion channel formed by these multimeric receptors. Subsequently, the receptor enters an inactive, closed-channel conformation; in other words, it becomes desensitized. The receptor will recover from desensitization after nicotine dissociates from the receptor, when the receptor can again be activated. This complex, dynamic process of

activation, desensitization, and resensitization is further complicated by the possible mobilization of nicotinic receptors from internal pools to membrane and from membrane to internal pools.[70] Although the precise mechanisms are not understood, the interaction of nicotine with nicotinic receptors initiates a cascade of effects that reinforces self-administration behavior. This initial site of action, the nicotinic receptor, is thus a logical target for substitution and/or blockade strategies that render cigarettes less reinforcing. Three types of treatments will be discussed that interact directly with nicotinic receptors: agonist substitution (NRT), antagonist blockade (mecamylamine), and the closely related approaches of mixed agonist–antagonist and partial agonist treatments (nicotine/mecamylamine, varenicline).

Nicotine Replacement Therapy

Nicotine replacement therapy, or NRT, has been a mainstay of smoking cessation treatment over the last 20 years. It is widely assumed that the main mechanism of action of NRT is to prevent or alleviate nicotine withdrawal symptoms.[71] Indeed, NRT has been shown in numerous studies to attenuate withdrawal symptoms.[72–74] Within the conceptual framework presented here, the relief or prevention of withdrawal symptoms can be viewed as an attenuation in the reinforcing potency of cigarettes—a reduction in their ability to remove or avoid an aversive withdrawal state (i.e., a reduction in negative reinforcement).

Although NRT can relieve withdrawal symptoms, other mechanisms of action have nevertheless been proposed.[75] For example, one alternative mechanism is the attenuation of the positively reinforcing effects of smoking through the induction of tolerance. Tolerance refers to the attenuation of the rewarding effects of inhaled nicotine resulting from the effects of the nicotine already present, such as effects on receptor desensitization. Thus, a cigarette will be less reinforcing if it is smoked when plasma nicotine levels are elevated than it will when smoked after a period of deprivation with low plasma nicotine levels.

Recent evidence indicates that attenuation of cigarette reward by NRT may indeed be an important aspect of its efficacy. For example, Shiffman *et al.*[76] conducted a study of smokers to track the progression of a "lapse" (a single episode of smoking) to a "relapse" (defined as 7 days of continuous smoking). If extinction of the reinforcing value of cigarettes depends on the number of times a cigarette is smoked without experiencing the usual rewarding effect ("nonreinforced trials"), one would predict that, as the number of lapses increases, NRT should have a greater effect relative to placebo in suppressing further progression to a full-blown relapse. This analysis of lapse episodes supports this conclusion. In the Shiffman *et al.* study,[76] smokers used electronic diaries to report smoking after receiving either nicotine patches (35 mg/24 h for 3 weeks and 21 mg/24 h for the next 2 weeks) or placebo patches. Active nicotine treatment promoted initial abstinence with a hazard ratio of 1.3. It decreased the risk of lapsing among those who had achieved abstinence with a hazard ratio of 1.6. The biggest effect of treatment, however, was to prevent progression from a lapse to relapse, with a hazard ratio of 7.1. The fact that NRT differentially affected different phases of quitting suggests that this approach has more than one mechanism of action. In particular, the large effect of preventing the progression from lapses to relapse is consistent with the view that NRT attenuates the reinforcing effects of cigarettes smoked during lapses, thereby reducing the likelihood that regular smoking will resume (see Shiffman *et al.*,[77] however, for alternative explanations). These results are also in accord with findings from clinical trials of nicotine patch treatment, in which subjective ratings of reward were lower in the active nicotine patch condition than in a placebo patch condition.[21,78]

Precessation NRT

It is therefore reasonable to hypothesize that administration of NRT during the weeks leading up to a target quit date, during which smokers might use NRT and cigarettes concurrently, will present the smoker with many occasions of smoking with attenuated reinforcement. This, in turn, may both lessen a smoker's dependence on cigarettes and facilitate cessation. Indeed, several studies have found a robust increase in abstinence rates after 2 weeks of precessation NRT.[20,79] In these studies, nicotine patch treatment before and after the quit date approximately doubled abstinence rates that are achieved when patches are applied only after the target quit date. A meta-analysis of precessation nicotine patch treatment[80] concluded that a consistent increase in abstinence rates occurred at 6 weeks after the quit date (odds ratio, 1.96) or 6 months after the quit date (odds ratio, 2.17) when NRT was initiated before the quit date compared with initiation of NRT on the quit date. A recent large-scale trial ($n = 400$) has replicated these findings: abstinence rates doubled when NRT was applied prior to the targeted quit date compared with conventional NRT.[81]

A similar trial using precessation nicotine chewing gum reported a trend for increased abstinence relative to conventional treatment beginning on the quit date.[82] It is possible, however, that precessation use of nicotine chewing gum or other on-demand nicotine dosing systems might not be as effective in precessation treatment as nicotine patches. If subjects alternate between smoking and using gum, nicotine levels just prior to smoking a cigarette might not be adequate to attenuate reinforcing effects. If on-demand nicotine formulations are used in precessation contexts, it will be important to compare *ad lib* dosing with fixed-time dosing (e.g., once per hour).

Mecamylamine

Mecamylamine is a noncompetitive nicotinic receptor antagonist that was introduced in the 1950s as an antihypertensive treatment[83] based on its ability to block preganglionic nicotinic receptors that help control arterial tone. Subsequently, it was shown to block many of the behavioral and physiological effects of nicotine.[84–86] In laboratory studies, mecamylamine administration acutely increases the intensity of smoking.[87–89] That finding, coupled with prominent anticholinergic side effects of high-dose mecamylamine (>10 mg/day), diminished enthusiasm for its use as a potential smoking cessation treatment.[90] The observed increase in smoking after mecamylamine administration is transient, however. Continued administration of mecamylamine leads to reduced smoking and attenuates the rewarding effects of smoking.[91,92] Moreover, low doses of mecamylamine (5–10 mg/day oral mecamylamine hydrochloride) can be reasonably well tolerated while exerting a significant blockade of smoking reward. Several controlled trials (discussed below in more detail) have shown that low-dose mecamylamine treatment, initiated during the weeks before a quit-smoking date, significantly increases rates of smoking abstinence relative to placebo.[91,93] The most prevalent side effect at these doses is constipation that can be managed using nonbulk laxatives, dose adjustment, or co-administration of an anticholinesterase.[94]

Mecamylamine/Nicotine Combination Treatment

The potential value of mecamylamine was more clearly appreciated when it was used in combination with NRT. Although usually thought of as diametrically opposite strategies, these two treatment approaches are not mutually incompatible. By administering a nicotinic receptor antagonist concurrently with NRT, Rose and Levin[95] hypothesized that the desired relief of withdrawal symptoms could be obtained while also attenuating the reinforcing effects of cigarette smoking. The strategy was likened to the use of a partial agonist, which will be discussed below. Two clinical trials

conducted in the 1990s showed that rates of continuous smoking abstinence were significantly increased by adding 5–10 mg/day mecamylamine hydrochloride to nicotine patch treatments (21 mg/24 h).[91,93]

Subsequently, in a large-scale Phase III clinical trial, mecamylamine administered in combination with NRT was again found to be more efficacious than either agent alone.[5] A total of 1191 smokers were randomly assigned to groups that received either nicotine and mecamylamine (Nic/Mec, $n = 447$), nicotine alone (Nic, $n = 446$), mecamylamine alone (Mec, $n = 149$), or placebo (Placebo, $n = 149$) beginning 2 weeks before, and continuing for 6 weeks after, the target quit-smoking date. A transdermal formulation was used to co-administer both drugs (21 mg/24 h nicotine and 6 mg mecamylamine base/24 h). Smoking cessation rates, based on a strict, continuous 4-week abstinence criterion, were 30% for Nic/Mec, 23.5% for Nic ($P = 0.023$ versus Nic/Mec), 17.4% for Mec ($P = 0.001$ versus Nic/Mec), and 6% for Placebo ($P < 0.001$ versus Nic/Mec).

Not all trials have had sufficient power to detect the modest increment in abstinence rates obtained when mecamylamine is added to precessation NRT.[96] However, given that the comparison condition of precessation (plus postcessation) NRT may be twice as effective as standard NRT, it is nonetheless noteworthy that combined mecamylamine/nicotine treatment surpassed this highly active "control" comparison condition.

Varenicline

Perhaps spurred by the suggestion to combine agonist and antagonist therapy[95] and/or encouraged by the clinical trial results from studies of mecamylamine in combination with NRT,[78] Coe *et al.*[97] set about developing a partial agonist for smoking cessation treatment. They based their synthesis efforts on (−)-cytisine, and were able to synthesize a derivative that had high binding affinity for α4β2 nicotinic acetylcholine receptors. Further functional studies using electrophysiological and *in vitro* dopamine release assay models confirmed that varenicline is a partial agonist: it activated α4β2 receptors in the absence of nicotine and attenuated responses to high concentrations of nicotine.[97]

Subsequent human clinical trials showed robust clinical efficacy of varenicline in smoking cessation treatment. Gonzales *et al.*,[98] in a randomized, controlled Phase III trial involving 1025 smokers, demonstrated superior efficacy of 12 weeks of varenicline treatment (titrated up to 1 mg twice daily [b.i.d.] after the first week) over bupropion (150 mg b.i.d.) and placebo. Continuous abstinence rates at weeks 9–12 postcessation were 44.0% for varenicline, 29.5% for bupropion, and 17.7% for placebo. Continuous abstinence rates from week 9 to week 52 were 21.9% for varenicline, 16.1% for bupropion, and 8.4% for placebo. Another Phase III trial with 1027 smokers similarly showed greater efficacy of 12-week treatment with varenicline than bupropion or placebo.[99] Continuous abstinence rates during weeks 9–12 were 43.9% for varenicline versus 29.8% for bupropion and 17.6% for placebo. For weeks 9–52, 23% of subjects in the varenicline group were continuously abstinent versus 12.6% who were continuously abstinent in the bupropion group and 7.3% in the placebo group. The most common adverse effect of varenicline in both studies was nausea, which was reported by about 29% of the participants.

Maintenance of varenicline treatment beyond 12 weeks has been shown to further increase efficacy. In a study conducted by Tonstad *et al.*,[100] 1210 smokers who were abstinent after 12 weeks of open-label varenicline treatment were randomized to receive either 12 additional weeks of varenicline or to be switched to placebo. Maintenance of varenicline treatment yielded a higher abstinence rate at weeks 13–24 than placebo (70.5% vs. 49.6%). Because 64.1% of those initially treated were abstinent at 12 weeks, these success rates translate to 45.2% and 31.8%, respectively, of the initial patient sample.

Treatment guidelines recommend beginning varenicline treatment 1 week before a target quit date.[101] Although the usual rationale provided is that this period is required to attain therapeutic blood levels of varenicline, the discussion in the previous section suggests that this timing might be important for other reasons. Specifically, it may also be important for the patient to experience an attenuation of the rewarding effects of cigarettes for some time while on varenicline treatment. Whether quit rates could be further improved by prolonging the precessation treatment period beyond 1 week has not yet been determined.

A recent clinical trial,[102] which included 746 participants, compared varenicline treatment with NRT (nicotine patch). The primary outcome, 4-week continuous abstinence, showed a significant advantage for varenicline: 55.9% versus 43.2%. Abstinence rates for weeks 9–52 were also slightly higher with varenicline: 26.1% versus 20.3% ($P = 0.056$). However, the nicotine patch was prescribed according to current recommendations, beginning on the quit date; by contrast, varenicline treatment began 1 week before the quit date. Thus, it is not known how varenicline treatment would compare with NRT were NRT initiated before the target quit-smoking date. The 4-week abstinence rates with varenicline are approximately four times those of placebo treatment.[103] The magnitude of effect is similar to that estimated for precessation NRT (i.e., an abstinence rate twice that of conventional NRT, which in turn doubles abstinence rates relative to placebo). A clinical trial that directly compared varenicline and precessation NRT might be highly interesting, although it might also be very costly because it might require well over a thousand participants to achieve adequate statistical power to detect what may be a small difference in efficacy.

Recently, rare but serious adverse reactions (e.g., suicidality) have been reported following varenicline treatment. Although nicotine withdrawal can trigger depression, it is difficult to attribute these reactions entirely to nicotine withdrawal because serious neuropsychiatric symptoms have also occurred in patients being treated with varenicline who continued to smoke. A causal relationship, however, between the use of varenicline and these symptoms has not yet been established.

Brain Reinforcement Pathways

Although nicotinic receptors are the initial sites of action of nicotine in the CNS, downstream events in dopamine reinforcement pathways may be critical in reinforcing smoking behavior. Nicotine, like other drugs of abuse, including opiates, alcohol, marijuana, and cocaine, is thought to be reinforcing, in part, because of the stimulation of mesolimbic dopamine reinforcement pathways arising from the dopamine neurons in the ventral tegmental area (VTA).[104–106] Animal self-administration studies, for example, have shown that local injection of nicotinic antagonists into the VTA block nicotine self-administration. The potentiation of the positive rewarding effects of cues by nicotine administration is also thought to be mediated via stimulation of dopamine release by nicotine, which then lends incentive salience to the cues.[107–109] Some studies of human smokers have found behavioral effects of dopaminergic manipulations, such as antagonist (haloperidol) or agonist (bromocriptine) administration.[110–112] Human brain imaging studies have also linked nicotine dependence and response to nicotine-associated cues to activity in the ventral striatum, a region that includes the nucleus accumbens, a key structure in the reward pathway.[113,114] Moreover, cigarette smoking acutely increases dopamine concentrations in the ventral striatum/nucleus accumbens.[115]

These neural pathways thus provide additional sites for interfering with nicotine-mediated reinforcement. Just as with pharmacologic treatments that act directly on nicotinic receptors, reward-modulating treatments can potentially either substitute for the

downstream rewarding actions of nicotine or, alternatively, antagonize these downstream effects. Either way, nicotine will become less effective at reinforcing smoking behavior.

Dopamine neurons are modulated by other neurotransmitters that mediate the reinforcing effects of nicotine;[116] these neurotransmitters include GABA, glutamate, endogenous opioids, endocannabinoids, and catecholamines (norepinephrine and dopamine). Several approaches to smoking cessation treatment are based on modulating dopamine reinforcement pathways through effects on these neurotransmitters. The following review of these pathways illustrates some of these points, although it is not intended to be an exhaustive review.

Agents Affecting GABA or Glutamate

Nicotine has been shown to act in part by decreasing GABA's inhibitory actions on VTA dopamine neurons.[117] It follows that augmenting GABA inhibitory tone on these dopamine systems might attenuate the reinforcing effects of addictive drugs such as nicotine. Indeed, Sofuoglu *et al.*[118] reported that the positive subjective response to intravenous nicotine was attenuated by tiagabine, which is thought to inhibit the GABA transporter type I and thereby increase synaptic GABA levels.

Vigabatrin, or γ-vinyl GABA (GVB) increases GABA transmission by inhibiting the GABA-degrading enzyme GABA transaminase; it has been proposed as an addiction treatment. In addition, Dewey *et al.* have reported that GVB attenuates the reinforcing effects of nicotine and other drugs in rats.[119] The studies in animal models are currently supported only by anecdotal clinical evidence; controlled human trials are planned.

Along with GABA, the excitatory amino acid neurotransmitter glutamate also modulates dopamine neuron firing rates in the VTA. The ability of nicotine to induce burst firing of VTA neurons has been linked in part to the release of glutamate that binds to *N*-methyl D-aspartate (NMDA) receptors.[120] A selective glycine antagonist (GW468816), which acts on an NMDA receptor modulatory site required for efficient ion channel activation, is currently being evaluated in smoking cessation trials.[121] A Phase I/II trial reported favorable results, with 57% abstinence rate in a group receiving 150 mg GW469916 compared with 36% abstinence in the placebo group.

Topiramate is an anticonvulsant that accentuates GABA-activated chloride channel activity and inhibits excitatory glutamate neurotransmission. A study of 94 smokers, who were also alcohol dependent, showed a higher quit-smoking rate in subjects receiving topiramate than in those receiving placebo.[122] Compared with patients receiving placebo, those receiving topiramate (in an escalating dose of 25–300 mg/day) were more likely to abstain from smoking (odds ratio, 4.46). For topiramate recipients, smoking cessation rates were 19.4% at week 9 and 16.7% at week 12 versus 6.9% at both time points for placebo recipients. In contrast, however, laboratory investigations have indicated that acute administration of topiramate potentiates, rather than blocks, some of the rewarding subjective effects of smoking.[123,124]

Gabapentin, an anticonvulsant with GABA-enhancing (and glutamatergic-reducing) properties, was investigated in a small ($n = 50$), preliminary open-label study.[125] Subjects received a dose of 1800 mg/day gabapentin. Prolonged abstinence was identified in 24% of the participants at the end of an 8-week treatment, and 20% were abstinent at the 6-month assessment.

In summary, GABA-enhancing or glutamate-reducing treatments show promise as potential smoking cessation aids. Further controlled trials are clearly warranted.

Opiate Antagonists

Mesolimbic dopamine neurons are also under the control of endogenous opioid pathways. By inhibiting the activity of GABA neurons that in turn inhibit dopamine neurons, opiates can trigger the release of dopamine in

the nucleus accumbens.[126] Preclinical studies have found that opiate antagonist treatment can induce nicotine withdrawal symptoms in dependent animals.[127] This connection supports a rationale for evaluating opiate antagonists for smoking cessation. Opiate antagonists such as naltrexone and nalmefene have been investigated as potential smoking cessation treatments. Although results have been mixed,[128,129] some studies obtained positive findings with naltrexone. In particular, Krishnan-Sarin *et al.*[130] reported a preliminary trial of naltrexone (50 mg/day) in combination with NRT; naltrexone reduced relapse in the first week of treatment among those who smoked. It also reduced the desire to smoke and weight gain. O'Malley *et al.*,[131] in a study of 400 smokers, found a trend ($P = 0.07$) for greater abstinence in those receiving 100 mg/day naltrexone versus placebo. Among treatment completers, a significant increase in abstinence was observed in those receiving naltrexone compared with those receiving placebo (71.6% vs. 48%).

Cannabinoid Antagonists

Dopamine reinforcement pathways are also modulated by the cannabinoid system. Cannabinoid CB_1 receptor activation contributes to the reinforcing properties of several drugs of abuse.[121] CB_1 receptor antagonists may therefore be efficacious in blocking the reinforcing effects of abused drugs, including nicotine. Rimonabant, a CB_1 receptor antagonist/inverse agonist that has been approved in Europe for weight loss, has shown efficacy in some smoking cessation trials.[121] For example, in one trial, smokers ($n = 784$) who expressed a desire to stop smoking were randomly assigned to placebo, rimonabant (5 mg/day), or rimonabant (20 mg/day) treatment. Subjects started treatment 2 weeks before stopping smoking and continued treatment for 8 weeks thereafter. A significantly greater number of subjects stopped smoking with rimonabant 20 mg/day compared with placebo (4-week abstinence rates of 36% vs. 21%). Weight gain was also less in the rimonabant 20-mg dose condition.

It might be anticipated that a potential drawback to reducing reward system activity would be a reduction in positive affect. Indeed, depressed mood has been reported as a side effect of rimonabant treatment. In particular, rimonabant (20 mg) treatment has been associated with an increase in both neurological and psychiatric symptoms,[132] including suicidal ideation. Rimonabant has not been approved by the FDA for any indication, including smoking cessation treatment.

Noradrenergic and Dopaminergic Agents

Bupropion was the first nonnicotine FDA-approved smoking cessation treatment.[133] Its promise for smoking cessation was based on serendipitous observations that individuals receiving bupropion treatment for depression had less difficulty quitting smoking.[121] Although the therapeutic mechanism for bupropion is unclear, the parent compound inhibits dopamine reuptake; thus, like other psychostimulants, it increases synaptic levels of dopamine. A principal metabolite also blocks the norepinephrine transporter. Bupropion enhances the value of reinforcing cues in the environment, an action similar to that demonstrated for nicotine.[134] In this sense, bupropion might function as a replacement therapy for the psychostimulant and reward-enhancing effects of nicotine. The ability of bupropion to alleviate withdrawal symptoms is also consistent with a substitution mechanism.[135,136]

However, bupropion and its major metabolite have also been shown to block nicotinic receptors.[137,138] Moreover, bupropion administration antagonizes some of the subjective rewarding effects of cigarette smoking.[139] Hence, bupropion could also act as an antagonist in an analogous fashion to mecamylamine (although if this is the case, bupropion likely has a different profile in terms of potency at different nicotinic receptor subtypes[140]).

The most common side effects with bupropion treatment include dry mouth and insomnia.

Nortriptyline, an antidepressant that shows modest selectivity for blocking the norepinephrine transporter,[141] is recommended as a second-line treatment by the AHCPR smoking cessation guidelines.[10] As with bupropion, clinical trials have consistently demonstrated the efficacy of nortriptyline.[142–144] Additional evidence also supports the efficacy of some other antidepressants that increase levels of dopamine or norepinephrine (e.g., doxepin[145]). By elevating monoamine levels in the brain, these agents may substitute for some of the postnicotinic receptor actions of nicotine. As with bupropion, this mechanism can be viewed as a substitution approach that lessens the positively rewarding effects of smoking. Alternatively, by alleviating depressive symptoms, these medications may reduce the negatively reinforcing effects of smoking. As with bupropion, however, nortriptyline and other antidepressants might also work through the blockade of nicotinic receptors.[146] Hence, these medications could have perhaps been listed under the previous section as nicotinic receptor antagonists. Further studies will be needed to dissociate their direct effects on nicotinic receptors from other actions in facilitating smoking cessation.

Although efficacious, frequent side effects are noted with nortriptyline treatment, including dry mouth, lightheadedness, blurred vision, constipation, difficulty urinating, and sexual difficulties.[142]

Clonidine is an antihypertensive medication that can reduce the withdrawal symptoms of several addictive drugs, including nicotine. Clonidine acts at presynaptic α_2 noradrenergic receptors to inhibit activity of the main source of noradrenergic fibers in the brain, the locus coeruleus. Although the locus coeruleus has generally been thought to regulate cortical arousal and responses to novel stimuli, recent evidence indicates that it may exert complex neuromodulatory influences over dopamine neurons in the VTA.[147] On one hand, noradrenergic pathways from the locus coeruleus may augment VTA activity, thus conceivably amplifying the rewarding effects of nicotine. On the other hand, however, burst firing of locus coeruleus cells depresses VTA cell activity; in an animal model, this firing induces symptoms of depression, possibly mediated by the neuropeptide galanin.[148] Interestingly, chronic cigarette smoking has been shown to downregulate tyrosine hydroxylase activity in the locus coeruleus.[149] This is a possible mechanism for the antidepressant effects of nicotine. In contrast, acute administration of nicotine acutely increases locus coeruleus activity.[150,151] Thus, the locus coeruleus may mediate some of the arousal- and/or cognitive-enhancing effects of nicotine as well as its antidepressant effects. Clonidine, by downregulating locus coeruleus activity, may therefore attenuate both of these potentially reinforcing effects of cigarette smoking.

Clinical trial results have not provided overwhelming support for the use of clonidine, although it appears to have some efficacy.[152] Some evidence suggests that it may be more helpful in heavily addicted smokers and in female smokers.[153] Side effects, including dry mouth and sedation, are prevalent and impede its widespread use.

Future Directions

The preceding analysis provides not only a heuristic for categorizing existing treatment approaches, but also potential avenues for novel treatment development. Future treatment development could include novel treatment combinations that attack two or more sites along the pathway from cigarette to brain. In addition, therapeutic approaches of the future will probably tailor treatment to different subpopulations of smokers or even to individual smokers.

Treatment Combinations

In addition to novel approaches, existing approaches might be combined in novel ways. Combining treatments that act at different points along the cigarette-to-brain continuum could be advantageous in that, with suitably chosen agents, therapeutic effects could be additive whereas side effects could be nonoverlapping. One potential example is the combination of denicotinized cigarettes and NRT mentioned earlier. Clinical trials using this method have been encouraging, although this approach is not yet approved by the FDA for smoking cessation treatment.

Another example to consider would be a combination of a reduced cigarette nicotine yield with nicotine vaccine treatment. If a smoker generates a sufficient antibody titer to slow brain uptake of nicotine by 50%, efficacy might be limited by this partial attenuation of nicotine's CNS effects. If, however, such an approach were combined with a prior step, switching the smoker to cigarettes with reduced nicotine yield (e.g., 0.3 mg), the combined effect of vaccine treatment and cigarette modification could result in a greater attenuation of nicotine reward than either approach alone. A potential advantage over switching to completely denicotinized cigarettes is that, although completely denicotinized cigarettes have unappealing sensory characteristics and are likely to pose a compliance issue for some smokers, cigarettes with moderately reduced nicotine yield can retain more of the acceptable peripheral sensory cues associated with nicotine.

Yet another example would be the combination of low-dose mecamylamine treatment with nicotine vaccine treatment. Such a combination might provide a more effective blockade of cigarette reward, with reduced side effects, than either treatment alone. Similarly, low-dose mecamylamine might be combined with bupropion, rimonabant, or other therapies. A rationale could also be suggested for combining mecamylamine with varenicline, in that they may have different potencies at various nicotinic receptor subtypes. Administering both agents in combination might attenuate nicotine reinforcement more than either treatment alone.

Numerous combination therapies can be considered based on the foregoing arguments. Clinical trials are obviously needed to test the efficacy of potential combination therapies.

Individualizing Treatment

Although combination treatments provide one strategy to enhance quit rates and thereby reach a greater proportion of the smoking population, an alternative strategy would be to determine for which smokers a given treatment is most efficacious. By tailoring the treatment to the smoker, overall treatment response rates could be enhanced. Genetic and phenotypic variables play a major role in the success or failure of a given treatment, both through efficacy and tolerability (see Uhl and colleagues, this volume). Thus, for example, some individuals will probably respond to NRT but not to bupropion, and vice versa, based on genetic factors.[154,155] Genetic and phenotypic markers may soon be used to tailor treatment to provide a given smoker with the treatment most likely to benefit him or her.

Psychiatric Populations

There is a strong association between psychiatric disorders and cigarette smoking.

The prevalence of cigarette smoking in populations with psychiatric disease or associated symptoms is substantially higher than in the general population.[156–158] These populations include not only those with clinically diagnosed psychiatric disorders, such as schizophrenia, bipolar disorder, substance abuse, anxiety, or major depression, but also those with subclinical depression, excessive alcohol consumption, or symptoms of attention-deficit/hyperactivity disorder (ADHD).[159,160] The application of therapeutic strategies to these psychiatric populations raises additional

considerations. The strategies for disrupting nicotine reinforcement outlined above are predicated on the assumption that, aside from their tobacco addiction problem, smokers do not require nicotine's effects for normal functioning. In psychiatric populations, however, this may not be the case. There is a plausible case to be made for the view that many smokers with psychiatric disorders are self-medicating their condition with nicotine (or potentially other components of cigarette smoke, such as MAO inhibitors).[48,49] Nicotine, for example, ameliorates the deficit in sensory gating in individuals with schizophrenia as well as their first-degree relatives.[161] Nicotine also has antidepressant,[162] anxiolytic,[163] and attention-enhancing[164] effects that may be sought by individuals with symptoms of depression, anxiety, or ADHD (see review by McLernon and colleagues, this volume).

The abovementioned logic raises the question of whether interfering with the rewarding aspects of nicotine will be effective in individuals who may be attempting to self-medicate their psychiatric symptoms. Mixed agonist–antagonist, or partial agonist approaches, which provide some of the functional benefits of nicotine while attenuating the rewarding effects of cigarette smoking, may therefore be more appropriate smoking cessation treatments for psychiatric populations. It is also important to ensure that psychiatric comorbidities are adequately managed while providing smoking cessation treatments.

Other Drugs of Abuse

In addition to nicotine and tobacco, it is clear that the same line of thinking pursued here might be applied to the treatment of addictions to other substances, such as "crack" cocaine, for which a series of intervention points could be delineated from the drug source to the brain. Whether a similar strategy will prove effective remains to be seen, but it appears promising and should be explored in laboratory studies and clinical trials.

Conclusion

Cigarette smoking is a highly reinforced behavior. Methods for interfering with the reinforcement of smoking may be efficacious in smoking cessation treatment. Indeed, many existing cessation treatments, including NRT, may be viewed as attenuating the positive and/or negative reinforcing effects of smoking. Viewed in this light, one may ask whether any smoking cessation treatments do not, in one manner or another, attenuate nicotine reinforcement. However, several alternative mechanisms can be listed, through which medication-based and behavioral therapies may work; these mechanisms include (1) enhancing decision making and self-control, (2) rendering nonnicotine components of cigarette smoke aversive (e.g., via silver acetate, which reacts with smoke components to create an aversive taste),[165] and (3) enhancing other behaviors incompatible with smoking (e.g., exercise). These and other treatment strategies lie outside the pathway of nicotine reinforcement as depicted in Figure 1. I hope that defining the cigarette-to-brain continuum explicitly may help further efforts to find more effective treatments operating within this scheme and intensify the search for treatments that lie beyond it.

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Conflict of Interest Disclosure

The author is a named inventor on several patents involving nicotine replacement systems and agonist–antagonist co-administration in the treatment of drug dependence.

References

1. Ezzati, M. & A.D. Lopez. 2003. Estimates of global mortality attributable to smoking in 2000. *Lancet* **362:** 847–852.
2. DHHS. 1988. *The Health Consequences of Smoking: Nicotine Addiction*. U.S. Department of Health and Human Services, Office on Smoking and Health. Rockville, MD.
3. Kalivas, P.W. & N.D. Volkow. 2005. The neural basis of addiction: A pathology of motivation and choice. *Am. J. Psychiatry* **162:** 1403–1413.
4. Shiffman, S. *et al.* 2004. The nicotine dependence syndrome scale: A multidimensional measure of nicotine dependence. *Nicotine Tob. Res.* **6:** 327–348.
5. Rose, J.E. 2006. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology (Berl.)* **184:** 274–285.
6. Dar, R. *et al.* 2007. Euphoriant effects of nicotine in smokers: Fact or artifact? *Psychopharmacology (Berl.)* **191:** 203–210.
7. Henningfield, J. *et al.* 1983. Cigarette smokers self-administer intravenous nicotine. *Pharmacol. Biochem. Behav.* **19:** 887–890.
8. Pomerleau, C.S. & O.F. Pomerleau. 1992. Euphoriant effects of nicotine in smokers. *Psychopharmacology (Berl.)* **108:** 460–465.
9. West, R. *et al.* 2006. Assessing DSM-IV nicotine withdrawal symptoms: A comparison and evaluation of five different scales. *Psychopharmacology (Berl.)* **184:** 619–627.
10. Fiore, M.C. 2000. Treating tobacco use and dependence: An introduction to the US Public Health Service Clinical Practice Guideline. *Respir. Care* **45:** 1196–1199.
11. Benowitz, N.L. & J.E. Henningfield. 1994. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N. Engl. J. Med.* **331:** 123–125.
12. Gray, N. *et al.* 2005. Toward a comprehensive long term nicotine policy. *Tob. Control* **14:** 161–165.
13. Henningfield, J.E. *et al.* 1998. Reducing the addictiveness of cigarettes. *Tob. Control* **7:** 281–293.
14. Benowitz, N.L. *et al.* 1983. Smokers of low-yield cigarettes do not consume less nicotine. *N. Engl. J. Med.* **309:** 139–142.
15. Kozlowski, L.T. *et al.* 1994. Misuse of "light" cigarettes by means of vent blocking. *J. Subst. Abuse* **6:** 333–336.
16. Conkling, M.A. *et al.*, inventors. 2002. Regulation of quinolate phosphoribosyl trasnferase expression. U.S. Patent 6,423,520.
17. Butschky, M.F. *et al.* 1995. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacol. Biochem. Behav.* **50:** 91–96.
18. Pickworth, W.B. *et al.* 1999. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine Tob. Res.* **1:** 357–364.
19. Rose, J. & F. Behm. 2004. Effects of low nicotine content cigarettes on smoke intake. *Nicotine Tob. Res.* **6:** 309–319.
20. Rose, J.E. *et al.* 2006. Pre-cessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine Tob. Res.* **8:** 89–101.
21. Rose, J.E. & F.M. Behm. 2004. Extinguishing the rewarding value of smoke cues: Pharmacological and behavioral treatments. *Nicotine Tob. Res.* **6:** 523–532.
22. Benowitz, N.L. *et al.* 2007. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol. Biomarkers Prev.* **16:** 2479–2485.
23. Benowitz, N.L. *et al.* 2006. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin. Pharmacol. Ther.* **80:** 703–714.
24. Nil, R. & K. Battig. 1989. Separate effects of cigarette smoke yield and smoke taste on smoking behavior. *Psychopharmacology* **99:** 54–59.
25. Robinson, M.L. *et al.* 2000. Placebo cigarettes in smoking research. *Exp. Clin. Psychopharmacol.* **8:** 326–332.
26. Strasser, A.A. *et al.* 2007. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug Alcohol Depend.* **86:** 294–300.
27. Donny, E.C. *et al.* 2007. Smoking in the absence of nicotine: Behavioral, subjective and physiological effects over 11 days. *Addiction* **102:** 324–334.
28. Heatherton, T.F. *et al.* 1991. The Fagerström test for nicotine dependence: A revision of the Fagerström tolerance questionnaire. *Br. J. Addict.* **86:** 1119–1127.
29. Hatsukami, D.K. 2007. *Denicotinized cigarettes: Toxicity, dependence and cessation*. Presented at the conference, Science and Future Directions for Nicotine Regulation. Rockville, MD, Nov. 29–30.
30. Becker, K.M. *et al.* 2008. A randomized trial of nicotine replacement in combination with reduced nicotine cigarettes for smoking cessation. *Nicotine Tob. Res.* **10**(7): 1139–1148.
31. Rezaishiraz, H. *et al.* 2007. Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine Tob. Res.* **9:** 1139–1146.
32. McClernon, F.J. *et al.* 2007. Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: Results of a preliminary functional magnetic resonance imaging study. *Addict. Biol.* **12:** 503–512.

33. Rose, J.E. *et al.* 2000. Dissociating nicotine and non-nicotine components of cigarette smoking. *Pharmacol. Biochem. Behav.* **67:** 71–81.
34. Westman, E.C. *et al.* 1996. Dissociating the nicotine and airway sensory effects of smoking. *Pharmacol. Biochem. Behav.* **53:** 309–315.
35. Rose, J.E. *et al.* 1984. Subjective response to cigarette smoking following airway anesthetization. *Addict. Behav.* **9:** 211–215.
36. Rose, J.E. *et al.* 1985. Sensory blockade of smoking satisfaction. *Pharmacol. Biochem. Behav.* **23:** 289–293.
37. Westman, E.C. *et al.* 1995. Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized, placebo-controlled trial using a citric acid inhaler. *Chest* **107:** 1358–1364.
38. Lee, L.-Y. *et al.* 1993. Nicotine is responsible for the airway irritation evoked by cigarette smoke inhalation in men. *J. Appl. Physiol.* **75:** 1955–1961.
39. Rose, J.E. *et al.* 1999. Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. *Pharmacol. Biochem. Behav.* **62:** 165–172.
40. Lee, L.Y. *et al.* 2007. Airway irritation and cough evoked by inhaled cigarette smoke: Role of neuronal nicotinic acetylcholine receptors. *Pulm. Pharmacol. Ther.* **20:** 355–364.
41. Lee, L.-Y. *et al.* 1989. Stimulation of vagal pulmonary C-fibers by a single breath of cigarette smoke in dogs. *J. Appl. Physiol.* **66:** 2032–2038.
42. Ginzel, K.H. & E. Eldred. 1977. Reflex depression of somatic motor activity from heart, lungs and carotid sinus. In *Krogh Centenary Symposium on Respiratory Adaptation, Capillary Exchange and Reflex Mechanisms*. A.S. Paintal & P. Gill-Kumar, Eds.: 358–395. Vallabhbai Patel Chest Institute, University of Delhi. Delhi, India.
43. Rennard, S.I. *et al.* 2006. Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. *Nicotine Tob. Res.* **8:** 555–564.
44. Schneider, N.G. *et al.* 2001. The nicotine inhaler: Clinical pharmacokinetics and comparison with other nicotine treatments. *Clin. Pharmacokinet.* **40:** 661–684.
45. Bolliger, C.T. *et al.* 2000. Smoking reduction with oral nicotine inhalers: Double blind, randomised clinical trial of efficacy and safety. *BMJ* **321:** 329–333.
46. Lunell, E. *et al.* 1996. Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography. *Clin. Pharmacol. Ther.* **59:** 593–594.
47. Katz, I.M. *et al.* 2001. Factors affecting the deposition of aerosolized insulin. *Diabetes Technol. Ther.* **3:** 387–397.
48. Fowler, J.S. *et al.* 1996. Inhibition of monoamine oxidase B in the brains of smokers. *Nature* **379:** 732–736.
49. Fowler, J.S. *et al.* 1996. Brain monoamine oxidase A inhibition in cigarette smokers. *Proc. Natl. Acad. Sci. USA* **93:** 14065–14069.
50. Ding, Y.S. *et al.* 2006. Determination of 14 polycyclic aromatic hydrocarbons in mainstream smoke from U.S. brand and non-U.S. brand cigarettes. *Environ. Sci. Technol.* **40:** 1133–1138.
51. Benowitz, N.L. 1998. Summary: Risks and benefits of nicotine. In *Nicotine Safety and Toxicity*. N.L. Benowitz, Ed.: 185–194. Oxford University Press. New York, NY.
52. Stead, L. *et al.* 2008. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst RevCD000146.
53. West, R. *et al.* 2000. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl.)* **149:** 198–202.
54. Jarvik, M.E. & K.M. Assil. 1988. Mecamylamine blocks the burning sensation of nicotine on the tongue. *Chem. Senses.* **13:** 213–217.
55. Rose, J.E. *et al.* 2001. Acute effects of nicotine and mecamylamine on tobacco withdrawal symptoms, cigarette reward and *ad lib* smoking. *Pharmacol. Biochem. Behav.* **68:** 187–197.
56. West, R. *et al.* 2007. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology (Berl.)* **197:** 371–377.
57. Russell, M.A.H. & C. Feyerabend. 1978. Cigarette smoking: A dependence on high-nicotine boli. *Drug Metabol. Rev.* **8:** 29–57.
58. Rose, J.E. *et al.* 1999. Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: Implications for addiction. *Drug Alcohol Depend.* **56:** 99–107.
59. Brewer, B.G. *et al.* 2004. Short-term distribution of nicotine in the rat lung. *Drug Alcohol Depend.* **75:** 193–198.
60. Muhkin, A.G. *et al.* 2008. *Comparison of brain nicotine accumulation after cigarette smoking in dependent and non-dependent smokers*. Presented at the Annual Meeting of the Society of Nuclear Medicine. New Orleans, LA, June 14–18.
61. LeSage, M.G. *et al.* 2006. Effects of a nicotine conjugate vaccine on the acquisition and maintenance of nicotine self-administration in rats. *Psychopharmacology (Berl.)* **184:** 409–416.
62. Pentel, P.R. *et al.* 2000. A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. *Pharmacol. Biochem. Behav.* **65:** 191–198.

63. Vocci, F.J. & C.N. Chiang. 2001. Vaccines against nicotine: How effective are they likely to be in preventing smoking? *CNS Drugs* **15:** 505–514.
64. Hatsukami, D. *et al.* 2005. *Results of a phase 2, multi-center, randomized, double-blinded, placebo-controlled, parallel-arm, dose comparison study to assess the immunogenicity and safety of 3′-aminomethylnicotine-P. aeruginosa R-exoprotein. A conjugate vaccine (NicVAX) administered to smokers*. Presented at the 11th Annual Meeting of the Society for Research on Nicotine and Tobacco 38, Prague, Czech Republic, March 20–23.
65. Maurer, P. & M.F. Bachmann. 2007. Vaccination against nicotine: An emerging therapy for tobacco dependence. *Expert. Opin. Investig. Drugs* **16:** 1775–1783.
66. Rennard, S.I. *et al.* 2007. A randomized placebo-controlled trial of a conjugate nicotine vaccine (NicVAX®) in smokers who want to quit: 12 month results. *Circulation* **116:** II_844.
67. Heading, C.E. 2007. Drug evaluation: CYT-002-NicQb, a therapeutic vaccine for the treatment of nicotine addiction. *Curr. Opin. Investig. Drugs* **8:** 71–77.
68. Changeux, J.P. *et al.* 1998. Brain nicotinic receptors: Structure and regulation, role in learning and reinforcement. *Brain Res. Brain Res. Rev.* **26:** 198–216.
69. Lindstrom, J. 1997. Nicotinic acetylcholine receptors in health and disease. *Mol. Neurobiol.* **15:** 193–222.
70. Cho, C.H. *et al.* 2005. Rapid upregulation of alpha7 nicotinic acetylcholine receptors by tyrosine dephosphorylation. *J. Neurosci.* **25:** 3712–3723.
71. Peters, M.J. & L.C. Morgan. 2002. The pharmacotherapy of smoking cessation. *Med. J. Aust.* **176:** 486–490.
72. Hughes, J.R. *et al.* 1984. Effect of nicotine on the tobacco withdrawal syndrome. *Psychopharmacology (Berl.)* **83:** 82–87.
73. Schneider, N.G. *et al.* 2008. Preferences among five nicotine treatments based on information versus sampling. *Nicotine Tob. Res.* **10:** 179–186.
74. Sweeney, C.T. *et al.* 2001. Combination nicotine replacement therapy for smoking cessation: Rationale, efficacy and tolerability. *CNS Drugs* **15:** 453–467.
75. Jasinski, D.R. & J.E. Henningfield. 1988. Conceptual basis of replacement therapies for chemical dependence. In *Nicotine Replacement: A Critical Evaluation.* O.F. Pomerleau & C.S. Pomerleau, Eds.: 13–34. Alan R. Liss, Inc. New York, NY.
76. Shiffman, S. *et al.* 2006. Analyzing milestones in smoking cessation: Illustration in a nicotine patch trial in adult smokers. *J. Consult. Clin. Psychol.* **74:** 276–285.
77. Shiffman, S. *et al.* 2006. Immediate hedonic response to smoking lapses: Relationship to smoking relapse, and effects of nicotine replacement therapy. *Psychopharmacology (Berl.)* **184:** 608–618.
78. Rose, J.E. *et al.* 1994. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin. Pharmacol. Ther.* **56:** 86–99.
79. Schuurmans, M.M. *et al.* 2004. Effect of pretreatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: A randomized controlled trial. *Addiction* **99:** 634–640.
80. Shiffman, S. & S.G. Ferguson. 2008. Nicotine patch therapy prior to quitting: A meta-analysis. *Addiction* **103:** 557–563.
81. Rose, J.E. *et al.* 2007. *Pre-cessation treatment with nicotine patch. Significantly increases abstinence rates relative to conventional treatment*. Presented at the 13th Annual Meeting of the Society for Research on Nicotine and Tobacco. Austin, TX, February 21–24.
82. Herrera, N. *et al.* 1995. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* **108:** 447–451.
83. Allanby, K.D. & J.R. Trounce. 1957. Excretion of mecamylamine after intravenous and oral administration. *BMJ* **1:** 1219–1221.
84. Clarke, P.B.S. 1991. Nicotinic receptor blockade therapy and smoking cessation. In *British Journal of Addiction, Vol. 86*. West, R. & N.E. Grunberg, Eds.: 501–506. Carfax Publishing Company. London.
85. Lundahl, L.H. *et al.* 2000. Mecamylamine blockade of both positive and negative effects of IV nicotine in human volunteers. *Pharmacol. Biochem. Behav.* **66:** 637–643.
86. Nemeth-Coslett, R. *et al.* 1986. Effects of mecamylamine on human cigarette smoking and subjective ratings. *Psychopharmacology* **88:** 420–425.
87. Pomerleau, C.S. *et al.* 1987. Mecamylamine pretreatment increases subsequent nicotine self-administration as indicated by changes in plasma nicotine level. *Psychopharmacology* **91:** 391–393.
88. Rose, J.E. *et al.* 1988. Mecamylamine increases nicotine preference and attenuates nicotine discrimination. *Pharm. Biochem. Behav.* **32:** 933–938.
89. Stolerman, I.P. *et al.* 1973. Influencing cigarette smoking with nicotine antagonists. *Psychopharmacology* **28:** 247–259.
90. Stolerman, I.P. 1986. Could nicotine antagonists be used in smoking cessation? *Br. J. Addict.* **81:** 47–53.
91. Rose, J.E. *et al.* 1998. Nicotine-mecamylamine treatment for smoking cessation: The role of

pre-cessation therapy. *Exp. Clin. Psychopharmacol.* **6:** 331–343.
92. Rose, J.E. & F.M. Behm. 2004. Extinguishing the rewarding value of smoke cues: Pharmacologic and behavioral treatments. *Nicotine Tob. Res.* **6:** 523–532.
93. Rose, J.E. *et al.* 1994. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin. Pharmacol. Ther.* **56:** 86–99.
94. Rose, J.E. & E.C. Westman. 1999. *Use of neostigmine in conjunction with nicotine/mecamylamine treatment for smoking cessation.* Presented at the 5th Annual Meeting of the Society for Research on Nicotine and Tobacco. San Diego, CA, March 5–7.
95. Rose, J.E. & E.D. Levin. 1991. Concurrent agonist-antagonist administration for the analysis and treatment of drug dependence. **41:** 219–226.
96. Glover, E.D. *et al.* 2007. A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* **102:** 795–802.
97. Coe, J.W. *et al.* 2005. Varenicline: An alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J. Med. Chem.* **48:** 3474–3477.
98. Gonzales, D. *et al.* 2007. Comment: Oral varenicline for smoking cessation. *Ann. Pharmacother.* **41:** 720–721.
99. Jorenby, D.E. *et al.* 2006. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *JAMA* **296:** 56–63.
100. Tonstad, S. *et al.* 2006. Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. *JAMA* **296:** 64–71.
101. Lam, S. & P.N. Patel. 2007. Varenicline: A selective alpha4beta2 nicotinic acetylcholine receptor partial agonist approved for smoking cessation. *Cardiol. Rev.* **15:** 154–161.
102. Aubin, H.J. *et al.* 2008. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. *Thorax* doi: 10.1136/thx.2007.090647
103. Oncken, C. *et al.* 2006. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch. Intern. Med.* **166:** 1571–1577.
104. Corrigall, W.A. *et al.* 1992. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology (Berl.)* **107:** 285–289.
105. Di Chiara, G. 2000. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur. J. Pharmacol.* **393:** 295–314.
106. Pich, E.M. *et al.* 1997. Common neural substrates for the addictive properties of nicotine and cocaine. *Science* **275:** 83–86.
107. Balfour, D.J. *et al.* 2000. The putative role of extrasynaptic mesolimbic dopamine in the neurobiology of nicotine dependence. *Behav. Brain Res.* **113:** 73–83.
108. Robinson, T.E. & K.C. Berridge. 2001. Incentive-sensitization and addiction. *Addiction* **96:** 103–114.
109. Wyvell, C.L. & K.C. Berridge. 2001. Incentive sensitization by previous amphetamine exposure: Increased cue-triggered "wanting" for sucrose reward. *J. Neurosci.* **21:** 7831–7840.
110. Brauer, L.H. *et al.* 2001. Haloperidol reduces smoking of both nicotine-containing and denicotinized cigarettes. *Psychopharmacology (Berl.)* **159:** 31–37.
111. Caskey, N.H. *et al.* 2002. Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine Tob. Res.* **4:** 259–266.
112. Dawe, S. *et al.* 1995. Nicotine intake in smokers increases following a single dose of haloperidol. *Psychopharmacology (Berl.)* **117:** 110–115.
113. McClernon, F.J. *et al.* 2007. Individual differences in nicotine dependence, withdrawal symptoms, and sex predict transient fMRI-BOLD responses to smoking cues. *Neuropsychopharmacology* **33:** 2148–2157.
114. Rose, J.E. *et al.* 2007. Regional brain activity correlates of nicotine dependence. *Neuropsychopharmacology* **32:** 2441–2452.
115. Brody, A.L. *et al.* 2004. Smoking-induced ventral striatum dopamine release. *Am. J. Psychiatry* **161:** 1211–1218.
116. Pidoplichko, V.I. *et al.* 2004. Nicotinic cholinergic synaptic mechanisms in the ventral tegmental area contribute to nicotine addiction. *Learn Mem.* **11:** 60–69.
117. Dani, J.A. & M. De Biasi. 2001. Cellular mechanisms of nicotine addiction. *Pharmacol. Biochem. Behav.* **70:** 439–446.
118. Sofuoglu, M. *et al.* 2005. Effects of tiagabine in combination with intravenous nicotine in overnight abstinent smokers. *Psychopharmacology (Berl.)* **181:** 504–510.
119. Dewey, S.L. *et al.* 1999. A pharmacologic strategy for the treatment of nicotine addiction. *Synapse* **31:** 76–86.
120. Schilstrom, B. *et al.* 2000. Putative role of presynaptic alpha7* nicotinic receptors in nicotine stimulated increases of extracellular levels of glutamate and aspartate in the ventral tegmental area. *Synapse* **38:** 375–383.
121. Heidbreder, C. 2005. Novel pharmacotherapeutic targets for the management of drug addiction. *Eur. J. Pharmacol.* **526:** 101–112.

122. Johnson, B.A. *et al.* 2005. Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial. *Arch. Intern. Med.* **165:** 1600–1605.
123. Reid, M.S. *et al.* 2007. Effects of topiramate on cue-induced cigarette craving and the response to a smoked cigarette in briefly abstinent smokers. *Psychopharmacology (Berl.)* **192:** 147–158.
124. Sofuoglu, M. *et al.* 2006. Effects of topiramate in combination with intravenous nicotine in overnight abstinent smokers. *Psychopharmacology (Berl.)* **184:** 645–651.
125. Sood, A. *et al.* 2007. Gabapentin for smoking cessation: A preliminary investigation of efficacy. *Nicotine Tob. Res.* **9:** 291–298.
126. Mansvelder, H.D. 2005. Yin and yang of VTA opioid signaling. Focus on "both kappa and mu opioid agonists inhibit glutamatergic input to ventral tegmental area neurons." *J. Neurophysiol.* **93:** 3046–3047.
127. Malin, D.H. *et al.* 1993. Naloxone precipitates nicotine abstinence syndrome in the rat. *Psychopharmacology (Berl.)* **112:** 339–342.
128. King, A.C. 2002. Role of naltrexone in initial smoking cessation: Preliminary findings. *Alcohol Clin. Exp. Res.* **26:** 1942–1944.
129. King, A. *et al.* 2006. Efficacy of naltrexone in smoking cessation: A preliminary study and an examination of sex differences. *Nicotine Tob. Res.* **8:** 671–682.
130. Krishnan-Sarin, S. *et al.* 2003. Naltrexone and nicotine patch smoking cessation: A preliminary study. *Nicotine Tob. Res.* **5:** 851–857.
131. O'Malley, S.S. *et al.* 2006. A controlled trial of naltrexone augmentation of nicotine replacement therapy for smoking cessation. *Arch. Intern. Med.* **166:** 667–674.
132. Steinberg, B.A. & C.P. Cannon. 2007. Cannabinoid-1 receptor blockade in cardiometabolic risk reduction: safety, tolerability, and therapeutic potential. *Am. J. Cardiol.* **100:** 27P-32P.
133. Ferry, L. & J.A. Johnston. 2003. Efficacy and safety of bupropion SR for smoking cessation: Data from clinical trials and five years of postmarketing experience. *Int. J. Clin. Pract.* **57:** 224–230.
134. Mays, K.L. *et al.* 2007. *Nicotine and bupropion have similar effects on responding for reinforcing non-drug stimuli*. Presented at the 13th Annual Meeting of the Society for Research on Nicotine and Tobacco. Austin, TX, February 21–24.
135. Mooney, M.E. & M. Sofuoglu. 2006. Bupropion for the treatment of nicotine withdrawal and craving. *Expert. Rev. Neurother.* **6:** 965–981.
136. Paterson, N.E. *et al.* 2007. Chronic bupropion attenuated the anhedonic component of nicotine withdrawal in rats via inhibition of dopamine reuptake in the nucleus accumbens shell. *Eur. J. Neurosci.* **25:** 3099–3108.
137. Damaj, M.I. *et al.* 2004. Enantioselective effects of hydroxy metabolites of bupropion on behavior and on function of monoamine transporters and nicotinic receptors. *Mol. Pharmacol.* **66:** 675–682.
138. Fryer, J.D. & R.J. Lukas. 1999. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. *J. Pharmacol. Exp. Ther.* **288:** 88–92.
139. Cousins, M.S. *et al.* 2001. Acute doses of d-amphetamine and bupropion increase cigarette smoking. *Psychopharmacology (Berl.)* **157:** 243–253.
140. Papke, R.L. *et al.* 2001. Analysis of mecamylamine stereoisomers on human nicotinic receptor subtypes. *J. Pharmacol. Exp. Ther.* **297:** 646–656.
141. Vaishnavi, S.N. *et al.* 2004. Milnacipran: A comparative analysis of human monoamine uptake and transporter binding affinity. *Biol. Psychiatry* **55:** 320–322.
142. Hall, S.M. *et al.* 2004. Extended nortriptyline and psychological treatment for cigarette smoking. *Am. J. Psychiatry* **161:** 2100–2107.
143. Hall, S.M. *et al.* 2005. Cost-effectiveness of bupropion, nortriptyline, and psychological intervention in smoking cessation. *J. Behav. Health Serv. Res.* **32:** 381–392.
144. Hughes, J.R. *et al.* 2007. Antidepressants for smoking cessation. Cochrane Database Syst RevCD000031.
145. Whelan, A.M. & S.K. Davis. 1990. Doxepin in smoking cessation. *DICP*. **24:** 598–599.
146. Gumilar, F. *et al.* 2003. Molecular mechanisms of inhibition of nicotinic acetylcholine receptors by tricyclic antidepressants. *Neuropharmacology* **45:** 964–976.
147. Wise, R.A. 1998. Drug-activation of brain reward pathways. *Drug Alcohol Depend.* **51:** 13–22.
148. Weiss, J.M. *et al.* 2005. Testing the hypothesis that locus coeruleus hyperactivity produces depression-related changes via galanin. *Neuropeptides* **39:** 281–287.
149. Klimek, V. *et al.* 2001. Effects of long-term cigarette smoking on the human locus coeruleus. *Arch. Gen. Psychiatry* **58:** 821–827.
150. Svensson, T.H. *et al.* 1990. Effect of nicotine on dynamic function of brain catecholamine neurons. *Ciba Found. Symp.* **152:** 169–180; discussion 180–5.
151. Tung, C.S. *et al.* 1989. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids. *Synapse* **4:** 313–318.
152. Gourlay, S.G. *et al.* 2004. Clonidine for smoking cessation. Cochrane Database Syst RevCD000058.

153. Fagerstrom, K.O. 1991. Towards better diagnoses and more individual treatment of tobacco dependence. *Br. J. Addict.* **86:** 543–547.
154. Uhl, G.R. *et al.* 2007. Molecular genetics of nicotine dependence and abstinence: Whole genome association using 520,000 SNPs. *BMC Genet*. **8:** 10.
155. Uhl, G.R. *et al.* 2008. Molecular genetics of successful smoking cessation: Convergent genome-wide association results. *Arch. Gen. Psychiatry* **65:** 683–693.
156. Breslau, N. *et al.* 2004. Psychiatric disorders and stages of smoking. *Biol. Psychiatry* **55:** 69–76.
157. Hughes, J.R. *et al.* 1986. Prevalence of smoking among psychiatric outpatients. *Am. J. Psychiatry* **143:** 993–997.
158. Lasser, K. *et al.* 2000. Smoking and mental illness: A population-based prevalence study. *JAMA* **284:** 2606–2610.
159. Hughes, J.R. 1999. Comorbidity and smoking. *Nicotine Tob. Res.* **1**(Suppl 2): S149–S152; discussion S165–166.
160. Kollins, S.H. *et al.* 2005. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. *Arch. Gen. Psychiatry* **62:** 1142–1147.
161. Adler, L.E. *et al.* 1992. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biol. Psychiatry* **32:** 607–616.
162. McClernon, F.J. *et al.* 2006. Transdermal nicotine attenuates depression symptoms in nonsmokers: A double-blind, placebo-controlled trial. *Psychopharmacology (Berl.)* **189:** 125–133.
163. Buckley, T.C. *et al.* 2007. The effect of nicotine and attention allocation on physiological and self-report measures of induced anxiety in PTSD: A double-blind placebo-controlled trial. *Exp. Clin. Psychopharmacol.* **15:** 154–164.
164. Conners, C.K. *et al.* 1996. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). *Psychopharmacol. Bull.* **32:** 67–73.
165. Hymowitz, N. & H. Eckholdt. 1996. Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking cessation. *Prev. Med.* **25:** 537–546.

Blockade of Smoking Satisfaction Using the Peripheral Nicotinic Antagonist Trimethaphan

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ABSTRACT

The present study was conducted to investigate the role of peripheral nicotinic receptors in mediating the rewarding effects of cigarette smoking. Twelve cigarette smokers rated cigarettes after intravenous infusion of the short-acting peripheral nicotinic receptor antagonist trimethaphan and after placebo (saline) infusions. Subjects were blinded to the infusion and cigarette conditions. Cigarette conditions included subjects' usual brand of cigarette, de-nicotinized tobacco cigarettes, and nicotine-injected cigarettes which had a tar delivery equal to that of the de-nicotinized cigarettes but with an enhanced nicotine delivery equal to that of subjects' usual brands. The latter cigarettes were rated as extremely harsh due to the high nicotine/tar ratio. Trimethaphan significantly attenuated the airway sensations associated with nicotine, and eliminated the difference in smoking satisfaction between the usual brand of cigarette and the other two cigarettes. These findings suggest that nicotinic receptors on peripheral nerve endings in the respiratory tract modulate smoking satisfaction and may be important in the maintenance of cigarette addiction.

nicotine smoking addiction antagonist trimethaphan

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Recent views of tobacco dependence, and of cigarette smoking in particular, have stressed the role of nicotine addiction in the maintenance of smoking behavior [36]. Moreover, an almost exclusive emphasis is usually placed on the role of CNS nicotinic receptors, which mediate a variety of reinforcing effects of nicotine [7]. It is generally assumed that nicotine acts at CNS receptors to induce dependence in a manner similar to that of opiates and cocaine. Indeed, evidence for nicotine's actions in the CNS is considerable; nicotine interacts directly with several subtypes of nicotinic receptors, consisting of various combinations of α and β subunit proteins [40]. Nicotine acts on these receptors to trigger a cascade of neurophysiologic effects, including facilitating the release of neurotransmitters such as dopamine, norepinephrine, acetylcholine, glutamate, GABA and serotonin [11,19,25]. The role of CNS dopamine release has received special attention inasmuch as there is considerable evidence that activation of mesolimbic reward pathways contributes to the reinforcing efficacy of a variety of abused drugs, including nicotine [21,26,31]. In a rodent model of nicotine self-administration, specific lesions in the mesolimbic dopamine system selectively block nicotine self-administration behavior [8].

Despite this evidence for direct CNS reinforcement of nicotine self-administration, it is likely that in humans the reinforcing effects of tobacco use are multifaceted. In addition to the direct CNS actions of nicotine, the peripheral actions of cigarette smoke, accompanied by perceptions labeled as "taste" and "impact", may be important conditioned or unconditioned reinforcing cues [28,33]. Smokers report enjoying the "feel" of cigarette smoke as it is inhaled, and when these sensory effects are blocked, as with local anesthesia, smoking satisfaction is blunted [27]. Conversely, previously studies in our laboratory have shown that stimulation of peripheral respiratory tract sensations relieves craving for cigarettes and can facilitate smoking cessation [3,32,38]. Other studies have shown that there are nicotinic receptors on vagal nerve endings in the respiratory tract. Ginzel [10], for example, showed that injection of nicotinic agonists into the right heart of cats caused an immediate

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skeletal muscle relaxation response, even before the nicotine reached the cerebral circulation. Lee [22] has shown in human subjects that the irritating actions of nicotine in the respiratory tract can be blocked with the antagonist hexamethonium.

Thus, there is considerable uncertainty as to the relative importance of peripheral sensory actions of cigarette smoke, the nicotinic components of these peripheral sensations, and the direct CNS action of nicotine in providing the reinforcing effects that maintain cigarette addiction.

We conducted the present study to explore the effect of trimethaphan, a peripherally acting nicotinic antagonist [20], on the immediate subjective effects of cigarette smoking. Trimethaphan has been used clinically in the control of blood pressure; it has both ganglion-blocking effects as well as direct vasodilating actions, but the ganglionic blocking action predominates at low doses [2]. Neurophysiologic studies suggest that trimethaphan has primarily a competitive antagonist of nicotine [37]. An advantage of trimethaphan for laboratory-based studies of human smoking behavior is its brevity of action; the effects of trimethaphan dissipate within several minutes after the intravenous infusion is terminated [2], making it well suited for repeated measures experimental designs. Also, because trimethaphan is a sulfonium compound with a permanent positive charge [20], it is likely that trimethaphan has limited penetration into the CNS.

Theories of smoking motivation that exclusively involve the CNS actions of nicotine would predict that trimethaphan should have little or no effect on the rewarding effects of smoking (whether assessed by subjective ratings or by behavioral measures of reinforcement), given that trimethaphan does not prevent inhaled nicotine from reaching the brain and providing primary reinforcement. However, based on the previous work in our laboratory, blockade of the peripheral sensory effects of nicotine was hypothesized to modify the pleasurable effects of smoking and reduce reported satisfaction. In this study we focused on the subjective satisfaction obtained from cigarette smoking as an index of reward. To gain as much information as possible regarding the effects of

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trimethaphan, subjects rated their usual brand of cigarette as well as research cigarettes that varied nicotine delivery while holding "tar" delivery constant, accompanied by either trimethaphan or saline infusions.

METHOD

Design: A 3 (usual brand, cigarette *vs* nicotine-injected research cigarette *vs* de-nicotinized cigarette) X 2 (trimethaphan *vs* saline infusion) factorial design. A within-subjects design was used, with all six conditions presented to subjects in a single session.

Subjects: 12 healthy male and female smokers were recruited from a pool of subjects previously contacted through responses to newspapers advertisements, who were interested in participating in a smoking cessation trial involving treatment with nicotine skin patches and mecamylamine. Subjects were offered the opportunity to participate in this laboratory study for monetary payment ($10/hr) prior to the initiation of smoking cessation treatment. Subjects were screened according to the following criteria: Inclusion Criteria: age 18-55 years old; smoke at least 20 cigarettes per day on average, with nicotine delivery at least 0.7 mg; afternoon expired carbon monoxide (CO) level ≥20 ppm; desire to quit smoking; general good health, based on physical examination, EKG, serum chemistries, CBC and urinalysis. Exclusion Criteria: hypertension (systolic >140 mmHg, diastolic >90 mmHg); hypotension (systolic < 90 mmHg, diastolic <60 mmHg); coronary artery disease; cardiac rhythm disorder; history of urinary retention; prostatic hypertrophy; glaucoma; impaired renal function; history of skin allergy; active skin condition (psoriasis) within the last 5 years; other major medical condition; current psychiatric disease; pregnancy or nursing mothers; use of oral contraceptives; current alcohol or drug abuse; current smokeless tobacco use, nicotine replacement therapy, or other smoking cessation treatment. Assessment of Eligibility: Each potential subject was screened by telephone to determine compatibility with the inclusion and exclusion criteria. If the criteria were met, the potential subject was scheduled for the screening history and physical examination at the study center. At this session, potential subjects completed a medical history

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form; blood pressure, pulse, blood and urine tests were also taken, as well as an EKG with rhythm strip.

Subject characteristics were as follows: Ten males and 2 females participated in the study; the mean age was 41.6 yr. (s.d.=10.64) and subjects had smoked for an average of 27.2 yr. (s.d.=10.57). They smoked on average 28 cigarettes/day, with a mean cigarette nicotine delivery (assessed by FTC method) of 0.94 mg (s.d.=0.297). The mean score on the Fagerström test for nicotine dependence [14] was 5.7 (s.d.=1.56).

Controlled puff volume apparatus. Puff volume was controlled with a simple apparatus validated in previous studies [23]. The device uses a glass syringe pre-loaded with a measured amount of air that is supplied to the burning cigarette with each puff. When the subject takes a puff, the syringe barrel slides within the glass housing until the specified volume of air (smoke) has been drawn into the mouth, and no further smoke can be obtained until the device is reset for the next puff. While the cigarettes are in the controlled puff delivery apparatus, a low air flow rate (5 cc/sec) was provided to prevent the cigarette from extinguishing while keeping side stream smoke from escaping. The apparatus was held in place with a ring stand situated conveniently in front of the subject, who could take puffs by leaning forward and drawing from a disposable plastic mouthpiece having a diameter comparable to a cigarette. This apparatus was used in a previous study of mecamylamine and nicotine administration, in which we found that subjects reported substantial smoking satisfaction taking puffs through the apparatus, and smoking satisfaction was significantly blocked by prior administration of mecamylamine or nicotine [29].

Puff volume was equated across nicotine-containing and de-nicotinized cigarettes; puff volume, number of puffs and inter-puff interval were individualized as described below. To minimize variability in nicotine absorption from variations in inhalation, subjects in all conditions were instructed to inhale deeply and hold their breath for 5 sec after each puff. Gilbert [9] found that this manipulation was adequate to ensure consistent

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boosts in plasma nicotine levels after smoking nicotine-containing cigarettes.

Individualized nicotine dosing: Cigarette smokers vary enormously in the nicotine extracted from cigarettes during *ad lib* smoking; in a study conducted by Benowitz [4], typical nicotine deliveries per cigarette were found to range from approximately 0.4 mg/cigarette to 1.6 mg/cigarette, with a mean of 1.0 mg. We have also found similar variability in smokers' nicotine intake during *ad lib* smoking in previous studies. In view of these findings, spurious results might be obtained if the same dose of nicotine were administered to all subjects, ignoring individual differences in sensitivity to nicotine. Therefore, we devised a procedure for administering nicotine doses equal to that self-administered by each subject during *ad lib* smoking. Nicotine intake after *ad lib* smoking was quantified by measuring puff volume, number of puffs and inter-puff intervals. This measurement was conducted directly using the same spirometric apparatus described above. When employed to measure puff volume, as opposed to controlling it, the air-containing syringe was initially filled with 70 cc prior to each puff, and the reading after each puff indicated the volume provided to the cigarette. The number of puffs and interpuff interval were also recorded, and during the controlled smoke presentations the same total number of puffs and average interpuff interval were used. In previous work we have verified that individualizing nicotine delivery using this method produces increases in plasma nicotine highly correlated with those of *ad lib* smoking ($r \approx 0.8$), and the mean plasma nicotine boosts agree within 10%.

Trimethaphan: Trimethaphan camsylate (Arfonad®) ampules were obtained from Roche Laboratories (Nutley, NJ). Each ampule contains 500 mg trimethaphan camsylate, which was diluted before intravenous administration.

Cigarettes: Three types of cigarettes were used: 1) subject's customary brand, 2) de-nicotinized tobacco cigarettes, and 3) de-nicotinized cigarettes injected with nicotine to raise their nicotine delivery to match subject's usual brands. We used de-nicotinized cigarettes manufactured

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by Phillip Morris, Inc., which our laboratory and others have studied previously [13,28]. These cigarettes contain tobacco from which the nicotine has been selectively extracted by high-pressure CO_2. The tar delivery of these cigarettes, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg. Hasenfratz et al. [13] measured smoking behavior and nicotine intake after smoking de-nicotinized *vs* nicotine-containing cigarettes and found that plasma nicotine levels increased less than 2 ng/ml after smoking the de-nicotinized cigarette. In studies using these cigarettes we have verified that they produce no significant boosts in plasma nicotine levels.

The technique to be used for manipulating cigarette nicotine delivery of these cigarettes, which we have validated in several previous studies (e.g [15]), involved injecting a measured amount of nicotine base into the filter of the control (de-nicotinized) cigarettes. As smoke particles pass through the filter, they absorb some of the nicotine and the nicotine delivery of the cigarette is thereby enhanced. A graded effect is seen with different amounts of nicotine injected. The standard FTC nicotine delivery of each subject's habitual brand of cigarette was matched by injecting a known amount of nicotine into a de-nicotinized cigarette. In this manner, nicotine dose was manipulated in a controlled way while also keeping non-nicotine constituents constant. To blind participants to the cigarette conditions, distinctive markings were covered with opaque strips of cigarette paper, taking care not to block visible ventilation holes in the cigarette filter.

Dependent variables:

Expired air carbon monoxide: Expired air carbon monoxide, an objective index of smoke intake [16], was measured with a breath carbon monoxide monitor (Vitalograph, Lenexa, KS). While sitting, patients held a deep inspiration for a minimum of ten seconds, then exhaled through the monitor. Exhaled CO was calculated by subtracting the background (ambient) CO from the exhaled CO reading.

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Cardiovascular measures: Measurement of pulse and blood pressure was taken each minute during trimethaphan infusion, and every 15 minutes between cigarette presentations. Continuous ECG monitoring was also performed.

Cigarette evaluation: A cigarette evaluation questionnaire was administered after smoking each cigarette, which included 7-point item ratings that clustered (based on previous factor analytic studies) into the following scales: *Satisfaction* ("was it satisfying?", "did it taste good?"), Similarity to usual brand ("how similar to your own brand?"), *Psychological Reward* ("did it calm you down?", "did it help you concentrate?", "did it make you feel more awake?", "did it reduce your hunger for food?", "did it make you feel less irritable?", *Aversion* ("did it make you nauseous?", "did it make you dizzy?"), *Enjoy respiratory sensations* ("Did you enjoy the sensations of the smoke in your throat and chest?"), *Craving reduction* (did it immediately reduce your craving fro cigarettes?"), and *Perceived strength* on "tongue", "nose", "back of mouth & throat", "windpipe" and "chest" [39].

Procedure:

After the screening physical, subjects participated in two sessions that were conducted after overnight abstinence from smoking. Smoking abstinence was confirmed at the beginning of each session by expired air CO measurement and subsequently by plasma nicotine analysis. The first session served to characterize the individual nicotine intake of each subject, upon which to base subsequent dosing. Subjects were allowed to smoke *ad lib* one cigarette of their usual brand, using the spirometric device (described above) that was later used to control smoke dose in the second session.

An intravenous line was established for infusion of trimethaphan (or saline) and for collection of blood samples for plasma nicotine assay. The study was conducted in the Durham Veterans Affairs Medical Center, with a physician present during the procedure.

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Six cigarettes were presented at 30 minute intervals; three of the smoking conditions (one of each type of cigarette) were accompanied by trimethaphan infusion and the other three smoking periods were accompanied by saline infusions (subjects were blind to the infusion condition). Before lighting each cigarette, intravenous trimethaphan infusions were started at a rate of 3-4 mg/min and titrated up until a mild hypotensive effect (5-10 mm Hg reduction in systolic blood pressure) was observed, continuing throughout the cigarette smoking period. The order of conditions was counterbalanced using a Latin square design. However, because previous studies had suggested that the nicotine-injected cigarettes, having a much higher nicotine/tar ratio, were extremely harsh [15], these cigarettes were always presented during the last hour of the session (the order of trimethaphan *vs* saline infusion was counterbalanced for these cigarettes).

Subjects rated the rewarding and/or aversive effects of each cigarette using the cigarette evaluation questionnaires described above.

Samples of venous blood (10 cc) were collected immediately before and after each cigarette (a total of 120 cc) to assess nicotine concentrations.

Data analysis: Quality checks were made in the process of data handling to minimize errors. The data were entered into a database twice, and the two resulting datasets were compared. Datapoints that were discrepant were reviewed and corrected by referring to the original data forms. Data analysis was performed using SUPERANOVA (Abacus Concepts Inc., Berkeley CA). This statistical software applies a multivariate approach to repeated measures analysis which is generally appropriate regardless of the correlation pattern among repeated measurements [1,24]. The effects of the repeated measures factors Cigarette and Infusion were analyzed, and, if significant main effects or interactions were found, follow-up tests were conducted according to the protected least significant difference test [18]. For each dependent measure, contrasts were also conducted to determine whether trimethaphan influenced the pattern of significant differences between cigarette conditions that were

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apparent in the saline infusion condition. The alpha criterion for assessing drug effects was taken to be .05 (two-tailed). Nonsignificant trends ($p<.1$) were also noted in some cases if they suggested potential mechanisms underlying the actions of trimethaphan.

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RESULTS

Nicotine delivery and plasma nicotine boosts for the three types of cigarette

The plasma nicotine boost following smoking of the usual brand cigarette was comparable in trimethaphan and saline infusion conditions, and was also similar to the nicotine boost in the nicotine-injected cigarette conditions (see Fig. 1). The mean boost of approximately 10 ng/ml is in good accord with the values reported in previous studies of cigarette smokers. The denicotinized cigarette had negligible effects on plasma nicotine, also confirming previous studies using these cigarettes. The plasma nicotine boost was highly correlated with the cigarette nicotine delivery, estimated by the multiplying the FTC nicotine rating by the number of puffs and puff volume ($r=.69$, $p=.01$). Subjects took an average of 6.2 puffs (s.d.=1.76), with a mean puff volume of 42.8 ml (s.d=10.66) and mean interpuff interval of 67.2 sec (s.d.=28.28).

The change in expired air CO following smoking was also similar in trimethaphan and saline infusion conditions (1.8 ppm (s.d.=1.70) *vs* 2.2 ppm (s.d.=1.71), $F(1,11)=1.00$, $p>.3$).

Cigarette ratings

Before assessing the influence of trimethaphan on cigarette ratings, the three cigarette conditions were first compared using data from the saline infusion conditions, in order to characterize the effects of the cigarettes *per se*. There were pronounced differences in satisfaction ratings, which differed across cigarettes ($F(2,22)=11.10$, $p=.0005$); the usual brand was rated more satisfying than the denicotinized cigarette ($F(1,22)=10.68$, $p=.003$) or the nicotine-injected cigarette ($F(1,22)=20.93$, $p=.0005$). The cigarettes were also rated differently in terms of the degree of similarity to the subjects' usual brand of cigarette ($F(2,22)=10.38$, $p=.0007$), with the usual brand being rated, not surprisingly, as significantly more similar than either the denicotinized cigarette ($F(1,22)=16.25$, $p=.0006$) or the nicotine-injected cigarette ($F(1,22)=14.87$, $p=.0009$).

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Subjects reported enjoying the airway sensations of smoking their usual brand more than the other two cigarette conditions ($F(1,22)=7.24$, $p=.01$ for the comparison of usual brand *vs* denicotinized cigarette and $F(1,22)=14.42$, $p=.001$ for the comparison of usual brand *vs* nicotine-injected cigarette).

Ratings of the strength of regional respiratory tract sensations also differed across cigarette conditions ($F(2,22)=3.53$, $p=.05$ for tongue; $F(2,22)=5.09$, $p=.02$ for nose; $F(2,22)=6.83$, $p=.005$ for back of mouth and throat; $F(2,22)=4.19$, $p=.03$ for windpipe and $F(2,22)=4.62$, $p=.02$ for chest). In contrast to the ratings of enjoyment previously described, which distinguished the usual brand from the other two cigarettes, in the case of respiratory tract sensations the nicotine-injected cigarette was generally rated stronger than the other two cigarettes in all regions; they were rated stronger than the denicotinized control cigarette for the tongue ($F(1,22)=6.03$, $p=.02$), nose ($F(1,22)=10.11$, $p=.004$), back of mouth and throat ($F(1,22)=16.67$, $p=.004$), windpipe ($F(1,22)=6.28$, $p=.02$), and chest ($F(1,22)=9.04$, $p=.006$). They were also rated as significantly more intense than the usual brand cigarettes with respect to sensations on the tongue ($F(1,22)=4.43$, $p=.05$), back of mouth and throat ($F(1,22)=10.25$, $p=.004$) and windpipe ($F(1,22)=6.28$, $p=.02$), with trends in the same direction for nose ($F(1,22)=3.30$, $p=.08$), and chest ($F(1,22)=3.60$, $p=.07$).

There was a difference between conditions in the immediate craving-reducing effect of smoking, with the two nicotine-containing cigarettes reducing craving more than the denicotinized cigarette ($F(1,22)=5.42$, $p=.03$).

Effects of trimethaphan on cigarette ratings: The effects of trimethaphan were assessed with respect to the differences between cigarettes noted above: 1) For satisfaction ratings, the difference between the usual brand and the two control cigarettes was contrasted between trimethaphan and saline infusion conditions; 2) For respiratory tract strength ratings, the difference between the nicotine-injected cigarettes and the other two cigarettes was contrasted between trimethaphan and saline conditions;

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also, the two nicotine-containing cigarette conditions were contrasted with the denicotinized control cigarette; and 3) for immediate craving reduction, the two nicotine-containing cigarettes were contrasted with the de-nicotinized control cigarette.

Smoking satisfaction: There was a significant interaction of infusion X cigarette condition ($F(1,20)=4.73$, $p=.04$), such that the difference between the usual brand and other cigarette conditions was abolished by trimethaphan (see Fig. 2). In the saline condition, the contrast between the usual brand and the other two cigarettes was highly significant ($F(1,20)=9.51$, $p=.006$), whereas the three cigarettes were rated similarly in terms of satisfaction during the trimethaphan infusions ($F(1,20)=.02$, $p=.9$). Thus, there was a strong trend for trimethaphan to reduce smoking satisfaction in the usual brand condition ($F(1,18)=4.21$, $p=.06$), while tending to increase satisfaction for the nicotine-injected cigarettes ($F(1,18)=2.93$, $p=.1$).

A similar finding held with regard to similarity to the usual brand cigarette; the difference between the usual brand and the other two cigarettes was significantly attenuated by trimethaphan ($F(1,22)=5.03$, $p=.04$). In the saline condition, the contrast between the usual brand and the other two cigarettes was highly significant ($F(1,22)=12.11$, $p=.002$), but in the trimethaphan condition, the cigarettes did not differ from each other in similarity ratings ($F(1,22)=.22$, $p=.6$).

The relatively greater enjoyment of the respiratory sensations reported for the usual brand of cigarette was also attenuated by trimethaphan ($F(1,20)=6.46$, $p=.02$ for the trimethaphan *vs* saline comparison of the difference between the usual brand and other two cigarettes).

To evaluate the hypothesis that trimethaphan would block the perception of nicotine in the respiratory tract, the reported intensity of sensations in the different respiratory regions was analyzed. In Fig. 3, for each type of cigarette and region, the rating for the trimethaphan condition is depicted immediately adjacent to the saline infusion condition to illustrate the attenuation of sensations by trimethaphan. There was a

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significant main effect of trimethaphan infusion, decreasing strength ratings for all cigarettes in several regions, especially in the windpipe and chest ($F(1,11)=6.36$, $p=.01$ for windpipe, and $F(1,11)=8.68$, $p=.01$ for chest). However, the difference in ratings between the nicotine-injected cigarette and the other two cigarettes was unaffected by trimethaphan (p's >.1 for all regions). On the other hand, for the chest, the difference between the two nicotine-containing cigarettes and the denicotinized control cigarette *was* attenuated by trimethaphan ($F(1,22)=5.63$, $p=.03$).

With respect to the immediate craving reduction after smoking, the effect of nicotine was not altered by trimethaphan, as shown in Fig. 4 ($F(1,20)=.41$, $p=.5$ for the contrast between the effect of nicotine in the saline infusion condition *vs* the effect of nicotine in the trimethaphan condition); thus, there was still a significant effect of nicotine (contrasting the two nicotine-containing cigarettes with the denicotinized cigarette) in both the trimethaphan condition ($F(1,20)=4.74$, $p=.04$) and in the saline condition ($F(1,20)=6.56$, $p=.02$).

Blood pressure and heart rate: There was a mild hypotensive effect of trimethaphan (relative to saline infusion) prior to cigarette smoking. Systolic blood pressure was lowered on average by trimethaphan from a mean of 115.6 mm Hg (s.d.=2.05) to 110.7 mm Hg (s.d.=1.76), $F(1,11)=17.18$, $p=.002$. Diastolic blood pressure was lowered from a mean of 71.5 (s.d.=10.92) to 66.5 mm Hg (s.d.=10.71), $F(1,11)=16.60$, $p=.002$. Smoking had no consistent effect on blood pressure.

Heart rate was increased by trimethaphan from an average (pre-smoking) of 67.2 bpm (s.d.=8.61) to 72.9 bpm (s.d.=9.04), $F(1,11)=22.2$, $p=.0006$. Cigarette smoking also increased heart rate in the nicotine-containing cigarette conditions relative to the denicotinized control ($F(1,20)=8.82$, $p=.008$); the heart rate boost after smoking averaged 6.6 bpm (s.d.=6.31) in the usual brand condition, 5.6 bpm (s.d.=5.73) in the nicotine-injected cigarette condition, and 3.5 bpm (s.d.=4.08) in the denicotinized cigarette condition.

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DISCUSSION

The main conclusion of the present study is that peripheral actions of nicotine are extremely important in mediating the immediate subjective effects of cigarette smoking. The importance of peripheral actions of nicotine was demonstrated by the attenuation of smoking satisfaction for the usual-brand cigarette condition accompanying trimethaphan infusions. In addition, the fact that the usual brand cigarette was rated so much more enjoyable than the nicotine-injected cigarette, despite having equal nicotine delivery (and presumably similar direct actions on the central nervous system), further highlights the importance of peripheral sensory cues in determining hedonic effects of cigarette smoking. The nicotine-injected cigarettes were rated as excessively harsh (relative to both the usual brand cigarettes and the denicotinized control cigarettes), which probably accounts for the low ratings of liking and satisfaction.

The harshness of the nicotine-injected cigarettes also explains why trimethaphan had opposite effects on reactions to the usual brand *vs* injected nicotine cigarettes. The usual brand cigarettes, which were rated high in satisfaction in the saline condition, showed a strong trend to be rated less satisfying in the trimethaphan condition, possibly due to the lack of the unique "feel" of nicotine in the lungs. In contrast, the nicotine-injected cigarettes, which produced excessive harshness, tended to become more enjoyable and satisfying when sensations were reduced to a more tolerable level by trimethaphan (see Fig. 2).

The finding that sensory cues are important determinants of the hedonic effects of smoking leaves open the question of whether these cues are primary reinforcing stimuli [10], or instead become reinforcing over time due to their familiarity or because they serve as a conditioned reinforcers signaling the rewarding CNS actions of nicotine. Studies examining whether the rewarding effects of peripheral cues extinguish over time, if presented in the absence of the CNS effects of nicotine, will be useful in addressing this issue.

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Interestingly, the ability of a cigarette to relieve craving may depend on different processes than those which mediate enjoyment and satisfaction. This was shown by the fact that trimethaphan did not attenuate the nicotine-related component of craving reduction (see Fig. 4). Thus, for the usual brand of cigarette, the peripheral actions of nicotine appear to be critical for mediating satisfaction, but the nicotine component of craving reduction is likely to be CNS-mediated. Evidence from other studies involving nicotine administration *via* skin patches, a mode of nicotine delivery that presents few peripheral sensations, but which reduces cigarette craving [28], also suggests that at least a portion of nicotine's effects on craving is centrally mediated. Additionally, there is a *non*-nicotine sensory component of craving reduction, as evidenced by the ratings of craving reduction for the denicotinized cigarette (which, although statistically lower, were nearly as high as for the usual brand (see also [6,13])).

Although brain concentrations of trimethaphan were not measured, there are several reasons for concluding that the marked effects on subjective ratings of smoking were due to peripheral nicotinic receptor, as opposed to CNS receptor, blockade: 1) molecules having a permanent positive charge such as trimethaphan and low lipid solubility generally show little penetration into the brain in the short-term [5]; 2) the opposite effects of trimethaphan on the desirability of the harsh, nicotine-injected cigarettes *vs* subjects' usual brands is consistent with an interpretation in terms of blockade of peripheral respiratory tract sensations, but would be difficult to explain in terms of CNS blockade inasmuch as both the nicotine-injected cigarettes and usual brand cigarettes had comparable nicotine delivery and presumably similar CNS actions; 3) the lack of effect of trimethaphan on the nicotine component of craving reduction is consistent with a lack of CNS blockade. Although this could also be explained by assuming that nicotine was acting peripherally but at a different nicotinic receptor subtype, not affected by trimethaphan, the most parsimonious account is that trimethaphan did not block the CNS actions of nicotine.

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The effect of trimethaphan in attenuating sensations in the windpipe and chest, and specifically the attenuation of nicotine-related sensations in the chest (as shown by the comparison between trimethaphan and saline conditions in the difference between the denicotinized cigarette and the two nicotine-containing cigarettes) is consistent with the existence of nicotinic receptors on vagal nerve endings [10]. However, the fact that trimethaphan also had a main effect in reducing the sensory intensity of all cigarettes (including the denicotinized cigarette), suggests that sensory input arising from non-nicotine stimuli may nonetheless be mediated through nicotinic pathways. It has been reported that there are nicotinic receptors in the solitary nucleus, a target of vagal afferent terminals [35], part of which is located in a region of the brain where the blood-brain barrier is absent [12]. Moreover, sensory ganglia contain nicotinic receptors which relay signals arising from nicotine and well as non-nicotine stimuli [17]. Thus, it is conceivable that trimethaphan would have access to these neural relay stations and could have attenuated sensations produced by the denicotinized cigarette, even though these sensations were almost certainly elicited by smoke constituents other than nicotine.

The present results have several implications for smoking cessation treatment. First, these results, along with previous studies suggest that the peripheral effects of nicotine are important to smokers and that adjuncts which can replace these sensations may be helpful smoking cessation aids [38]. Second, the aversive irritation that can result from some existing nicotine-containing smoking cessation aids, such as the nicotine nasal spray, might best be attenuated by nicotinic antagonist treatment in order to enhance compliance with effective use.

Third, these results suggest that selective nicotinic antagonists might be developed which block the enjoyment of smoking by blocking the nicotinic receptors in the respiratory tract. Previous research in our laboratory has shown that the nicotinic antagonist mecamylamine can be used fruitfully in smoking cessation treatment [30,34]. Initiation of blockade treatment two weeks prior to smoking cessation appears to enhance subsequent abstinence, suggesting that extinction of smoking behavior resulting from

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blockade of smoking reward mediates the therapeutic effect of mecamylamine. However, mecamylamine blocks both central and peripheral nicotinic receptors, and the question is left open as to how much of the action of mecamylamine might be mediated by blockade of peripheral nicotinic receptors. Blockade of these receptors alters the sensory characteristics of cigarette smoke and may account for a significant portion of the blockade of smoking satisfaction we have previously reported using mecamylamine. If the therapeutic effect of mecamylamine were shown to result in large part from its action on peripheral nicotinic receptors, then more selective antagonists might be developed to target these receptors with minimal side effects. Thus, further studies using chronic administration of peripheral nicotinic receptor antagonists will be important for evaluating theories of tobacco dependence, for understanding the mechanisms underlying nicotine antagonist treatment, and potentially for developing still more efficacious therapies.

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REFERENCES

1. Abacus Concepts. SuperANOVA. Berkeley: Abacus Concepts, Inc.; 1989.

2. Adams, A. P.; Hewitt, P. B. Clinical pharmacology of hypotensive agents. Int. Anesthesiol. Clin. 20:95-109; 1982.

3. Behm, F. M.; Schur, C.; Levin, E. D.; Tashkin, D. P.; Rose, J. E. Clinical evaluation of a citric acid inhaler for smoking cessation. Drug Alc. Depend. 31:131-138; 1993.

4. Benowitz, N. L.; Porchet, H.; Jacob, P. I. Pharmacokinetics, metabolism, and pharmacodynamics of nicotine. In Wonnacott, S.;Russell, M. A. H.; Stolerman, I. P. (Ed.), Nicotine Psychopharmacology (pp. 112-157). Oxford: Oxford University Press;1990.

5. Bowman, W. C.; M.J., R. Textbook of Pharmacology. London: Blackwell Scientific Publication; 1980.

6. Butschky, M. F.; Bailey, D.; Henningfield, J. E.; Pickworth, W. B. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. Pharmacol. Biochem. Behav. 50:91-96; 1995.

7. Clarke, P. B. S. The central pharmacology of nicotine: electrophysiological approaches. In Wonnacott, S.;Russell, M. A. H.; Stolerman, I. P. (Ed.), Nicotine Psychopharmacology: Molecular, Cellular, and Behavioural Aspects (pp. 158-193). New York: Oxford University Press;1990.

8. Corrigall, W. A.; Coen, K. M.; Adamson, K. L. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res. 653:278-284; 1994.

9. Gilbert, D. G.; Jensen, R. A.; Meliska, C. J. A system for administering quantified doses of tobacco smoke to human subjects: Plasma nicotine and filter pad validation. Pharmacol. Biochem. Behav. 31:905-908; 1989.

2060579227

10. Ginzel, K. H.; Eldred, E. Reflex depression of somatic motor activity from heart, lungs and carotid sinus. In Paintal, A. S.; Gill-Kumar, P. (Ed.), Krogh Centenary Symposium on Respiratory Adaptation, Capillary Exchange and Reflex Mechanisms. (pp. 358-395). Delhi: Vallabhbai Patel Chest Institute, University of Delhi;1977.

11. Gray, R.; Rajan, A. S.; Radcliffe, K. A.; Yakehiro, M.; Dani, J. A. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383:713-716; 1996.

12. Gross, P. M.; Wall, K. M.; Pang, J. J.; Shaver, S. W.; Wainman, D. S. Microvascular specializations promoting rapid interstitial solute dispersion in nucleus tractus solitarius. Am. J. Physiol. 259:R1131-R1138; 1990.

13. Hasenfratz, M.; Baldinger, B.; Battig, K. Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology 112:253-258; 1993.

14. Heatherton, T. F.; Kozlowski, L. T.; Frecker, R. C.; Fagerström, K. O. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionaire. Br. J. Addict. 86:1119-1127; 1991.

15. Herskovic, J. E.; Rose, J. E.; Jarvik, M. E. Cigarette desirability and nicotine preference in smokers. Pharmacol. Biochem. Behav. 24:171-175; 1986.

16. Horan, J. J.; Hackett, G.; Linberg, S. E. Factors to consider when using expired air carbon monoxide in smoking assessment. 3:25-28; 1978.

17. Jafri, M. S.; Kamatchi, G.; Kao, J. P. Y.; Weinrich, D. Nicotinic receptors mediate a calcium-dependent decrease in membrane excitability in vagal afferents in vitro. Poster presentation at the Society for Neurosciences meeting, New Orleans, LA, October 25-30, 1997.: 1997.

20060579228

18. Keppel, G. Design and Analysis: A Researcher's Handbook. (2nd ed.). Englewood Cliffs, New Jersey: Prentice-Hall, Inc.; 1982.

19. Khan, I. M.; Marsala, M.; Printz, M. P.; Taylor, P.; Yaksh, T. L. Intrathecal nicotinic agonist-elicited release of excitatory amino acids as measured by in vivo spinal microdialysis in rats. J. Pharmacol. Exp. Ther. 278:97-106; 1996.

20. Klowden, A. J.; Ivankovitch, A. D.; Miletich, D. J. Ganglionic blocking drugs: General Considerations and metabolism. Int. Anesthesiol. Clin. 16:113-150; 1978.

21. Koob, G. F.; Nestler, E. J. The neurobiology of drug addiction. J. Neuropsych. Clin. Neurosci. 9:482-497; 1997.

22. Lee, L.-Y.; Gerhardstein, D. C.; Wang, A. L.; Burki, N. K. Nicotine is responsible for the airway irritation evoked by cigarette smoke inhalation in men. J. Appl. Physiol. 75:1955-1961; 1993.

23. Levin, E. D.; Rose, J. E.; Behm, F. Controlling puff volume without disrupting smoking topography. Behav. Res. Meth. Instr. Comput. 21:383-386; 1989.

24. Maxwell, S. E.; Delaney, H. D. Designing Experiments and Analyzing Data. Belmont, CA: Wadsworth; 1990.

25. McGehee, D. S.; Heath, M. J. S.; Gelber, S.; Devay, P.; Role, L. W. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science 269:1692-1696; 1995.

26. Pontieri, F. E.; Tanda, G.; Orzi, F.; Di Chiara, G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382:255-257; 1996.

2060579229

27. Rose, J. E. The role of upper airway stimulation in smoking. In Pomerleau, O. F.; Pomerleau, C. S. (Ed.), Nicotine Replacement: A Critical Evaluation (pp. 95-106). New York: Alan R. Liss, Inc.;1988.

28. Rose, J. E.; Behm, F. M. There is more to smoking than the CNS effects of nicotine. Effects of nicotine on biological systems II (pp. 9-16). Basel: Burkhäuser Verlag;1995.

29. Rose, J. E.; Behm, F. M.; Westman, E. C.; Levin, E. D.; Stein, R. M.; Lane, J. D.; Ripka, G. V. Combined effects of nicotine and mecamylamine in attenuating smoking satisfaction. Exp. Clin. Psychopharmacol. 2:1-17; 1994.

30. Rose, J. E.; Behm, F. M.; Westman, E. C.; Levin, E. D.; Stein, R. M.; Ripka, G. V. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. Clin. Pharmacol. Ther. 56:86-99; 1994.

31. Rose, J. E.; Corrigall, W. A. Nicotine self-administration in animals and humans: Similarities and differences. Psychopharmacology 130:28-40; 1997.

32. Rose, J. E.; Hickman, C. S. Citric acid aerosol as a potential smoking cessation aid. Chest 92:1005-1008; 1987.

33. Rose, J. E.; Levin, E. D. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. In West, R.; Grunberg, N. E. (Ed.), British Journal of Addiction (pp. 605-610). London: Carfax Publishing Company;1991.

34. Rose, J. E.; Westman, E. C.; Behm, F. M. Nicotine/mecamylamine combination treatment for smoking cessation. Drug Devel. Res. 38:243-256; 1996.

2060579230

35. Shiraki, T.; Toyoda, A.; Sugino, H.; Hori, A.; Kobayashi, S. Possible nicotinic receptor-mediated modulation of synaptic transmission in nucleus of the solitary tract. Am. J. Physiol. 41:R869-R873; 1997.

36. U.S.D.H.H.S. The Health Consequences of Smoking: Nicotine Addiction. Rockville, MD: Office on Smoking and Health; 1988.

37. Weaver, W. R.; Wolf, K. M.; Chiappinelli, V. A. Functional heterogeneity of nicotinic receptors in the avian lateral spiriform nucleus detected with trimethaphan. Mol. Pharmacol. 46:993-1001; 1994.

38. Westman, E. C.; Behm, F. M.; Rose, J. E. Airway sensory replacement as a treatment for smoking cessation. 38 257-262; 1996.

39. Westman, E. C.; Levin, E. D.; Rose, J. E. Smoking while wearing the nicotine patch: Is smoking satisf ying or harmful? Clin. Res. 40:871A; 1992.

40. Wonnacott, S. Characterization of nicotine receptor sites in the brain. In Wonnacott;Russell, M. A. H.; Stolerman, I. P. (Ed.), Nicotine Psychopharmacology: Molecular, Cellular, and Behavioural Aspects (pp. 226-277). New York: Oxford University Press;1990.

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FIGURE LEGENDS

Fig. 1. Plasma nicotine boosts (mean±s.e.m.) resulting from smoking the three types of cigarette used in the study. Nicotine boosts were similar for the two nicotine-containing cigarettes and negligible for the denicotinized cigarette.

Fig. 2. Smoking satisfaction (mean±s.e.m.) reported after smoking each type of cigarette in trimethaphan and saline infusion conditions. The increased satisfaction for the usual brand of cigarette was abolished by trimethaphan.

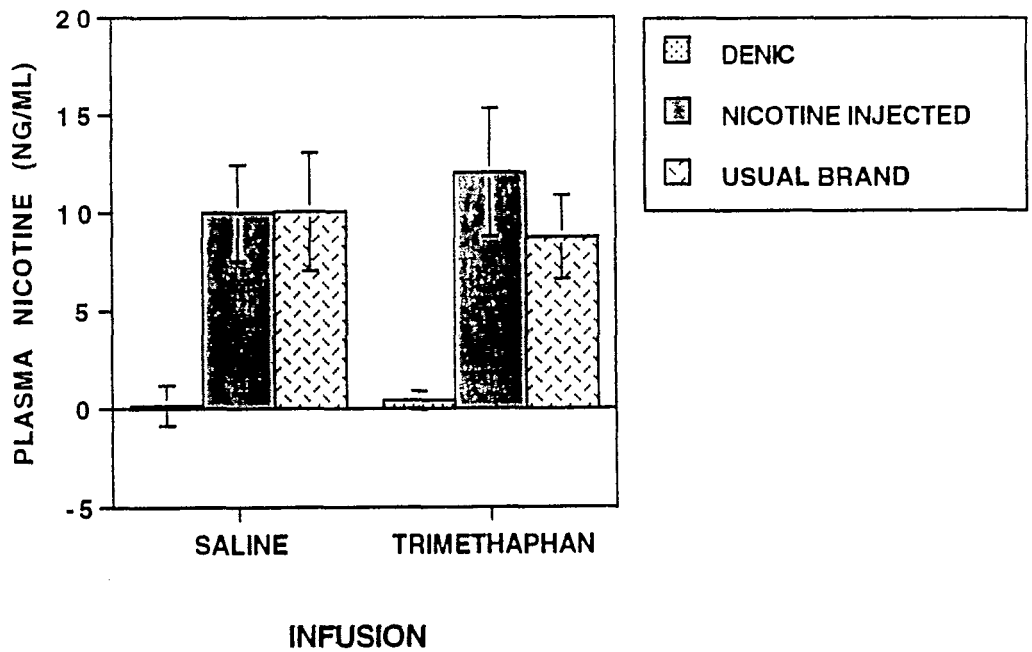
Fig 3. Regional airway sensory ratings (mean±s.e.m.) for the three types of cigarette, in both saline and trimethaphan infusion conditions (for each type of cigarette and region, the rating for the trimethaphan condition is depicted immediately adjacent to the saline infusion condition to illustrate the attenuation of sensations by trimethaphan).

Fig. 4. Ratings of craving reduction (mean±s.e.m.) obtained by smoking the three types of cigarette in the trimethaphan and saline infusion conditions. Trimethaphan did not block the craving reduction produced by the nicotine-containing cigarettes relative to the denicotinized control cigarette, suggesting a CNS site of action for nicotine.

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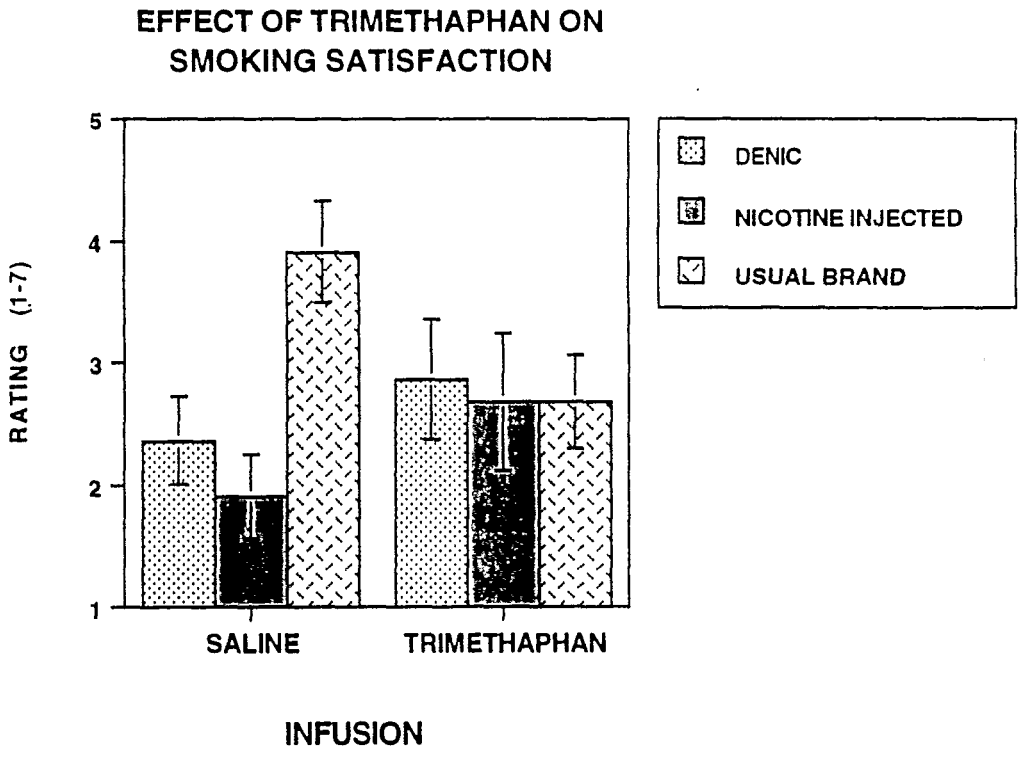
FIG. 1

PLASMA NICOTINE BOOST AFTER SMOKING



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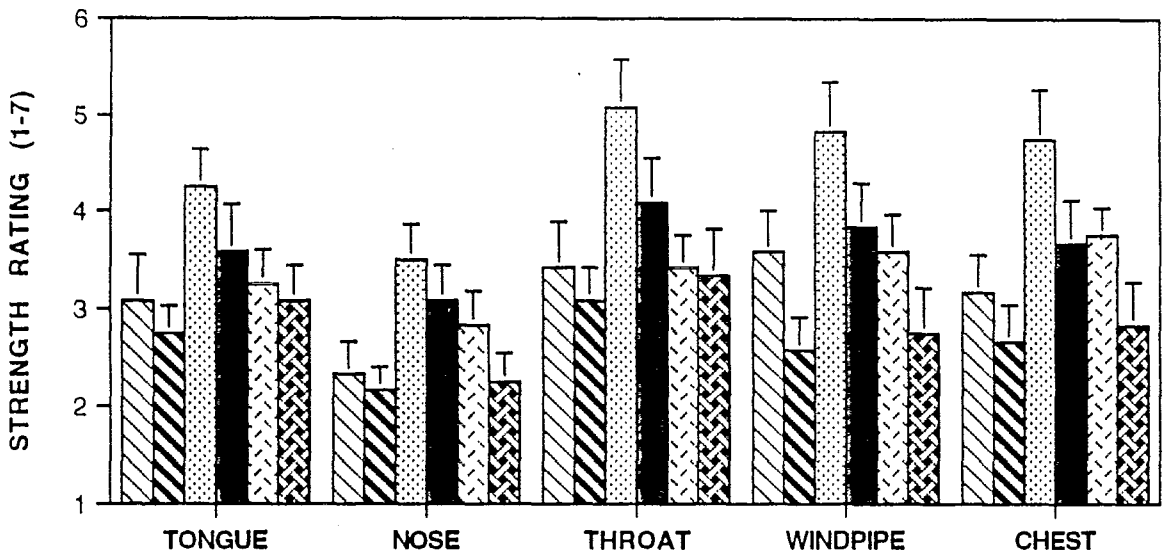
Fig. 2



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Fig. 5

REGIONAL SENSORY RATINGS BY CONDITION

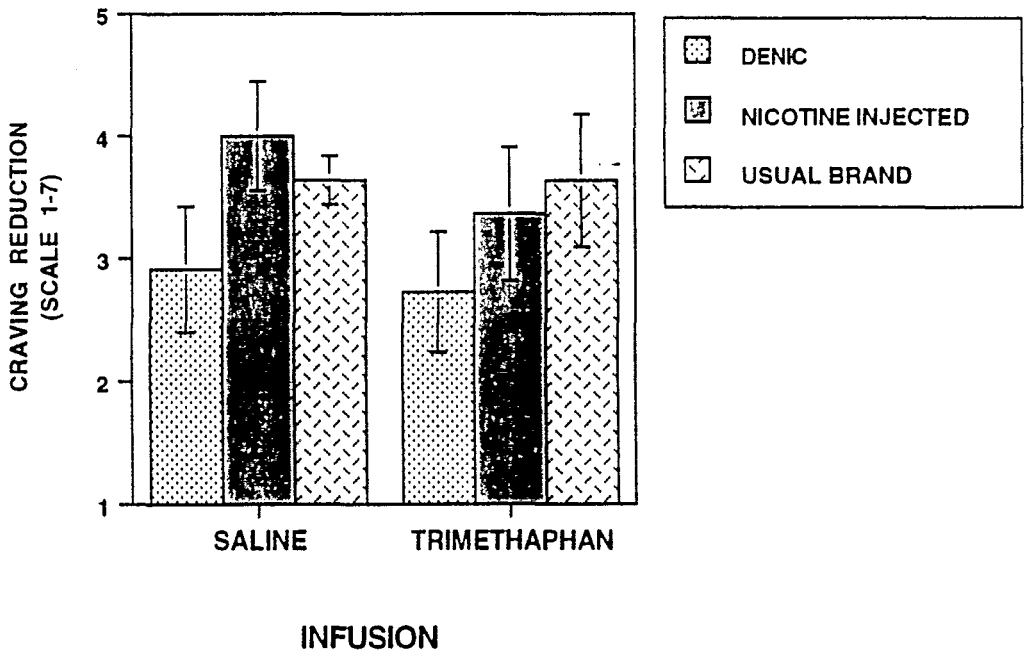


DENIC CIG + SALINE	DENIC CIG + TRIMETHAPHAN
NICOTINE INJECTED CIG + SALINE	NICOTINE INJECTED CIG + TRIMETHAPHAN
USUAL BRAND CIG + SALINE	USUAL BRAND CIG + TRIMETHAPHAN

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Fig 4

EFFECT OF TRIMETHAPHAN ON
CRAVING REDUCTION



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Extinguishing the rewarding value of smoke cues: Pharmacological and behavioral treatments

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The present study examined several pharmacological and behavioral treatments designed to promote extinction of the responses to rewarding cigarette smoke cues. Pharmacological treatments comprised nicotine skin patches (21 mg/24 hr) and the nicotinic acetylcholine receptor antagonist mecamylamine (10 mg/day), administered separately or in combination. Behavioral manipulations included switching to denicotinized cigarettes, to cigarettes having different menthol flavor, or to ventilated-filter (low tar and nicotine) cigarettes. Smokers were assigned to the various treatments for 2 weeks before they quit smoking. During weekly test sessions, subjects rated the rewarding effects of their usual brands of cigarettes or cigarettes with different menthol content (mentholated vs. nonmentholated). Over the 2-week treatment period, all pharmacological treatments reduced ratings of reward for the usual-brand test cigarettes. Switching to smoking denicotinized cigarettes for 2 weeks similarly decreased rewarding effects of the usual-brand test cigarettes. Subjects also strongly preferred cigarettes with the same menthol content to which they were accustomed. However, manipulating the menthol content of the cigarettes smoked during the 2 weeks of treatment had different effects, depending on whether smokers habitually smoked mentholated or nonmentholated cigarettes. For menthol smokers, removal of the menthol cue hampered extinction of reward ratings for the usual-brand (mentholated) test cigarette. For nonmenthol smokers, addition of the menthol cue did not affect the progress of extinction of nonmenthol smoke cues. These findings demonstrate the importance of sensory cues in determining subjective reward and show that the reward value of these cues can be altered by removal of nicotine from tobacco or by pharmacological manipulations that interfere with the reinforcing effects of nicotine.

Introduction

Studies have shown that a smoker's reaction to cigarettes is affected by distinctive smoking cues, as well as by the delivery of nicotine (Herskovic, Rose, & Jarvik, 1986; Rose, 1988; Rose & Behm, 1995). For example, blocking the sensations produced by smoking, either with local airway anesthesia or by administration of a peripheral nicotinic antagonist, reduces ratings of smoking satisfaction (Rose, Tashkin, Ertle, Zinser, & Lafer, 1985; Rose, Westman, Behm, Johnson, & Goldberg, 1999b; Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984). Smokers also rate intravenous administration of nicotine in the absence of smoke cues as less desirable than cigarette smoking (Westman, Behm, & Rose, 1996). In this paper the term *smoke cues* refers to the stimulus aspects of cigarette smoke (as opposed to environmental cues), which elicit sensations via taste, olfactory, or other respiratory tract nerve fibers.

Smoke cues are important in affecting cigarette reward, and may be important in clinical treatment, if, for example, devaluing smoke cues were to lead to a decrease in smoking behavior or more successful smoking cessation. Despite the potential significance of such cues, there has been little investigation of how the rewarding value of smoke cues might be altered by pharmacological or behavioral treatments. The present study examined the effects of several such manipulations. Pharmacological treatments included nicotine and the nicotinic acetylcholine receptor antagonist mecamylamine, administered separately and in combination. In previous studies, the administration of nicotine alone or mecamylamine alone reduced ratings of the subjective enjoyment of

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smoking (Levin et al., 1994; Rose et al., 1994a,b; Rose, Behm, & Westman, 1998). Moreover, we have reported promising results in smoking cessation treatment with the use of the mecamylamine in conjunction with nicotine replacement therapy (Rose et al., 1994b, 1998; Rose, Westman, & Behm, 1996).

Nicotine or mecamylamine administration is thought to interfere with the reinforcing effects of nicotine in cigarette smoke; over time, this attenuation of the effects of inhaled nicotine, and resultant breaking of the association between smoking and nicotine reinforcement, should lead to a reduction in the conditioned reinforcing effects of smoke cues (i.e., extinction; Bouton & Swartzentruber, 1991). The present study was conducted to study the effects of 2 weeks exposure to treatment with nicotine, mecamylamine, or both to ascertain whether the subjective reward associated with familiar smoke cues would be attenuated. In addition, we sought to compare the results of pharmacological treatment with an unconventional behavioral extinction treatment approach designed to reduce cigarette reward (i.e., having subjects switch to smoking denicotinized cigarettes for 2 weeks). Assuming that subjects would comply with this treatment, the removal of nicotine from the cigarettes should have had an effect similar to the pharmacological blockade of the effects of nicotine, in terms of promoting the extinction of smoke cues.

To evaluate these hypotheses, participants were periodically presented with test cigarettes to rate for rewarding properties, during 2 weeks of exposure to one or more of several pharmacological and behavioral treatments. At each session, subjects smoked one of their usual brand of cigarettes. By observing a reduction in the subjective reward associated with the same cigarette across sessions, we could assess the time course of extinction. A second type of cigarette that was smoked at each session differed from the other test cigarette in menthol flavor (i.e., mentholated vs. nonmentholated cigarettes) but delivered the same nicotine dose. Based on the extinction hypothesis, we predicted that pharmacological blockade treatment would attenuate the reward associated with the usual brands of cigarettes. We also predicted that changing the cigarette cues during the treatment period would retard extinction of responses to the usual-brand cigarette cues. This prediction was based on the well-established finding in studies of conditioning that the degree of extinction measured during a given test stimulus shows a generalization gradient depending on how similar the test stimulus is to the stimulus that has been extinguished (Rilling, 1977). Finally, we hypothesized that pharmacological blockade would reduce the acquisition of conditioned rewarding properties by a relatively novel cue (i.e., menthol) paired with nicotine reinforcement.

Method

Participants were recruited for a quit-smoking study and exposed to various experimental manipulations for 2 weeks before a target quit-smoking date. Different groups of participants were asked either to switch to other brands of cigarettes during these 2 weeks or to continue smoking their usual brands, as summarized in Table 1, which also shows the pharmacological treatments received by each group. Subjects were randomly assigned to each group, and pharmacological treatments were administered double-blind. Because the data in the present study were collected prior to the quit-smoking date, the postcessation treatments are not described in detail here.

The precessation treatments comprised administration of nicotine skin patches, mecamylamine, or both; and cigarette brand-switching, as follows:

- Nicotine skin patches. Nicotine skin patches (Habitrol), delivering 21 mg of nicotine in 24 hr, and placebo patches were donated by Ciba Self-Medication, Inc. (Woodbridge, New Jersey).
- Mecamylamine. Mecamylamine (Inversine) was purchased from Merck & Co., Inc., (West Point, Pennsylvania), and capsules containing 5 mg of mecamylamine or placebo (lactose) capsules were prepared by the Duke Medical Center Pharmacy. Subjects were instructed to swallow one capsule in the morning and one at night (10 mg/day total dose).
- Cigarettes. Nicotine-containing cigarettes (menthol and nonmenthol) of various brands were purchased locally; subjects' usual brands or brands differing in menthol content (but having the same nicotine yield) were used as test cigarettes. The terms *mentholated* and *nonmentholated* are based on package labeling, inasmuch as nonmenthol cigarettes contain a small amount of menthol. Denicotinized cigarettes were donated by Philip Morris, Inc. (Richmond, Virginia). These cigarettes contained tobacco from which the nicotine had been extracted by high-pressure carbon dioxide. The tar delivery, when smoked by U.S. Federal Trade Commission (FTC) criteria, was 9 mg, whereas the

Table 1. Number of subjects in each condition.

Brand switch	NIC/MEC	NIC only	MEC only	Placebo
Usual brand	30	8	43	12
Denicotinized cigarette	31	12	–	7
Menthol cigarette	32	–	–	13
Low tar and nicotine cigarette	28	9	–	8
Total *n*	121	29	43	40

MEC, mecamylamine; NIC, nicotine; NIC/MEC, nicotine plus mecamylamine.

nicotine delivery was extremely low (approximately .08 mg). Hasenfratz, Baldinger, and Battig (1993), and Rose, Behm, Westman, and Coleman (1999) measured nicotine intake after subjects smoked these cigarettes and found that plasma nicotine levels increased less than 2 ng/ml.

Subject recruitment

A total of 233 healthy male and female smokers interested in quitting smoking were recruited from the community by newspaper and radio advertisements and by word of mouth. These subjects were randomly selected from a larger subject sample ($n = 454$) that received identical pharmacological and behavioral treatments for 2 weeks; however, the other 221 subjects participated in a different study and were asked to smoke different types of test cigarettes, having different nicotine deliveries, to evaluate hypotheses regarding nicotine tolerance (in contrast to the present study, which assessed reactions to test cigarettes of equal nicotine delivery but that differed in menthol flavor). Results from the other study sample are not presented here.

Study participants were between the ages of 18 and 65 years. To be included in the study they had to smoke at least 20 cigarettes per day on average; express a desire to quit smoking within the next 30 days; and be in general good health, based on physical examination, electrocardiogram, serum chemistries, complete blood count, and urinalysis. Additionally, subjects had to express a willingness to switch to a mentholated brand of cigarettes from their usual brand (or vice versa) if assigned to that experimental condition. The following criteria were bases for exclusion: Hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg); hypotension (systolic blood pressure < 90 mmHg, blood pressure diastolic < 60 mmHg); coronary artery disease; cardiac rhythm disorder; history of urinary retention; prostatic hypertrophy; glaucoma; impaired renal function; history of skin allergy; active skin condition (psoriasis) within the past 5 years; other major medical condition; current psychiatric disease; pregnancy or nursing; current alcohol or drug abuse; or current smokeless tobacco use, nicotine replacement therapy, or other smoking cessation treatment.

Procedure

During the 2 weeks of the study, subjects applied a skin patch daily, swallowed capsules twice daily, and smoked cigarettes; the content of each varied according to the group assignment. In addition, subjects attended three laboratory sessions, 1 week apart, conducted after overnight (12-hr) abstinence from smoking. Compliance with the smoking abstinence requirement was assessed at the beginning of the session by expired-air carbon monoxide (CO) measurement. At these three laboratory sessions, subjects were given two test cigarettes to smoke, mentholated and nonmentholated, 30 min apart (order counterbalanced). The FTC nicotine and tar delivery of the two cigarettes was similar and was chosen to be as close as possible to each subject's usual brand of cigarette. Each cigarette was smoked through a controlled puff delivery apparatus (Levin, Rose, & Behm, 1989), which regulated the volume of each puff. The number of puffs and interpuff interval also were controlled, so that the same amount of smoke was delivered from each test cigarette. This procedure ensured that changes in reward ratings induced by the various treatments were not confounded with changes in smoke dose. The puffing parameters were individualized based on the measurement of each subject's ad libitum smoking of a single cigarette (of his or her usual brand) at the screening session.

Subjects were supplied with sufficient quantities of cigarettes of the appropriate type (according to the brand-switch condition to which they were assigned) to last until the following week (a 9-day supply, based on self-reported consumption at screening). They were instructed to begin the following day smoking only the assigned brand and to take capsules (containing 5 mg of mecamylamine HCl or placebo) twice daily (morning and evening) and to apply skin patches (21 mg/24 hr vs. placebo) daily. They also were given diary cards and asked to record the study medications taken, as well as the number of cigarettes smoked (including slips, which were defined as smoking of their usual brand if they were in a different brand-switch condition).

Dependent measures

Cigarette evaluation questionnaire. This questionnaire, used in several previous studies (e.g., (Rose, Behm, & Westman, 2001; Westman, Levin, & Rose, 1992), was administered immediately after smoking during the test sessions, to measure the subjective rewarding effects of smoking. Each item was rated using a seven-point scale ranging from "not at all" to "extremely." A composite reward score was computed by averaging responses on the following items: "Was it satisfying?", "Was there a good taste?", "Did it calm you down?", "Did it make you feel more awake?", Did it reduce your hunger for food?", "Did it make you feel less irritable?", "Did it immediately reduce your craving for cigarettes?", and "Did you enjoy the sensations in your throat and chest?"

Plasma nicotine and cotinine concentrations. At each session, venous blood samples (10 cc) were collected

and centrifuged to separate plasma. For a subset of smokers, plasma samples were packed on dry ice and shipped from Durham, North Carolina, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay by gas chromatograph, modified for use with a capillary column.

Expired-air carbon monoxide. Subjects' expired-air CO concentrations were measured at each session to verify overnight abstinence and to measure smoke intake during the test sessions, using a portable CO monitor (Vitalograph, Inc., Lenexa, Kansas). The criterion for assessing overnight abstinence was derived on both theoretical and empirical grounds and was implemented using a formula that assigned a threshold CO for each subject, which took into account that individual's CO level measured in the afternoon, the estimated accumulation of CO during smoking the remainder of the day, and the half-life for elimination during the night (assumed to be 6 hr). For a subject with an afternoon CO level of 30 ppm, a morning measurement of less than or equal to 20 ppm was required.

Self-reported cigarette smoking. Subjects were asked to record the number of cigarettes smoked daily; separate counts were conducted for the cigarette type to which subjects were assigned and for their usual brand (reflecting noncompliance in the brand-switch conditions).

Nicotine dependence. Subjects completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) at the baseline session and at 2 weeks after initiating treatment.

Statistical analysis

All statistical analysis was performed using SUPER-ANOVA and STATVIEW (SAS Institute, Cary, North Carolina). In analyzing subjective reward evaluation, we entered test cigarette (usual brand vs. menthol-switch) and session (1, 2, or 3) into the analysis as repeated factors. A multivariate approach to repeated-measures analysis of variance (ANOVA) was used, which appropriately took into account the correlation pattern among repeated measurements. Additional between-subjects factors were included as described below. To interpret significant interactions, we analyzed the simple effects of one factor for different levels of the other factor (Keppel, 1982).

The experimental design of the clinical trial from which participants were selected was nonorthogonal, with unequal numbers of subjects receiving different combinations of nicotine and mecamylamine treatment, and not all treatment combinations being represented. Type III sums of squares were calculated in the statistical analyses to deal with this nonorthogonal design (Maxwell & Delaney, 1990). In addition, the analyses were conducted in two phases. The first set of analyses addressed whether nicotine skin patch and mecamylamine treatment, alone or in combination, affected the subjective reward associated with smoking. In these analyses, results were averaged across the brand-switching manipulation that took place during the first 2 weeks of the study. The results described below showed that active treatment, comprising nicotine skin patch, mecamylamine, or both, attenuated the reward of the usual brands of cigarettes.

In the second phase, the analysis included the between-subject factors of treatment (active vs. placebo) and brand-switch condition (usual brand, menthol-switch, denicotinized, or low tar and nicotine). Active treatments comprised nicotine, mecamylamine, or both. As before, the within-subject factors were test cigarette and session.

Finally, we compared smokers whose usual brands of cigarettes were nonmentholated with those who smoked mentholated brands, in terms of how they responded to being switched to cigarettes of different menthol content. To obtain sufficient sample sizes for this analysis, we pooled data from all active treatments that had been shown to reduce the rewarding value of smoke cues (the active pharmacological treatments and the behavioral extinction treatment of switching to denicotinized cigarettes).

Results

Subject characteristics

Table 2 shows characteristics of the subject sample, including age, race, gender, and information about cigarette smoking habits. No significant differences were found in demographic or smoking history variables across treatment groups, with the exception

Table 2. Demographic information ($n = 233$).

Characteristic	Mean (*SD*)
Sex	
Males	119
Females	114
Race	
White	199
Black	27
Other	4
Age (years)	44.2 (10.1)
Number of cigarettes per day	27.8 (10.7)
Years smoked	24.8 (10.2)
Federal Trade Commission nicotine (mg)	0.75 (.32)
Fagerström Test for Nicotine Dependence score	6.4 (2.1)
Baseline carbon monoxide (ppm)	32.8 (13.9)

of sex. A slight but statistically significant difference was found in the proportion of females across the different pharmacological treatment conditions (nicotine-only, 58%; mecamylamine-only, 53%; combination, 55%; and placebo, 45%). However, when sex was included as a covariate in the analyses discussed below, none of the conclusions was affected. Another issue to be noted in the analyses of menthol vs. nonmenthol smokers is the strong correlation between menthol preference and race (Clark, Gautam, & Gerson, 1996). However, the results presented below were not affected when the analyses were restricted to the subset of White smokers.

Effects of nicotine patch and mecamylamine treatment on reward ratings

A significant interaction of nicotine, mecamylamine, session, and test cigarette was found, $F(2, 366) = 4.06$, $p = .02$, on the composite reward ratings of the test cigarettes. As shown in Figure 1, this interaction could be characterized as follows: Ratings of the usual-brand test cigarettes decreased across sessions in conditions in which active pharmacological treatments (i.e., nicotine patch, mecamylamine, or combination treatments vs. placebo) were presented. In each of the three active pharmacological treatment conditions a significant decrease was found across sessions in the ratings of the usual-brand test cigarettes, $F(2, 52) = 1.41$, $p = .0002$, for nicotine patch; $F(2, 72) = 21.06$, $p = .0001$, for mecamylamine; $F(2, 182) = 13.18$, $p = .0001$, for the combination). Ratings during placebo treatment did not change significantly across sessions, $F(2, 64) = .67$, $p = .51$. Ratings of the menthol-switch test cigarettes were low and remained relatively constant across sessions regardless of pharmacological treatment (all p values $> .1$).

Effects of the 2-week brand-switch manipulation

Given the similar effects of the three active pharmacological treatment conditions, we averaged ratings across these conditions in examining the effects of the brand-switching manipulation, comparing active and placebo pharmacological treatment conditions. In exploring possible interactions of pharmacological treatment with brand switching, we first examined compliance with smoking the assigned brand (assessed by self-report). The number of usual-brand cigarettes smoked during the brand-switching period was significantly related to reward ratings, $F(2, 164) = 3.74$, $p = .03$, for the interaction between number of usual-brand cigarettes smoked, test cigarette, session, and treatment. Therefore, we restricted the analyses to the subgroup of participants who reported minimal smoking of their usual brands when instructed to smoke a different brand. Because a histogram of the amount of usual-brand smoking showed a breakpoint at 50 cigarettes (total for the 2-week period), only subjects who reported smoking less than 50 cigarettes of their usual brands during the 2 weeks were included

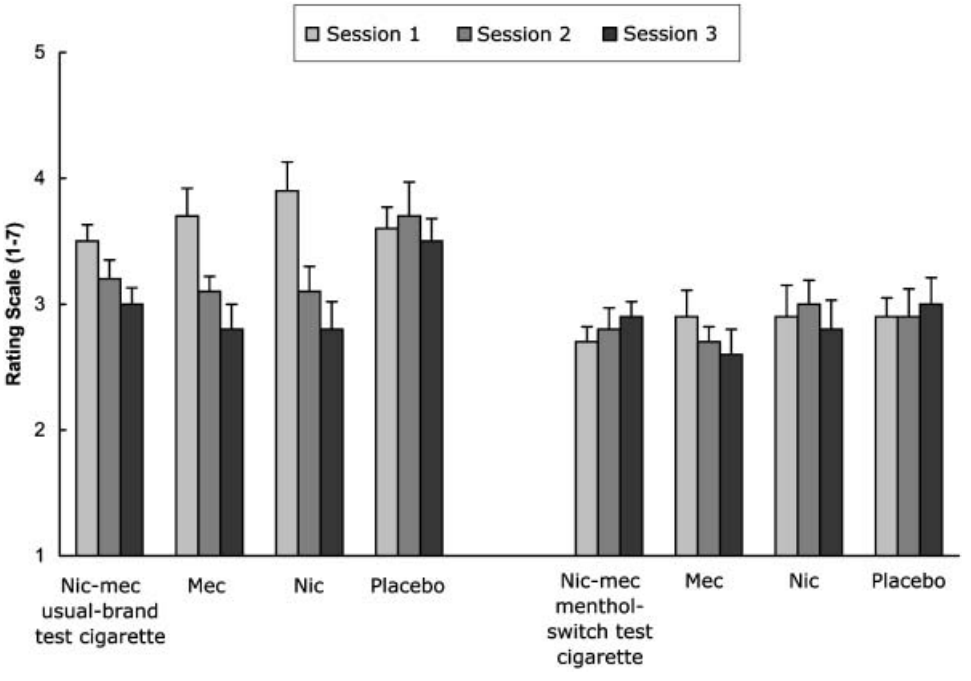


Figure 1. Mean ($\pm$ *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three test sessions. Session 1 was conducted before drug treatment, and sessions 2 and 3 were held weekly after initiation of treatment with nicotine plus mecamylamine (NIC/MEC), mecamylamine (MEC), nicotine (NIC), or placebo (PLAC).

(however, all subjects assigned to the usual-brand groups were included). This approach resulted in retaining most of the subjects (189/233). For subjects who met that compliance criterion, a significant interaction was observed between brand-switch condition, session, pharmacological treatment, and test cigarette, $F(6, 308) = 2.14$, $p = .048$. This interaction was interpreted by conducting analyses for each of the brand-switch conditions separately. For all brand-switch conditions except the denicotinized cigarette condition, pharmacological treatment attenuated the reward ratings of the usual-brand test cigarette across sessions relative to placebo treatment (Figure 2). For the session × treatment interaction, $F(2, 52) = 5.46$, $p = .007$, in the low tar and nicotine cigarette condition; $F(2, 150) = 4.01$, $p = .02$, in the usual-brand condition; and $F(2, 54) = 2.34$, $p = .1$, in the menthol-switch condition. In the denicotinized cigarette condition, no effect of pharmacological treatment was detected, and reward ratings dropped across sessions in both active and placebo conditions, $F(2, 56) = 5.02$, $p = .01$, including active and placebo conditions. However, with only five subjects in the placebo condition, the decrease in reward ratings for that subgroup considered separately failed to reach statistical significance.

Comparison of menthol and nonmenthol smokers

We further explored the effects of the cue manipulation of switching the mentholation of the brands of cigarettes smoked during the 2-week treatment period, by comparing smokers whose usual brands were mentholated cigarettes at the outset with smokers of nonmentholated brands. This analysis included only subjects who were assigned to conditions in which the cigarettes smoked for 2 weeks were opposite in mentholation to their usual brands (including subjects in the menthol-switch condition and menthol smokers assigned to the nonmenthol denicotinized-switch condition). Moreover, we pooled the results from subjects in active pharmacological treatment conditions with those in the denicotinized-cigarette extinction regimen, because both types of treatment had

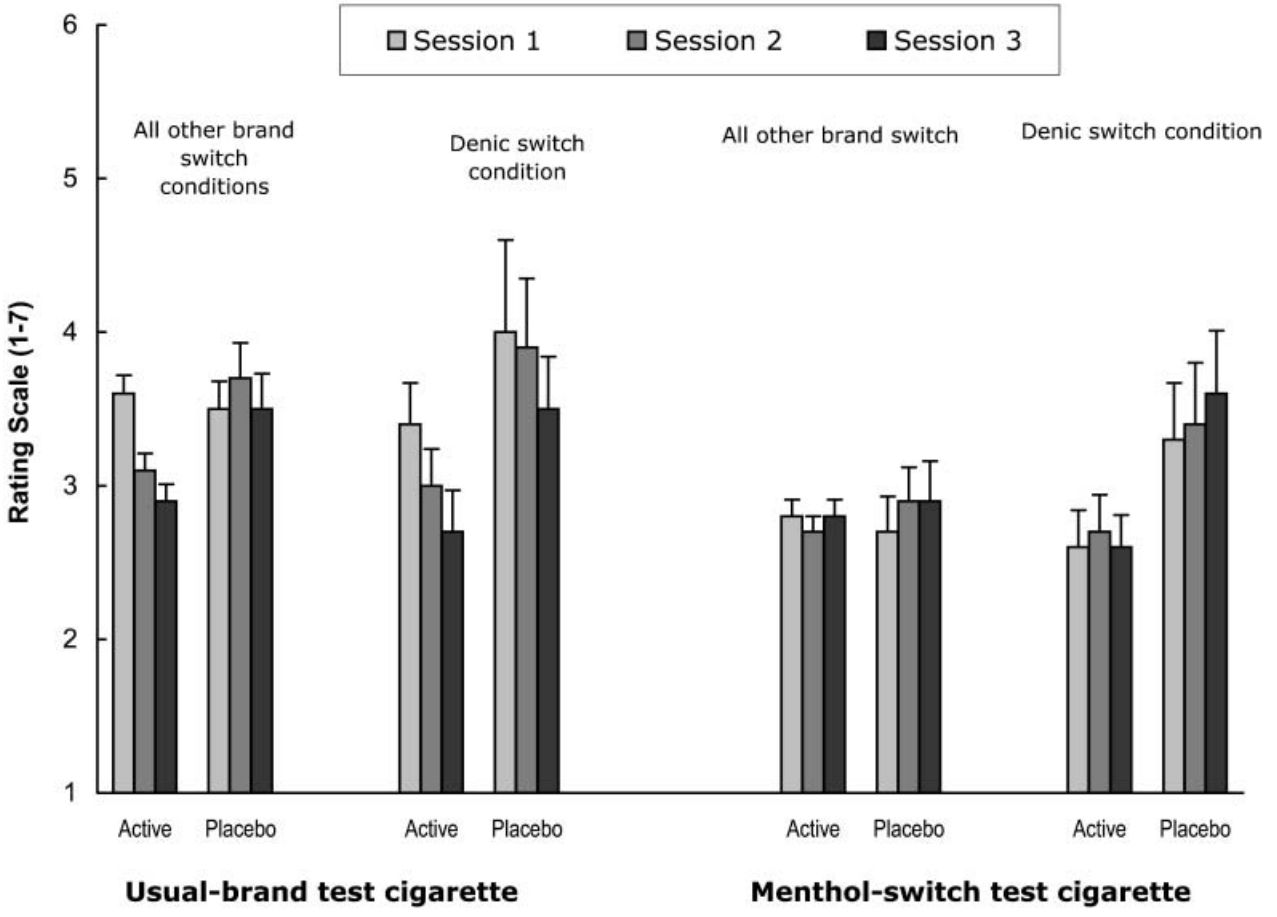


Figure 2. Mean (± *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three test sessions. Session 1 was conducted before drug treatment, and sessions 2 and 3 were held weekly after initiation of active treatment (ACT, comprising nicotine plus mecamylamine, mecamylamine, or nicotine) or placebo (PLAC). Results for subjects switched to denicotinized cigarettes for 2 weeks (DENIC SWITCH) are plotted separately from results for subjects in the other three brand-switch conditions (usual-brand, low tar and nicotine, and menthol-switch conditions).

been found to attenuate the rewarding effects of the usual-brand test cigarettes. With respect to ratings of the usual-brand test cigarettes (left side of Figure 3), a significant interaction was found between smoker (menthol or nonmenthol) and the effect of treatment, $F(2, 44) = 7.19$, $p = .002$. Menthol smokers on active treatment, who were switched to nonmenthol cigarettes for 2 weeks ($n = 7$), did not show a reduction in reward ratings of their usual-brand (menthol) test cigarettes across sessions, $F(2, 12) = .42$, $p = .67$, whereas habitual smokers of nonmentholated brands, who were switched to menthol cigarettes while receiving active treatment ($n = 17$), showed a significant decrease in ratings of reward of their usual-brand (nonmenthol) cigarettes, $F(2, 32) = 16.04$, $p = .0001$.

A further analysis was conducted on data from menthol smokers who continued to smoke their usual mentholated brands during the 2-week treatment period and who received active pharmacological treatment ($n = 15$); these smokers, like their nonmenthol counterparts, showed a significant decrease in reward over sessions, $F(2, 28) = 8.54$, $p = .001$ (not shown in Figure 3). Reward ratings of the menthol-switch test cigarettes, which were mentholated for habitual smokers of nonmentholated brands, and

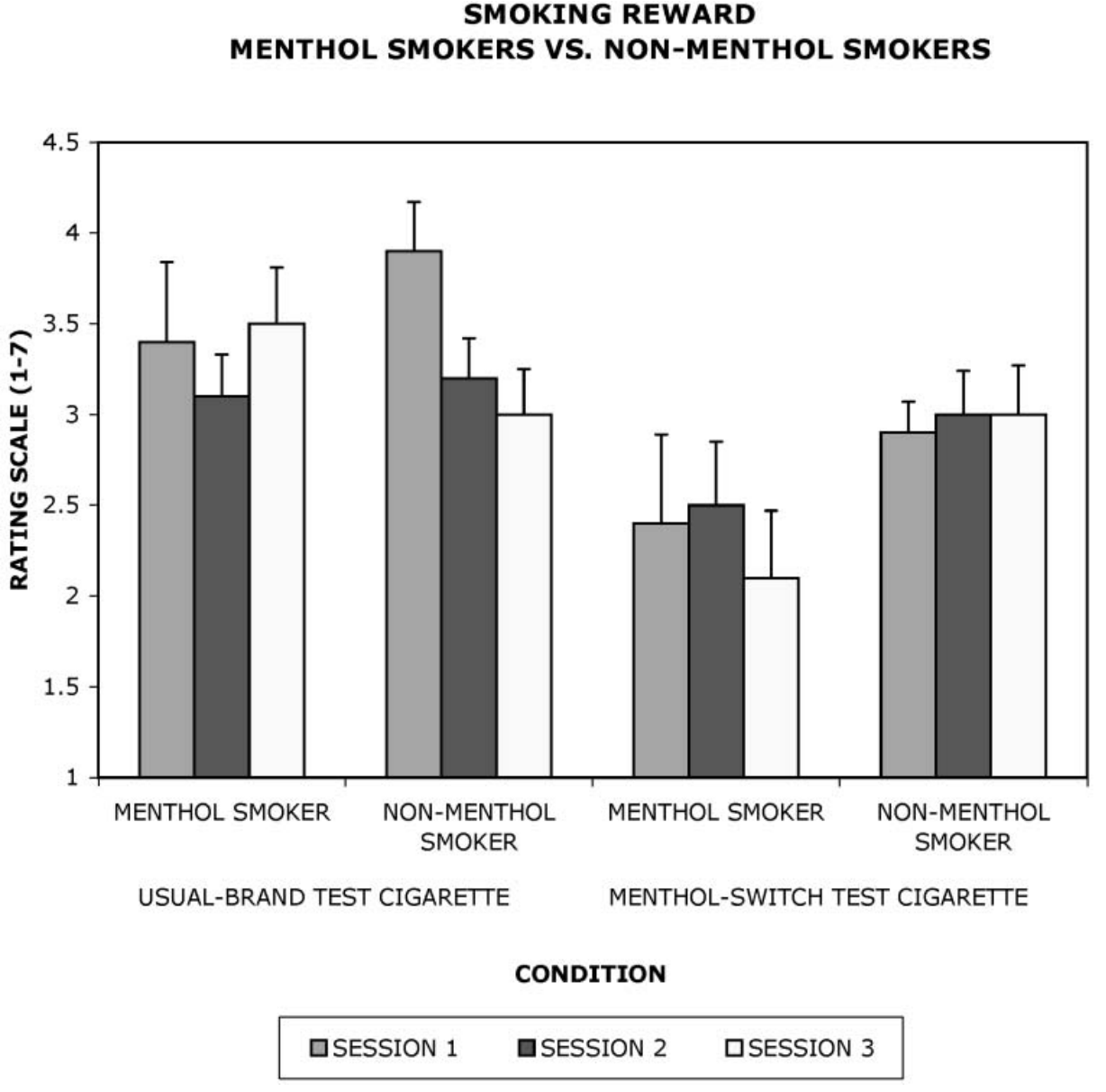


Figure 3. Mean ($\pm$ *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three weekly test sessions. After session 1, all subjects received active treatment (either pharmacological treatment with nicotine, mecamylamine, or both, or behavioral extinction treatment entailing switching to smoking denicotinized cigarettes for 2 weeks). The cigarettes smoked for 2 weeks had a different menthol content than the usual brands (i.e., menthol smokers were switched for 2 weeks to nonmenthol brands, and nonmenthol smokers were switched for 2 weeks to menthol brands).

nonmentholated for habitual smokers of mentholated brands, were uniformly low and showed no change over sessions (right side of Figure 3).

Relationship between subjective reward and other measures

For subjects in active behavioral or pharmacological treatment conditions, the change in subjective reward evaluation of the usual-brand test cigarettes over the 2 weeks of treatment was positively correlated with the change in FTND score from baseline to week 2, $F(1, 138) = 7.54$, $r = .2$, $p = .007$. This correlation remained significant when the change in cigarette consumption was entered as a covariate in a multiple regression model, $F(1, 135) = 4.71$, $p = .03$.

Discussion

The main result of the present study was that nicotine-patch treatment, nicotine blockade, and removal of nicotine from cigarettes similarly affected the ratings of the usual-brand test cigarettes. The subjective reward associated with these cigarettes was significantly attenuated by 2 weeks of exposure to the active treatments.

The effects of mecamylamine treatment were generally in accord with previously published results. In those studies, 2 weeks (Rose et al., 1994b) or 4 weeks (Rose et al., 1998) of treatment with 5–10 mg of mecamylamine, nicotine skin patches, or both substantially reduced smoking behavior as well as subjective measures of smoking reward. In the present study, however, treatment with nicotine alone or mecamylamine alone was as effective as combined nicotine-mecamylamine treatment; in fact nicotine-only treatment showed a trend to attenuate reward to a greater extent (Figure 1). Of the two previous small-scale studies, one found that the effect of nicotine patch alone was comparable with combined nicotine-mecamylamine treatment; the other study found greater effects of the combination treatment (Rose et al., 1998). The present results, based on a much larger subject sample, suggest that nicotine administration from a skin patch can function in a manner analogous to that of blockade treatment. One mechanism by which this may happen is receptor desensitization (Quick & Lester, 2002), whereby steady administration of nicotine causes receptors to shift into an inactive conformation. If receptor desensitization were substantial, then mecamylamine administration would have little or no added effect. An alternative possibility is that nicotine, via an agonist action, partially satisfied the desire to smoke, indirectly rendering cigarettes less rewarding.

A second observation was that changing one cigarette cue, menthol, had a profound influence on ratings of reward. Although this result is not surprising, little published literature has examined the role of mentholation in cigarette preference or reward. Despite having comparable nicotine delivery, the mentholated cigarettes were substantially less rewarding to smokers of nonmentholated brands; conversely, removing the menthol cue for smokers accustomed to mentholated brands led to a decrease in reward. This result is in keeping with previous research showing that sensory attributes have a major influence on smoking reward, often overshadowing the immediate effects of nicotine (Pritchard, Robinson, Guy, Davis, & Stiles, 1996; Rose, 1988; Westman et al., 1996).

The prediction that altering the menthol cue during the 2-week pharmacological treatment period would attenuate the effect of treatment received partial support. For menthol smokers, changing to a nonmenthol cigarette during either extinction (i.e., switching to denicotinized cigarettes) or pharmacological treatment (with nicotine or mecamylamine) prevented the decrease in ratings of reward for the usual-brand test cigarettes, as assessed in the weekly laboratory test sessions. However, for smokers of nonmentholated brands of cigarettes, changing to a menthol cigarette during treatment did not appear to affect the course of extinction. That is, the reward ratings of the usual-brand (nonmenthol) test cigarettes still declined. This asymmetry in results for menthol vs. nonmenthol smokers might be accounted for when we consider that, for nonmenthol smokers, adding the menthol cue to cigarettes did not alter the fact that other smoke cues were presented without the usual nicotine reinforcement (i.e., reinforcement was attenuated by the pharmacological treatments). Hence, the reward value of these nonmenthol smoke cues should have declined.

In contrast, for a habitual smoker of mentholated cigarettes, a treatment involving switching to nonmenthol cigarettes (i.e., removing the menthol cue), would be expected to prevent the menthol cue from extinguishing, although the reward value of nonmenthol smoke cues would be expected to extinguish. However, to the extent that menthol is a major component of the conditioned reward, as it appears to be, then the overall reward value of the usual-brand test cigarettes (mentholated cigarettes) for this subgroup would tend to be maintained.

This result, while needing confirmation in larger studies, has potential implications for the use of treatments designed to devalue smoke cues. Specifically, extinction might be facilitated by ensuring that salient smoke cues are kept as similar as possible to those of the usual brand of cigarette during treatment. Some of the treatments tested in this study, including mecamylamine, have been shown to modify the

sensory properties of cigarette smoke, in that nicotine functions as a sensory cue as well as having direct central nervous system actions (Rose et al., 1999b). To the extent that this nicotine sensory cue has conditioned reinforcing value, extinction might be retarded when mecamylamine or use of denicotinized cigarettes, either of which modifies sensory cues, is employed in treatment. One approach to avoid this potential problem would be to develop nicotinic antagonists that target central nervous system receptors but do not block nicotine-related peripheral cues. In a similar vein, when using denicotinized cigarettes as an extinction treatment, nonaddictive constituents that mimic the nicotine cue might be added to the cigarettes to make them indistinguishable from nicotine-containing cigarettes, potentially facilitating extinction.

Thus far, we have discussed the decrease in ratings of reward for the usual-brand test cigarettes across sessions in terms of extinction. However, other mechanisms may have been involved in the active pharmacological treatment conditions. For example, nicotine and mecamylamine treatments may have directly interfered with the rewarding effects of nicotine delivered in the test cigarettes. However, the results from smokers in the denicotinized cigarette condition who received placebo treatment are not susceptible to this interpretational problem. In addition, for subjects receiving active pharmacological treatments, direct effects of treatment on nicotine reward would have been expected to reduce ratings of reward for the menthol-switch test cigarettes; however, no change was observed. Moreover, the results from menthol smokers, which showed that cue-change determined whether reward ratings declined over sessions, controlling for pharmacological treatment, argue in favor of an extinction hypothesis. Nonetheless, to further evaluate the extinction hypothesis, it might be advantageous in future studies to measure smokers' reactions to test cigarettes after discontinuing pharmacological treatment, to avoid any direct effects of these treatments on cigarette evaluations. In addition, studies that determine whether a reduction in the rewarding value of smoke cues is related to nonreinforced presentations of smoke cues, as opposed to being related to a reduction in nicotine dependence that follows withdrawal from nicotine, would be informative. If the reduction in ratings of reward in the present study was indeed related to a weakening of the learned association between smoke cues and nicotine reinforcement, then it is remarkable that as little as 2 weeks of treatment could significantly modify the subjective evaluation of the usual-brand smoke cues, which had presumably been reinforced thousands of times over many years. This is especially true given that some studies of evaluative conditioning have suggested that evaluations of subjective liking are relatively resistant to extinction (DeHouwer, Thomas, & Baeyens, 2001), although those studies were of much shorter duration.

Interestingly, no evidence was obtained for a conditioning effect (i.e., an increase in ratings of reward for the menthol-switch test cigarettes in the menthol-switch condition, during 2 weeks of nicotine reinforcement in the condition without pharmacological treatment). Possibly the duration of the study was insufficient to reveal an acquisition of reward associated with the menthol cue. It would be interesting to study longer exposure periods to determine whether the reward ratings would eventually reach the levels of usual-brand preference. The presence of cues already associated with nicotine reward may have retarded the acquisition of conditioning to the menthol cue, analogous to the blocking effect documented in animal learning paradigms (Kamin, 1969; Williams, 1999). If so, acquisition of conditioned reinforcing value to a menthol (or other) cue might be facilitated by presenting that cue alone (i.e., outside of the context of other smoke cues), followed by nicotine.

It is intriguing that the reward ratings of the usual-brand test cigarettes reached a "floor" that was similar to ratings of the menthol-switch test cigarettes, and that ratings of the menthol-switch test cigarettes were not affected by any of the experimental manipulations. This finding implies that the measured changes in reward value were related to the unique sensory properties of the preferred cigarettes and, therefore, involved cue-related incentive properties rather than direct central nervous system effects of nicotine. The magnitude of these changes was nevertheless substantial, resulting in a decrease in ratings by approximately one point.

Also noteworthy is the finding that pharmacological treatment apparently had little effect during 2 weeks of exposure to the denicotinized cigarette condition, in which ratings of reward decreased equivalently in active and placebo pharmacological treatment conditions. Although this conclusion is tentative in view of the limited statistical power for that comparison, the result is nonetheless plausible when we consider that pharmacological manipulations designed to attenuate the effects of nicotine would have been superfluous when subjects smoked cigarettes containing insignificant amounts of nicotine.

One limitation of the present study was the nonorthogonal design, in which not all combinations of cigarette brand-switch manipulations and pharmacological treatments were represented equally. For example, in the mecamylamine-only treatment condition, all subjects continued to smoke their usual brands of cigarettes, instead of being switched to other brands for 2 weeks. Hence, any interaction between this specific pharmacological treatment and the brand-switching manipulation would not have been detected.

Conceivably, a bias in assessing the effects of pharmacological treatments could result from pooling data from different brand-switch conditions; however, the pattern of means for subjects who continued smoking their usual brands for 2 weeks (in which all pharmacological treatments were represented, as shown in Table 1) was virtually identical to those for the entire subject sample. Similarly, the differential impact of pharmacological treatment in the denicotinized cigarette-switch condition was apparent in an examination of the means for the nicotine-mecamylamine combination treatment, in which all brand-switch conditions were represented. The comparison of menthol and nonmenthol smokers also yielded similar results when restricted to the nicotine-mecamylamine combination treatment condition. Nonetheless, the conclusions reached based on pooling results from different conditions should be regarded as preliminary, and confirmation should be sought in future studies that have adequate samples representing treatment cells missing from the current design.

In conclusion, the present study showed that pharmacological and nonpharmacological manipulations can influence the rewarding properties of cigarettes. Changes in reward value were modestly correlated with decreases in dependence, as measured by the FTND. To the extent that changes in the rewarding effects of cigarette smoking affect dependence or the propensity to relapse after quitting smoking, manipulations that affect reward might be put to clinical use. The efficacy of these treatments demonstrates the importance of the precessation period as an opportunity to provide treatment interventions that may affect the outcome of smoking cessation treatment (Rose et al., 1998). Further studies will continue to explore the therapeutic potential of these methods.

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References

Bouton, M. E., & Swartzentruber, D. (1991). Sources of relapse after extinction in Pavlovian and instrumental learning. *Clinical Psychology Review*, *11,* 123–140.

Clark, P. I., Gautam, S., & Gerson, L. W. (1996). Effect of menthol cigarettes on biochemical markers of smoke exposure among Black and White smokers. *Chest*, *110,* 1194–1198.

DeHouwer, J., Thomas, S., & Baeyens, F. (2001). Associative learning of likes and dislikes: A review of 25 years of research on human evaluative conditioning. *Psychological Bulletin*, *127,* 853–869.

Hasenfratz, M., Baldinger, B., & Battig, K. (1993). Nicotine or tar titration in cigarette smoking behavior? *Psychopharmacology*, *112,* 253–258.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. L. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86,* 1119–1127.

Herskovic, J. E., Rose, J. E., & Jarvik, M. E. (1986). Cigarette desirability and nicotine preference in smokers. *Pharmacology, Biochemistry, and Behavior*, *24,* 171–175.

Kamin, L. J. (1969). Predictability, surprise, attention, and conditioning. In B. Campbell & R. Church (Eds.), *Punishment and aversive behavior.* New York: Appleton-Crofts.

Keppel, G. (1982). *Design and analysis: A researcher's handbook* (2nd ed.). Englewood Cliffs, NJ: Prentice-Hall.

Levin, E. D., Rose, J. E., & Behm, F. (1989). Controlling puff volume without disrupting smoking topography. *Behavior Research Methods, Instruments, & Computers*, *21,* 383–386.

Levin, E. D., Westman, E. C., Stein, R. M., Carnahan, E., Sanchez, M., Herman, S., Behm, F. M., & Rose, J. E. (1994). Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms and attenuates rewarding effects of smoking. *Journal of Clinical Psychopharmacology*, *14,* 41–49.

Maxwell, S. D., & Delaney, H. D. (1990). *Designing experiments and analyzing data*. Belmont, CA: Wadsworth.

Pritchard, W. S., Robinson, J. H., Guy, T. D., Davis, R. A., & Stiles, M. E. (1996). Assessing the sensory role of nicotine in cigarette smoking. *Psychopharmacology*, *127,* 55–62.

Quick, M. W., & Lester, A. J. (2002). Desensitization of neuronal nicotinic receptors. *Journal of Neurobiology*, *53,* 457–478.

Rilling, M. (1977). Stimulus control and inhibitory processes. In W. K. Honig & J. E. R. Staddon (Eds.), *Handbook of operant behavior* (pp. 432–480). Englewood Cliffs, NJ: Prentice-Hall.

Rose, J. E. (1988). The role of upper airway stimulation in smoking. In O. F. Pomerleau & C. S. Pomerleau (Eds.), *Nicotine replacement: A critical evaluation* (pp. 95–106). New York: Liss.

Rose, J. E., & Behm, F. M. (1995). There is more to smoking than the CNS effects of nicotine. In P. B. S. Clark, M. Quik, F. Adlkofer, & K. Thurau (Eds.), *Effects of nicotine on biological systems II* (pp. 9–16). Basel, Switzerland: Burkhäuser Verlag.

Rose, J. E., Behm, F. M., & Westman, E. C. (1998). Nicotine/mecamylamine treatment for smoking cessation: The role of precessation therapy. *Experimental and Clinical Psychopharmacology*, *6,* 331–343.

Rose, J. E., Behm, F. M., & Westman, E. C. (2001). Acute effects of nicotine and mecamylamine on tobacco withdrawal symptoms, cigarette reward and *ad lib* smoking. *Pharmacology, Biochemistry, and Behavior*, *68,* 187–197.

Rose, J. E., Behm, F. M., Westman, E. C., & Coleman, R. E. (1999a). Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: Implications for addiction. *Drug and Alcohol Dependence*, *56,* 99–107.

Rose, J. E., Behm, F. M., Westman, E. C., Levin, E. D., Stein, R. M., Lane, J. D., & Ripka, G. V. (1994a). Combined effects of nicotine and mecamylamine in attenuating smoking reward. *Experimental and Clinical Psychopharmacology*, *2,* 1–17.

Rose, J. E., Behm, F. M., Westman, E. C., Levin, E. D., Stein, R. M., & Ripka, G. V. (1994b). Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clinical Pharmacology and Therapeutics*, *56,* 86–99.

Rose, J. E., Tashkin, D. P., Ertle, A., Zinser, M. C., & Lafer, R. (1985). Sensory blockade of smoking satisfaction. *Pharmacology, Biochemistry, and Behavior*, *23,* 289–293.

Rose, J. E., Westman, E. C., & Behm, F. M. (1996). Nicotine/mecamylamine combination treatment for smoking cessation. *Drug Development Research*, *38,* 243–256.

Rose, J. E., Westman, E. C., Behm, F. M., Johnson, M. P., & Goldberg, J. S. (1999b). Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. *Pharmacology, Biochemistry, and Behavior*, *62,* 165–172.

Rose, J. E., Zinser, M. C., Tashkin, D. P., Newcomb, R., & Ertle, A. (1984). Subjective response to cigarette smoking following airway anesthetization. *Addictive Behaviors*, *9,* 211–215.

Westman, E. C., Behm, F. M., & Rose, J. E. (1996). Dissociating the nicotine and airway sensory effects of smoking. *Pharmacology, Biochemistry, and Behavior*, *53,* 309–315.

Westman, E. C., Levin, E. D., & Rose, J. E. (1992). Smoking while wearing the nicotine patch: Is smoking satisfying or harmful? *Clinical Research*, *40,* 871A.

Williams, B. A. (1999). Associative competition in operant conditioning: Blocking the response-reinforcer association. *Psychonomic Bulletin and Review*, *6,* 618–623.

Nicotine replacement therapy for smoking cessation (Review)

Stead LF, Perera R, Bullen C, Mant D, Lancaster T



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[Intervention review]

Nicotine replacement therapy for smoking cessation

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ABSTRACT

Background

The aim of nicotine replacement therapy (NRT) is temporarily to replace much of the nicotine from cigarettes to reduce motivation to smoke and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence.

Objectives

The aims of this review were:

To determine the effect of NRT compared to placebo in aiding smoking cessation, and to consider whether there is a difference in effect for the different forms of NRT (chewing gum, transdermal patches, nasal spray, inhalers and tablets/lozenges) in achieving abstinence from cigarettes.

To determine whether the effect is influenced by the dosage, form and timing of use of NRT; the intensity of additional advice and support offered to the smoker; or the clinical setting in which the smoker is recruited and treated.

To determine whether combinations of NRT are more likely to lead to successful quitting than one type alone.

To determine whether NRT is more or less likely to lead to successful quitting compared to other pharmacotherapies.

Search strategy

We searched the Cochrane Tobacco Addiction Group trials register for papers with 'nicotine' or 'NRT' in the title, abstract or keywords. Date of most recent search July 2007.

Selection criteria

Randomized trials in which NRT was compared to placebo or to no treatment, or where different doses of NRT were compared. We excluded trials which did not report cessation rates, and those with follow up of less than six months.

Data collection and analysis

We extracted data in duplicate on the type of participants, the dose, duration and form of nicotine therapy, the outcome measures, method of randomization, and completeness of follow up.

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The main outcome measure was abstinence from smoking after at least six months of follow up. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. We calculated the risk ratio (RR) for each study. Where appropriate, we performed meta-analysis using a Mantel-Haenszel fixed-effect model.

Main results

We identified 132 trials; 111 with over 40,000 participants contributed to the primary comparison between any type of NRT and a placebo or non-NRT control group. The RR of abstinence for any form of NRT relative to control was 1.58 (95% confidence interval [CI]: 1.50 to 1.66). The pooled RR for each type were 1.43 (95% CI: 1.33 to 1.53, 53 trials) for nicotine gum; 1.66 (95% CI: 1.53 to 1.81, 41 trials) for nicotine patch; 1.90 (95% CI: 1.36 to 2.67, 4 trials) for nicotine inhaler; 2.00 (95% CI: 1.63 to 2.45, 6 trials) for oral tablets/lozenges; and 2.02 (95% CI: 1.49 to 3.73, 4 trials) for nicotine nasal spray. The effects were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. The effect was similar in a small group of studies that aimed to assess use of NRT obtained without a prescription. In highly dependent smokers there was a significant benefit of 4 mg gum compared with 2 mg gum, but weaker evidence of a benefit from higher doses of patch. There was evidence that combining a nicotine patch with a rapid delivery form of NRT was more effective than a single type of NRT. Only one study directly compared NRT to another pharmacotherapy. In this study quit rates with nicotine patch were lower than with the antidepressant bupropion.

Authors' conclusions

All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50-70%, regardless of setting.

The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.

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PLAIN LANGUAGE SUMMARY

Can nicotine replacement therapy (NRT) help people quit smoking

NRT aims to reduce withdrawal symptoms associated with stopping smoking by replacing the nicotine from cigarettes. NRT is available as skin patches that deliver nicotine slowly, and chewing gum, nasal spray, inhalers, and lozenges/tablets, all of which deliver nicotine to the brain more quickly than from skin patches, but less rapidly than from smoking cigarettes. This review includes 132 trials of NRT, with over 40,000 people in the main analysis. It found evidence that all forms of NRT made it more likely that a person's attempt to quit smoking would succeed. The chances of stopping smoking were increased by 50 to 70%. Most of the studies were performed in people smoking more than 15 cigarettes a day. What limited evidence there is suggests no overall difference in effectiveness of different forms of NRT nor a benefit for using patches beyond 8 weeks. NRT works with or without additional counselling, and does not need to be prescribed by a doctor. Heavier smokers may need higher doses of NRT. People who use NRT during a quit attempt are likely to further increase their chance of success by using a combination of the nicotine patch and a faster acting form. Preliminary data suggests that starting to use NRT shortly before the planned quit date may increase the chance of success. Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. There is no evidence that NRT increases the risk of heart attacks.

BACKGROUND

Nicotine replacement therapy (NRT) aims to reduce motivation to smoke and the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking, and therefore increase the likelihood of remaining abstinent (West 2001). Nicotine undergoes first pass metabolism in the liver, reducing the overall bioavailability of swallowed nicotine pills. A pill that could reliably produce high enough nicotine levels in the central nervous system would risk causing adverse gastrointestinal effects To avoid this problem, nicotine replacement products are formulated for absorption through the oral mucosa (chewing gum, lozenges, sublingual tablets, inhaler/inhalator) or skin (transdermal patches). Other products are also under development (Park 2002; D'Orlando 2004; Ikinci 2006; Bolliger 2007).

Nicotine patches differ from the other products in that they deliver the nicotine dose slowly and passively. They do not replace any of the behavioural activities of smoking. In contrast the other types are faster acting, but require more effort on the part of the user. Transdermal patches are available in several different doses, and deliver between 5 mg and 22 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers (Fiore 1992). Some brands of patch are designed to be worn for 24 hours whilst others are intended to be worn for 16 hours each day. Nicotine lozenges and nicotine chewing gum are available in both 2 mg and 4 mg strengths. None of the available products deliver such high doses of nicotine as quickly as cigarettes. An average cigarette delivers between 1 and 3 mg of nicotine and the typical pack-per-day smoker absorbs 20 to 40 mg of nicotine each day (Henningfield 2005).

The availability of NRT products on prescription or for over-the-counter purchase varies from country to country. Table 1 summarises the products currently licensed in the United Kingdom.

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Table 1. Nicotine replacement therapies

Type	Available doses
Nicotine transdermal patches	5 mg, 10 mg, 15 mg doses worn over 16 hours 7 mg, 14 mg, 21 mg doses worn over 24 hours
Nicotine chewing gum	2 mg and 4 mg doses
Nicotine sublingual tablet	2 mg dose
Nicotine lozenge	1mg, 2 mg and 4 mg doses
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 10mg
Nicotine metered nasal spray	0.5mg dose/spray

In earlier versions, this review focused on the effect of nicotine replacement therapy in comparison to placebo for helping people stop smoking. The evidence that NRT helps some people to stop smoking is now well accepted, and many clinical guidelines recommend NRT as a first line treatment for people seeking pharmacological help to stop smoking (Fiore 2000; West 2000; NZ NACHD 2002; Woolacott 2002; Italy ISS 2004; Zwar 2004; Le Foll 2005). This review still provides an estimate of the expected effect of using NRT, using meta-analysis. We also address questions about when and how to use NRT most effectively. This includes consideration of the effect of the type of NRT used, including the use of combinations of different types of NRT, the effect of the setting in which it is used (including purchasing over the counter versus prescription use), the effect of dosing according to characteristics of the individual quitter and whether the effect of NRT is altered by different levels of behavioural support. NRT is now one of several forms of pharmacotherapy available to support quit attempts, including antidepressants such as bupropion and the nicotine receptor partial agonist varenicline. These pharmacotherapies are evaluated in separate Cochrane reviews (Hughes 2007; Cahill 2007). This review includes in its scope evaluations of randomized trials directly comparing NRT to these treatments, or combining NRT with them.

OBJECTIVES

To determine the effectiveness of nicotine replacement therapy (NRT), including gum, transdermal patch, intranasal spray and inhaled and oral preparations, in achieving long-term smoking cessation.

We addressed the following questions:

- Is NRT more effective than a placebo or 'no NRT' intervention in promoting smoking cessation?
- Is NRT relatively more effective when given with higher levels of behavioural support?
- Is NRT relatively more effective for people who are highly motivated to quit smoking?
- Is 4 mg nicotine gum more effective than 2 mg nicotine gum?
- Are fixed dosing schedules for nicotine gum more effective than ad lib use?
- Is higher dose nicotine patch therapy more effective than standard dose (~1mg/hour) therapy?
- Are nicotine patches worn for 24 hours more effective than 16-hour patches?
- Is a longer duration of nicotine patch use more effective than shorter treatment?
- Is weaning from nicotine patch use more effective than an abrupt end of therapy?
- Are combinations of different forms of NRT more effective than the usual dose of a single type?
- Does NRT assist cessation amongst people who have relapsed after recent use of NRT?
- Is initiating nicotine patch use before making a quit attempt more effective than starting on the quit day?
- Is NRT more or less effective than bupropion for smoking cessation?
- Are there harms associated with using NRT?

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METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. Trials where allocation to treatment was by a quasi-randomized method were also included, but appropriate sensitivity analysis was used to determine whether their inclusion altered the results.

Types of participants

Men or women who smoked were included irrespective of the setting from which they were recruited and/or their initial level of nicotine dependence. We included studies that randomized therapists, rather than smokers, to offer NRT or a control, provided that the specific aim of the study was to examine the effect of NRT on smoking cessation. Trials that randomized physicians or other therapists to receive an educational intervention, which included encouraging their patients to use NRT, were not included, but have been reviewed separately (Lancaster 2000).

Types of interventions

Comparisons of NRT (including chewing gum, transdermal patches, nasal spray, inhalers and tablets or lozenges) versus placebo or no nicotine replacement therapy control. The terms 'inhaler' and 'inhalator' (a cigarette-like device which delivers nicotine to the buccal mucosa by sucking) are used interchangeably in the literature. We have used the term 'inhaler' throughout the rest of this review.

We also included trials comparing different doses of NRT and comparing more than one type of NRT to a single type.

In some analyses we categorized the trials into groups depending on the level of additional support provided (low or high). The definition of the low-intensity category was intended to identify a level of support that could be offered as part of the provision of routine medical care. If the duration of time spent with the smoker (including assessment for the trial) exceeded 30 minutes at the initial consultation or the number of further assessment and reinforcement visits exceeded two, the level of additional support was categorized as high. The high intensity category included trials where there were a large number of visits to the clinic/trial centre, but these were often brief, spread over an extended period during treatment and follow up, and did not include a specific counselling component. It also included trials where the support included multi-session group-based counselling, with frequent sessions around the quit date. In the present update of the review we have attempted to provide a more fine-grained analysis and have distinguished between high intensity group-based support and other trials within the high intensity category.

Types of outcome measures

The review evaluates the effects of NRT versus control on smoking cessation, rather than on withdrawal symptoms. We excluded trials that followed up participants for less than six months. For each study we chose the strictest available criteria to define abstinence. For example, in studies where biochemical validation of cessation was available, only those participants who met the criteria for biochemically confirmed abstinence were regarded as being abstinent. Wherever possible we chose a measure of sustained cessation rather than point prevalence. People who were lost to follow up were regarded as being continuing smokers.

Trials that evaluated the effect of NRT for individuals who were attempting to reduce the number of cigarettes smoked rather than to quit are no longer included in this review. They are covered by a separate review on harm reduction approaches (Stead 2007)

Search methods for identification of studies

We searched the specialized register of the Cochrane Tobacco Addiction Group in July 2007 for trials with any reference to the use of nicotine replacement therapy of any type, by searching for 'nicotine' or 'NRT' in the title, abstract or keywords. The most recent issues of the databases included in the register as searched for the current update of this review are: the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) Issue 4, 2006, MEDLINE (Ovid) update code 20070629, EMBASE (Ovid) week 20 2007, PsycINFO (Ovid) update code 20070709, Science Citation Index (Web of Science) 1/2007. The trials register also includes trials identified by handsearch of abstract books from meetings of the Society for Research on Nicotine & Tobacco. For earlier versions of this review we performed searches of additional databases; Cancerlit, Health Planning and Administration, Social Scisearch, Smoking & Health and Dissertation Abstracts. Since the searches did not produce any additional trials we did not search these databases after December 1996. During preparation of the first version of this review, we also sent letters to manufacturers of NRT preparations. Since this did not result in additional data we did not repeat the exercise for subsequent updates.

Data collection and analysis

Two individuals independently extracted data from the published reports and abstracts. Disagreements were resolved by discussion or referral to a third party. We made no attempt to blind these individuals either to the results of the primary studies or to which treatment participants received. Reports published only in non-English language journals were examined with the assistance of translators.

We extracted smoking cessation rates in the intervention and control groups from the reports at six or 12 months. Since not all studies reported cessation rates at exactly these intervals, we allowed a window period of six weeks at each follow-up point. For trials without 12-month follow up we used six-month data. For

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trials which also reported follow up for more than a year we used 12-month outcomes in most cases. (We note exceptions in the included study table.) Following changes to the Cochrane Tobacco Addiction Group's recommended method of data analysis since this review was last updated, we have changed the way in which we summarize the effects of treatment. We now use the risk ratio rather than the odds ratio for summarizing individual trial outcomes and for estimates of pooled effect. Treatment effects will seem smaller when expressed as risk ratios than when expressed as odds ratios, unless the event rates are very low. For example, if 20 out of 100 participants have quit in the intervention group, and 10 out of 100 in the control group, the risk ratio is 2.0 [(20/100)/(10/100)], whilst the odds ratio is 2.25 [(20/80)/(10/90)]. Whilst there are circumstances in which odds ratios may be preferable, there is a danger that they will be interpreted as if they are risk ratios, making the treatment effect seem larger (Deeks 2005). We estimated a pooled weighted average of risk ratios using a Mantel-Haenszel method, with 95% confidence intervals.

To investigate heterogeneity we use the I^2 statistic, given by the formula [(Q - df)/Q] x 100%, where Q is the chi-squared statistic and df is its degrees of freedom (Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to indicate substantial heterogeneity. When there are large numbers of trials as in this review, the chi-squared test for heterogeneity will be unduly powerful and may identify statistically significant but clinically unimportant heterogeneity

In comparing NRT to placebo, we performed subgroup analysis for each form of NRT. We did additional subgroup analyses within type of NRT (gum, patch etc) to investigate whether the relative treatment effect differed according to the way in which smoking cessation was defined, the intensity of behavioural support and the clinical setting of treatment. We also used subgroup analyses to compare effect sizes across nicotine patch trials using different lengths of treatment, durations of daily use and tapering of dose at the end of treatment. Where the estimates of effect clearly differed across subgroups we used metaregression to test for significance. For descriptive purposes we calculated an average quit rate for the control groups in some subgroup analyses, weighting by the inverse variance. To provide a clinical perspective in the Discussion we estimated the number of people who would need to be treated (NNT) with NRT in order to produce one successful quitter at 12 months beyond that which would be achieved from a quit attempt without NRT. To do this we specified baseline quit rates and used the risk ratio derived from meta-analysis to calculate the quit rate likely with treatment: we then calculated the NNT as the inverse of the difference between the treated and untreated quit rates (Altman 2002).

We include in this updated review the Cochrane Tobacco Addiction Group's Glossary of smoking-related terms (Table 2).

Table 2. Glossary of terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products, May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence
Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation': A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood.
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence.

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Table 2. Glossary of terms

(*Continued*)

Cessation	Also called 'quitting'
Continuous abstinence	Also called 'sustained abstinence' A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence
'Cold Turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support.
Craving	A very intense urge or desire [to smoke]. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614
Dopamine	A neurotransmitter in the brain which regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size': The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco.
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse.
nAChR	[neural nicotinic acetylcholine receptors]: Areas in the brain which are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking.
Nicotine Replacement Therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges.
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial.

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Table 2. Glossary of terms

(*Continued*)

Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. NRT, bupropion
Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation which typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes et al 'Measures of abstinence in clinical trials: issues and recommendations'; Nicotine & Tobacco Research, 2003: 5 (1); 13-25
Relapse	A return to regular smoking after a period of abstinence
Secondhand smoke	Also called passive smoking or environmental tobacco smoke [ETS] A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins.
Self-efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively.
Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Tar	The toxic chemicals found in cigarettes. In solid form, it is the brown, tacky residue visible in a cigarette filter and deposited in the lungs of smokers.
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects.
Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614

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RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The review includes 132 studies. Trials were conducted in North America (66 studies), Europe (55), Australasia (4 studies), Japan (2 studies), South Africa (2 studies), Taiwan, Thailand, and Venezuela, or in multi-region trials (3 studies). The median sample size was around 200 but ranged from less than 50 to over 1500 participants.

Participants

Participants were typically adult cigarette smokers with an average age of 40 to 50. One trial recruited adolescents (Moolchan 2005). Most trials had approximately similar numbers of men and women. Kornitzer 1987 recruited only men, in a workplace setting. Cooper 2005 and Pirie 1992 recruited only women and Wisborg 2000 recruited only pregnant women. Two trials recruited African-American smokers (Ahluwalia 1998; Ahluwalia 2006).

Trials typically recruited people who smoked at least 15 cigarettes a day. Although some trials included lighter smokers as well, the average number smoked was over 20 per day in most studies. One trial recruited only people who smoked 10 or fewer cigarettes/day (Ahluwalia 2006). Killen 1999 recruited people smoking 25 or more per day and two trials recruited only people smoking 30 or more per day (Hughes 1990; Hughes 2003). Two trials recruited people with a history of alcohol dependence (Hughes 2003; Kalman 2006). One study recruited people with a history of cardiac disease (Joseph 1996).

Type and dose of nicotine replacement therapy

One hundred and eleven studies contributed to the primary analysis of the efficacy of one or more types of NRT compared to a placebo or other control group not receiving any type of NRT. In this group of studies there were 53 trials of nicotine gum, 41 of transdermal nicotine patch, six of an oral nicotine tablet or lozenge, four of intranasal nicotine spray, four of nicotine inhaler, one providing patch and inhaler (Hand 2002) and two offering a choice of products (Kralikova 2002; Molyneux 2003). Trials that did not contribute to the primary analysis addressed a range of other questions including treatment duration, dose, combinations of different types of NRT compared to a single type, and using NRT for a short period before the target quit day.

Most trials comparing nicotine gum to control provided the 2 mg dose. A few provided 4 mg gum to more highly addicted smokers, and two used only the 4mg dose (Blondal 1989; Puska 1979). Five trials included a comparison of 2 mg and 4 mg doses (Garvey 2000; Herrera 1995; Hughes 1990; Kornitzer 1987; Tonnesen 1988). In three trials the physician offered nicotine gum but participants did not necessarily accept or use it (Ockene 1991; Page 1986; Russell 1983). Two trials compared a fixed dosage regimen with an ad lib regimen (Killen 1990; Goldstein 1989). The treatment period was typically 2-3 months, but ranged from 3 weeks to 12 months. Some trials did not specify how long the gum was available. Many of the trials included a variable period of dose tapering, but most encouraged participants to be gum-free by six to 12 months.

In nicotine patch trials the usual maximum daily dose was 15 mg for a 16-hour patch, or 21 mg for a 24-hour patch. Thirty-one studies used a 24-hour formulation and ten a 16-hour product. If studies tested more than one dose we combined all active arms in the comparison to placebo. For one study we included an arm with a lower maximum dose of 14 mg but excluded a 7 mg dose arm (TNSG 1991). One trial (Daughton 1991) included a direct comparison between groups wearing 16-hour or 24-hour patches in addition to a placebo control. Seven trials directly compared a higher dose patch to a standard dose (CEASE 1999; Dale 1995; Hughes 1999; Jorenby 1995; Kalman 2006; Killen 1999; Paoletti 1996). The minimum duration of therapy ranged from three weeks (Glavas 2003a, half the participants of Glavas 2003b) to three months, with a tapering period, if required, in 31 of the trials. Four trials directly compared two durations of therapy (Bolin 1999; CEASE 1999; Glavas 2003b; Hilleman 1994).

There are five studies of nicotine sublingual tablets or lozenges. Three used 2 mg sublingual tablets (Glover 2002; Tonnesen 2006; Wallstrom 2000). One used a 1 mg nicotine lozenge (Dautzenberg 2001). A fifth trial used 2 mg or 4 mg lozenges according to dependence level based on participants' time to first cigarette of the day (TTFC). Smokers whose TTFC was more than 30 minutes were randomized to 2 mg lozenges or placebo (Shiffman 2002 (2mg)), whilst smokers with a TTFC less than 30 minutes had higher dose 4 mg lozenges or placebo (Shiffman 2002 (4mg)). The two groups are treated in the meta-analysis as separate trials making 6 in total. There are four trials of intranasal nicotine spray (Blondal 1997; Hjalmarson 1994; Schneider 1995; Sutherland 1992), and four trials of nicotine inhaler (Hjalmarson 1997; Leischow 1996; Schneider 1996; Tonnesen 1993). One trial of a nicotine inhaler was excluded as follow up was for only three months (Glover 1992). Leischow refers to another unpublished study by different investigators that did not demonstrate any benefit of a nicotine inhaler. One trial compared four different types of NRT (patch, gum, inhaler and nasal spray) but only followed patients for 12 weeks and was excluded (Hajek 1999).

Six trials compared combinations of two forms of nicotine therapy with only one form; patch with gum to patch alone (Kornitzer 1995); patch with gum to gum alone (Puska 1995); patch with nasal spray to patch alone (Blondal 1999); patch with inhaler to inhaler alone (Bohadana 2000), patch with inhaler to either one alone (Tonnesen 2000) and patch with nasal spray to either one alone (Croghan 2003). In addition to these last two trials allowing a direct comparison between two single types, Lerman 2004 compared patch to nasal spray. A factorial trial compared nicotine and bupropion (Zyban) (Jorenby 1999). Two unpublished trials of combination therapies with only three-month fol-

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low up are excluded but contribute to a sensitivity analysis in the results (Sutherland 1999; Finland unpublished).

Treatment setting

Twelve of the gum trials and six of the patch trials in the main comparison were conducted in a primary care setting where smokers were usually recruited in response to a specific invitation from their doctor during a consultation. A further two gum trials were undertaken in workplace clinics (Fagerstrom 1984; Roto 1987), and one in a university clinic (Harackiewicz 1988). One trial recruited via community physicians (Niaura 1994). Since participants in these trials were recruited in a similar way to primary care, we aggregated them in the subgroup analysis by setting. One patch trial conducted in Veterans Affairs Medical Centers and recruiting patients with cardiac diseases (Joseph 1996) was also included in the primary care category. One trial in an antenatal clinic (Wisborg 2000) is kept in a separate category. Six of the gum trials, one of the nasal spray trials and one of the inhaler trials, were carried out in specialized smoking cessation clinics to which participants had usually been referred. Eight trials (three gum, four patch, one giving a choice of products and one giving a combination of products) were undertaken with hospital in- or out-patients, some of who were recruited because they had a coexisting smoking-related illness. Three patch trials were undertaken in settings intended to resemble 'over-the-counter' (OTC) use of NRT (Davidson 1998; Hays 1999; Sonderskov 1997). One of these also allowed a comparison between purchased and free patches with minimal support (Hays 1999). Two trials compared purchased NRT without behavioural support (simulating an OTC setting) to purchased NRT with brief physician support (using patch, Leischow 1999, using inhaler, Leischow 2004). These two trials did not have a non-NRT control so do not contribute to the primary comparison. One trial in a primary care setting evaluated the effect of cost on the use and efficacy of nicotine gum (Hughes 1991). The remaining gum, patch, inhaler and nasal spray trials were undertaken in participants from the community, most of whom had volunteered in response to media advertisements, but who were treated in clinical settings. One of the patch trials was conducted in relapsed smokers (Gourlay 1995).

Pre-cessation use of NRT

Four trials (Rose 1994; Rose 1998; Rose 2006; Schuurmans 2004) tested the use of nicotine patch compared to placebo initiated two weeks before the quit date. Following the quit date all study arms received active NRT. Three of the studies included other factorial arms testing mecamylamine. We combined the arms with the same pre-quit NRT conditions in our analysis.

Excluded studies are listed with reasons in the Table of Excluded Studies. Some studies were excluded due to short follow up. Some of these had as their primary outcome withdrawal symptoms rather than cessation. Studies that provided NRT or placebo to people trying to cut down their smoking but not make an immediate quit attempt are now excluded and are considered in detail in a separate review of interventions for reduction (Stead 2007). We exclude one trial which included a test of mailed patches (Velicer 2006). This trial proactively recruited people by telephone and those in one intervention group were mailed a six-week course of nicotine patches if they were judged to be in the preparation stage or in contemplation and had more pros than cons for quitting. They did not need to be intending to make a quit attempt.

Risk of bias in included studies

Four trials are included based on data available from abstracts or conference presentations (Dautzenberg 2001; Kralikova 2002; Mori 1992; Nakamura 1990) so had limited methodological details.

Thirty-five studies (28%) reported allocation procedures in sufficient detail to be rated A for their attempts to control selection bias by using a system whereby treatment allocation could not be known or predicted until a participant is enrolled and assigned to a study condition. The majority of studies either did not report how randomization was performed and allocation concealed, or reported it in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made (rated B). A small number of nicotine gum trials randomized to treatment according to day or week of clinic attendance (Page 1986; Richmond 1993; Russell 1983), birth date (Fagerstrom 1984), or smokers' clinic group (McGovern 1992) (rated C). One study (Nebot 1992) randomized by physician and there was no information about avoidance of selection bias in enrolment of smokers so this was also rated C. The main findings were not sensitive to the exclusion of C, or B and C grade studies from the meta-analysis.

Fifteen gum trials (Gilbert 1989; Gross 1995; Hall 1985; Harackiewicz 1988; Jensen 1991; McGovern 1992; Nakamura 1990; Nebot 1992; Niaura 1994; Niaura 1999; Richmond 1993; Roto 1987; Segnan 1991; Villa 1999; Zelman 1992) and four patch trials (Cinciripini 1996; Otero 2006; Velicer 2006; Wong 1999) did not have a matched placebo control, and a further two had both a placebo and non-placebo control which were combined for the meta-analysis control group (Buchkremer 1988; Russell 1983). The main findings were not sensitive to the exclusion of studies and arms without a placebo.

Definitions of abstinence varied considerably. Eighty-six (65%) reported some measure of sustained abstinence, which included continuous abstinence with not even a slip since quit day, repeated point prevalence abstinence (with or without biochemical validation) at multiple follow ups, or self-reported abstinence for a prolonged period. Thirty-two (24%) reported only the point prevalence of abstinence at the longest follow up. In five studies it was unclear exactly how abstinence was defined. In one trial, participants who smoked up to three cigarettes per week were still classified as abstinent (Abelin 1989). Most studies reported follow up at least 12 months from start of treatment. Thirteen gum trials, 12 patch trials and one lozenge trial in the primary analysis had only six months follow up. We report the findings of a subgroup

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analysis by type of abstinence and length of follow up in the results section.

Biochemical validation of self-reported smoking cessation was used in all but 14 of the trials. Validation of abstinence was carried out by measurement of nicotine metabolites in saliva, urine or blood in 27 trials. The most common form of validation was measurement of carbon monoxide (CO) in expired air. The 'cut-off' level of CO used to define abstinence varied from less than 4 to 11 parts per million. The main findings were not sensitive to the exclusion of studies that did not attempt to validate abstinence.

Some of the studies involve NRT versus usual care and are inevitably not double-blind in design. We did not assess whether trials reported an assessment of the integrity of blinding, in line with the CONSORT guidelines (CONSORT 1996). Where they are done, assessments of blinding integrity should always be carried out before the clinical outcome has been determined, and the findings reported (Altman 2004). Mooney 2004 notes that few published trials report this information. While those that do provide some evidence that participants are likely to assess their treatment assignment correctly, it is insufficient to assess whether this is associated with differences in treatment effects. Further, there may be an apparent breaking of the blinding in trials where the treatment effect is marked, for either an intended outcome or an adverse effect, but participants who successfully decipher assignment may disguise their unblinding actions (Altman 2004). Also it is possible that those who believe that they are receiving a placebo may be more likely to stop trying to quit.

Effects of interventions

Each of the five forms of nicotine replacement therapy (NRT) significantly increased the rate of cessation compared to placebo, or no NRT (Comparison 1). This meta-analysis included 111 trials, with over 43,000 participants. For the different types of NRT the risk ratio (RR) was 1.43 (95% confidence interval (CI): 1.33 to 1.53, 53 trials) for nicotine gum, 1.66 (95% CI: 1.53 to 1.81, 41 trials) for nicotine patch, 1.90 (95% CI: 1.36 to 2.67, 4 trials) for nicotine inhaler, 2.00 (95% CI: 1.63 to 2.45, 6 trials) for oral tablets/lozenges, and 2.02 (95% CI: 1.49 to 2.73, 4 trials) for nicotine nasal spray. Although the estimated effect sizes varied across the different products, confidence intervals were wide for the products with higher estimates which had small numbers of trials. In a metaregression with gum as baseline, only the difference with the tablets/lozenges group was statistically significant (P value = .014), whilst the difference with nasal spray was marginally significant (P = .055). The pooled risk ratio for abstinence for any form of NRT relative to control was 1.58 (95% CI: 1.50 to 1.66). The I^2 statistic was 24%, indicating that little of the variability was attributable to between-trial differences. Seven nicotine gum and two patch trials had lower quit rates in the treatment than control groups at the end of follow up, and in a further 56 (50%) of trials the 95% confidence interval for the risk ratio included 1 (i.e. the trials did not detect a significant treatment effect). Many of these trials had small numbers of smokers, and hence insufficient power to detect a modest treatment effect with reasonable certainty. One large trial of nicotine patches for people with cardiovascular disease had lower quit rates in the intervention than control group (Joseph 1996). At six months the quit rates were 14% for active patch and 11% for placebo, but after 48 weeks there had been greater relapse in the active group and rates were 10% and 12% respectively.

Sensitivity to definition of abstinence

For the nicotine gum and patch trials we assessed whether trials that reported sustained abstinence at 12 months had different treatment effects from those that only reported a point prevalence outcome, or had shorter follow up (Comparison 2). Subgroup categories were sustained abstinence at 12 months or more, sustained abstinence at six months, point prevalence or unclear definition at 12 months, and point prevalence/unclear at six months. For nicotine gum 32/53 studies (60%) reported sustained 12-month abstinence and the estimate was almost identical to that for all 53 studies (sustained 12-month RR 1.43, 95% CI 1.31 to 1.56, I^2 = 34%). For nicotine patch, 21/41 studies (51%) reported sustained 12-month abstinence, and the relative risk estimate was lowest in this subgroup (sustained 12-month RR 1.51, 95% CI 1.35 to 1.70, I^2 = 27%). For neither the gum nor patch trials was there evidence from metaregression that the risk ratios differed significantly between subgroups.

Sensitivity to intensity of behavioural support

Each trial provided the same behavioural support in terms of advice, counselling, and number of follow-up visits to the active pharmacotherapy and control groups, but different trials provided different amounts of support. We conducted subgroup analyses by intensity of support for gum and patch trials separately (Comparison 3). For nicotine gum the relative risk estimate was similar across all three subgroups. The control group quit rates did vary as expected, averaging 5.9% with low intensity support, 9.8% with high intensity individual support and 11.7% with group-based support. Nicotine patch trials showed the same pattern; the relative risk estimates were similar for each subgroup and the average control group quit rates were 6.3% with low intensity support, 6.7% with high intensity individual support and 14.8% with group-based support. Using metaregression we confirmed that there was no evidence that the relative effect differed by type of support.

Two small studies in primary care directly compared the effect of providing high versus low intensity follow up to participants receiving nicotine gum (Fagerstrom 1984; Marshall 1985). The pooled results favoured intensive follow up but the result was not statistically significant. In the one patch trial that compared minimal counselling with two forms of more intensive counselling in patients receiving one of two nicotine doses, the intensive intervention did not lead to improved outcomes (Jorenby 1995). Pooling all three studies showed no effect of increased behavioural support (Comparison 3.3, RR 1.14, 95% CI 0.88 to 1.47). It should be emphasised that these three studies do not address the efficacy

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of NRT and that only a factorial placebo-controlled trial with different intensities of support can adequately investigate whether pharmacotherapy and behavioural interventions have interactive effects.

Sensitivity to treatment settings

We did a further subgroup analysis based on the setting in which smokers were recruited or treated, for each type of NRT (Comparison 4). For nicotine gum there was no evidence that the relative effect differed substantially across the main subgroups. The subgroup of three trials recruiting hospital in- or outpatients had a lower and non-significant estimated effect. As expected the average control group quit rate was highest amongst smokers recruited and treated in specialist smoking clinics (16%), lower in community volunteers (11%) and lowest in people recruited and treated in primary care settings (5%).

For nicotine patch, effects in subgroups were again generally similar. We did not think that any of the patch trials recruited people attending smoking cessation clinics, but it is possible that some trials in community volunteers provided treatment in specialist clinics. For patches used in hospital settings the results, based on four trials, are consistent with those seen in other settings. In the single trial of a nicotine patch for women trying to quit during pregnancy no benefit of the patch was detected (Wisborg 2000). Nasal spray and inhaler trials did not show differences in effect by setting, and all lozenge trials involved community volunteers. Two other trials of other types of NRT involved hospital patients; Molyneux 2003 offered a choice of type of NRT to hospital inpatients, in which 63% chose patch; the use of NRT increased quit rates but the difference was not significant. Hand 2002 provided a combination of patch and inhaler to hospital in- or outpatients for three weeks, compared to individual counselling alone, and quit rates were similar at 12 months. Three patch studies have assessed the effect of patch amongst community volunteers treated in an 'Over the Counter' (OTC) setting offering low levels of support and little or no contact with healthcare professionals. The effect estimate was similar to that in other settings (RR 1.98, 95% CI 1.40 to 2.79, Comparison 04.02.02).

Two trials compared patch (Leischow 1999) or inhaler (Leischow 2004) with minimal physician support and patch/inhaler with no support in a simulated OTC setting. Abstinence rates were low in both conditions and confidence intervals wide, but when pooled there was a significant advantage of the physician support compared to no support (RR 4.58, 95% CI: 1.18 to 17.88) (Comparison 13).

Nicotine gum - effects of dose and scheduling

Most trials used the 2 mg dose so we did not do a subgroup analysis for indirect comparison. Four trials directly compared 4 mg and 2 mg gum for treating highly dependent smokers with a pooled estimate suggesting a significant benefit of the higher dose (RR 1.85, 95% CI: 1.36 to 2.50, Garvey 2000; Herrera 1995; Kornitzer 1987; Tonnesen 1988. Comparison 5.1.1). In low dependence or unselected smokers there was no evidence for an effect (RR 0.77, 95% CI 0.49 to 1.21, Garvey 2000 ; Hughes 1990 ; Kornitzer 1987. Comparison 5.1.2).

Two trials compared a fixed dose regimen of 2 mg nicotine gum against use of an ad lib regimen (Goldstein 1989; Killen 1990). The fixed dose regimen had higher quit rates but the difference was non-significant (RR 1.22 95% CI: 0.92 to 1.61, Comparison 6).

Nicotine patch - effects of dose and scheduling

Seven trials have compared a high dose patch to standard dose (Comparison 7). Four used 24-hour patches and compared 42/44 mg doses to standard 21/22 mg doses (Dale 1995; Hughes 1999; Jorenby 1995 ; Kalman 2006). Three used 16-hour patches and compared a 25 mg high dose to 15 mg standard dose (CEASE 1999; Killen 1999; Paoletti 1996). Three studies (Hughes 1999; Killen 1999; Kalman 2006) specifically recruited heavy smokers, and one selected smokers with baseline cotinine levels of over 250 mg/ml (Paoletti 1996). One study was in heavy smokers with a history of alcohol dependence (Kalman 2006). Pooling all seven studies gives an estimated RR of 1.15 (95% CI: 1.01 to 1.30) providing only marginal evidence of a small benefit from higher doses. Three studies had point estimates favouring the lower dose group but there was no evidence of significant heterogeneity in the results (I^2 = 25%). Only one study showed a significantly higher quit rate with the higher dose (CEASE 1999).

Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups. There was some evidence of heterogeneity in the results of the 10 trials that used a 16-hour patch (I^2= 54%) (Comparison 8). One trial directly compared the effect of 16-hour and 24-hour patch use (Daughton 1991). The study did not detect a significant difference, but with just 106 participants had low power (24-hour patch versus 16-hour patch: RR 0.70, 95% CI: 0.36 to 1.34).

Nicotine patch - effect of treatment duration and dose tapering

Indirect comparisons did not suggest a difference in treatment effect between 15 trials providing up to eight weeks of pharmacotherapy and 26 offering a longer period. (Comparison 9). One large trial that compared a 28- to a 12-week course of treatment did not detect evidence of benefit from longer treatment (CEASE 1999). Smaller trials comparing a three-week to a 12-week course (Bolin 1999) and a three-week to a six-week course (Glavas 2003b) also found no evidence for a difference.

Indirect comparison did not detect a difference in effect between 31 trials where participants were weaned from patch use by gradually tapering the dose and eight trials where withdrawal was abrupt (Comparison 10). Similarly, no difference was detected in the two trials that directly compared weaning with abrupt withdrawal, (Hilleman 1994; Stapleton 1995).

Combinations of different forms of nicotine therapy

Six trials compared the use of two types of NRT with using a single type only, and one compared two types to no NRT (Hand 2002). Pooling all seven trials suggests a statistically significant benefit

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(Comparison 11, RR 1.35, 95% CI: 1.11 to 1.63), with little statistical heterogeneity (I^2=25%), but the trials are relatively clinically heterogeneous in the combinations and comparison therapies used. The effect was similar when excluding the trial with a no-NRT control. Only one of the trials, comparing nasal spray and patch with patch alone, showed a significantly higher rate of sustained abstinence at one year with the combined therapy (Blondal 1999). We are aware of two unpublished studies that failed to detect significant short-term effects and did not have longer-term follow up (Sutherland 1999; Finland unpublished). Brief details in Table of Excluded Study). In case their exclusion biased the outcome we tested the sensitivity of the meta-analysis to including their results for cessation at three months. The meta-analysis maintained a significant, though slightly smaller, effect. We also tested the sensitivity to including only comparisons between a combination therapy and a nicotine patch only control. The effect remained just significant, with or without the relevant unpublished study.

Direct comparison between different types of NRT

Three trials have directly compared types (Comparison 12). None detected significant differences. Pooling the two that compared nasal spray with patch also failed to detect a significant difference (Nasal spray versus patch RR 0.90, 95% CI 0.64 to 1.27). Whilst confidence intervals are wide, the direct comparison is consistent with indirect comparisons reported above in the primary analysis, suggesting that the different types have similar effects.

Pre-cessation use of NRT

The pooled estimate from four trials suggests that using a nicotine patch for a brief period before the target quit day significantly increases the rate of cessation compared with initiating active patch use on the quit day (Comparison 14, RR 1.79, 95% CI 1.17 to 2.72). One other trial included groups who began using nicotine gum or placebo gum before quit day (Herrera 1995). This procedure did not significantly increase quitting at six weeks and long-term outcomes were not reported, but when we tested the inclusion of short-term outcomes in the meta-analysis with the four patch trials a significant effect remained.

Relapsed smokers

Although many of the trials reported here did not specifically exclude people who had previously tried and failed to quit with NRT, one trial recruited people who had relapsed after patch and behavioural support in an earlier phase of the study but were motivated to make a second attempt (Gourlay 1995). This study did not detect an effect on continuous abstinence (RR 1.25 95% CI 0.34 to 4.60), although it did detect a significant increase in 28-day point prevalence abstinence (RR 2.49, 95% CI 1.11 to 5.57). Quit rates were low in both groups with either definition of abstinence.

Cost of therapy

One study comparing the effectiveness of free and purchased patch in an OTC model setting found no significant difference in quit rates between the two conditions; 8.7% (28/321) quit with free patch, 11% (34/315) with purchased patch, RR 0.81, 95% CI 0.50 to 1.30 (Hays 1999). Those receiving free NRT were part of a placebo-controlled substudy. One small study of the cost of nicotine gum for patients receiving brief physician advice found non-significantly higher quit rates for participants who could obtain free gum compared to those paying close to full price; 6/32 (22%) versus 3/38 (12%). People who could get free gum were much more likely to obtain it (Hughes 1991).

Comparison with bupropion

In one study the cessation rate was significantly lower for nicotine patch and placebo tablet than bupropion and placebo patch (Jorenby 1999). The combination of bupropion and nicotine patch significantly increased the rate over placebo alone or patch alone, but not over bupropion alone (Comparison 15). Another trial compared nicotine gum and bupropion to bupropion alone (Piper 2007); pooling this and the patch+bupropion combination trial also failed to detect a significant additional benefit from NRT.

Adverse Effects

No attempt was made in this overview to synthesize quantitatively the incidence of the various side effects reported with the different NRT preparations. This was because of the extensive variation in reporting the nature, timing and duration of symptoms. The major side effects usually reported with nicotine gum include hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems (Fiore 1992; Palmer 1992). The only side effect that appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use (Fiore 1992). The major side effects reported with the nicotine inhaler and nasal spray are related to local irritation at the site of administration (mouth and nose respectively). For example, symptoms such as throat irritation, coughing, and oral burning were reported significantly more frequently with subjects allocated to the nicotine inhaler than to placebo control (Schneider 1996); none of the experiences, however, were reported as severe. With the nasal spray, nasal irritation and runny nose are the most commonly reported side effects. Nicotine sublingual tablets have been reported to cause hiccoughs, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers (Wallstrom 1999).

A review of adverse effects based on 35 trials with over 9,000 participants did not find evidence of excess adverse cardiovascular events amongst those assigned to nicotine patch, and the total number of such events was low (Greenland 1998). There has been concern about the safety of NRT in smokers with cardiac disease (TNWG 1994). A trial of nicotine patch (Joseph 1996) that recruited smokers aged over 45 with at least one diagnosis of cardiovascular disease found no evidence that serious adverse events were more common in smokers in the nicotine patch group. Events related to cardiovascular disease such as an increase in angina severity occurred in approximately 16% of patients, but did not differ according to whether or not patients were receiving NRT. A review of safety in patients with cardiovascular disease found no evidence

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of an increased risk of cardiac events (Joseph 2003). This included data from two randomized trials with short-term follow up that are excluded from the present review (Tzivoni 1998; Working Group 1994) and a case-control study in a population-based sample. An analysis of 187 smokers admitted to hospital with acute coronary syndromes who received nicotine patches showed no evidence of difference in short- or long-term mortality compared to a propensity-matched sample of smokers in the same database who did not receive NRT (Meine 2005).

DISCUSSION

This overview provides reliable evidence from trials including over 40,000 participants that offering nicotine replacement therapy (NRT) to dependent smokers who are prepared to try to quit increases their chance of success over that achieved with the same level of support without NRT. This applies to all forms of NRT and is independent of any variations in methodology or design characteristics of trials included in the meta-analysis. In particular we did not find evidence that the relative effect of NRT was smaller in trials with longer follow up beyond our six-month minimum for inclusion. We did not compare end of treatment risk ratios with post-treatment follow up, and relapse rates may be higher in active treatment participants once they stop using NRT products, but later relapse is probably unrelated to NRT use.

The absolute effects of NRT use will depend on the baseline quit rate, which varies in different clinical settings. Studies of people attempting to quit on their own suggest that success rates after six to 12 months are 3-5% (Hughes 2004a). Use of NRT might be expected to increase the rate by 2-3%, giving a number needed to treat (NNT) of 33-50. If however the quit rate without pharmacotherapy was estimated to be 15%, either because the population had other predictors of successful quitting or received intensive behavioural support, then another 8% might be expected to quit, giving an NNT of 12.

Type and dose of NRT

The conclusion that the relative effects of the different forms of NRT are similar is largely based on indirect comparisons. Although the estimated risk ratio was highest for the nasal spray the confidence intervals are wide. In a metaregression the estimated difference in effect between gum and the tablet/lozenge subgroup was statistically significant. Most of the trials included in the comparison of nicotine gum versus placebo used 2 mg gum, although the 4 mg dose has been shown to be better for highly dependent smokers. One lozenge study used a 4 mg dose and excluding this would reduce the difference between gum and tablet/lozenge subgroups. There have been no direct comparisons between these different forms. Three studies have directly compared different types, and differences between them were non-significant individually and when pooled. One study that randomized people to use nicotine gum, patch, spray or inhaler did not detect significant differences in abstinence rates after 12 weeks (Hajek 1999), supporting the indirect estimates from the longer term studies. Where a range of products are available, choice of product may be guided by patients' preferences (McClure 2006), although one study showed that allowing people to try different products may alter their perceptions (Schneider 2004). In one study directly comparing nicotine patch and nasal spray there were no overall difference in quit rates but there were three significant subgroup/treatment interactions (Lerman 2004). The patch showed better results for white smokers while the spray showed better results for obese smokers and highly nicotine-dependent smokers. These effects need confirmation in additional studies before they can be relied on for treatment matching.

Direct comparisons support the use of 4 mg gum for more nicotine dependent smokers. There is borderline evidence for a small benefit from use of the nicotine patch at doses higher than the standard dose (21 mg for 24 hours or 15 mg for 16 hours). Use of these may be considered for heavy smokers (i.e. smoking 30 or more cigarettes a day), or for patients relapsing because of persistent craving and withdrawal symptoms on standard dose therapy (Hughes 1995).

Combinations of NRT products

The evidence suggests that using a combination of NRT products is better than one product alone. The trials showed fairly consistent effects, with a range of different comparators. The combined therapies all included the patch and an acute dosing type. The 2000 US clinical practice guidelines (Fiore 2000) recommended the use of nicotine patch with another form of NRT as a second-line therapy for patients unable to quit on a single type of NRT or bupropion. At that time the strength of evidence was recognized as less than optimal due to the clinical heterogeneity of the studies in the meta-analysis. Two further trials have been published since then, strengthening the evidence. It is not entirely clear whether the benefit of combination therapy is due to the sensory effects provided by multiple types of delivery systems, to the higher percentage of nicotine substitution achieved, the better relief of craving by ad lib use of acute dosing forms or some combination of these and other factors (Sweeney 2001).

Intensity of additional support

We did not detect important differences in relative effect within patch or gum studies by our classification of level of support. A recent letter (Walsh 2007) identified inconsistencies in the classification of low and high intensity support in this review. In response we have changed the classification of a small number of trials. This has not altered the conclusion that intensity of support does not appear to be an important moderator of NRT effect. Most of the trials in the low intensity category were conducted in medical settings and the cut off for level of support was not intended to distinguish between 'over the counter' use of NRT and use with

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support from healthcare providers. We did a separate analysis of OTC type trials in the treatment setting subgroup analysis. As judged by the average control group quit rate, people receiving support and placebo had similar quit rates in low intensity and high intensity individual support groups, and one interpretation of this is that although the latter group typically had more frequent contact with study co-ordinators, this was not markedly increasing quitting or preventing relapse. Control group quit rates were however higher when people had intensive group-based support provided by specialists.

Treatment setting

We did not detect differences in relative effect within patch or gum studies according to the setting of recruitment and treatment. These subgroup analyses had considerable overlap with the support subgroup since for example people recruited in primary care settings typically had lower intensity support. Again there was variation between the control group quit rates, attributable to differences in motivation and to the level of behavioural support. People recruited from primary care who received placebo had average quit rates around 5 to 7%. This was similar to the rate amongst community volunteers who were treated in 'OTC' settings. People recruited in smoking clinics had much higher control group quit rates, averaging 15%, but this reflects both their motivation and the high level of behavioural support provided. Although some trials of NRT use in hospital inpatients have reported relatively less successful results, in the subgroup of four studies of nicotine patch amongst people recruited in inpatient and outpatient settings there was evidence of benefit.

There has been continuing debate about the amount of evidence for efficacy of NRT when obtained OTC without advice or support from a healthcare professional (Hughes 2001; Walsh 2000; Walsh 2001). The small number of placebo-controlled trials in settings intended to replicate OTC settings support the conclusion that the relative effect of NRT is similar to settings where more advice and behavioural support is provided, although quit rates in both control and intervention groups have been low. One other meta-analysis supports the conclusion of efficacy, although it differs in its inclusion criteria (Hughes 2003). In addition to the same three trials comparing nicotine patch to placebo in an OTC setting (Davidson 1998; Hays 1999; Sonderskov 1997), that review includes one study excluded here due to short follow up (Shiffman 2002a). It also pools four trials comparing NRT provided OTC to NRT provided under prescription. We exclude one paper that compared both gum and patch in these settings, but was not randomized (Shiffman 2002b), and another that has not been published and for which we have been unable to obtain reliable data for inclusion (Korberly 1999). The abstract reported that there were no significant differences in quit rates between users of nicotine patch who purchased it via a non-healthcare facility, and those receiving it on prescription. On the basis of one published and one unpublished study we find a marginally significant benefit of NRT with prescription compared to OTC, but the confidence intervals are wide.

It has been suggested that the 'real world' effectiveness of NRT declines or disappears once it becomes available to purchase without a requirement for contact with a health professional who can offer behavioural support and guidance on appropriate use (Pierce 2002). This was based on a comparison of two cross sectional surveys in California. Before OTC availability quit rates for self-selected NRT users were higher than rates for non-users but after the switch to OTC this difference disappeared. We and others have questioned the conclusions from this study (Franzon 2002; Stead 2002). One source of confounding which may have been incompletely controlled is the level of addiction of people who chose to use NRT compared to those who did not (Shiffman 2005). People who have used NRT may also be more likely to recall quit attempts. A second study suggested that both use of NRT and quit rates rose in the immediate aftermath of OTC availability (Hyland 2005). In this longitudinal study of smokers in the COMMIT study cohort there was a small reduction in the average success rates for patch users after the switch but no reduction in success rates for gum users. A more recent multicountry prospective study (West 2007) found that NRT users who did not use formal behavioural support had higher quit rates than non-users, even when controlling for baseline differences in motivation and other possible predictors of success. Although no study in which participants self-select treatment can be free from the possibility of bias due to unmeasured confounders, the results of this study provide additional reassurance. A review on the impact of NRT on population trends in smoking behaviour concluded that at the moment not enough smokers are using NRT during quit attempts for there to have been a measurable effect (Cummings 2005).

Trials in special populations

One trial of nicotine patch in pregnant women is now included in the review. Women still smoking after their first trimester were recruited, and they were followed up until one year post partum. No significant benefit of treatment was detected, although the confidence interval does not exclude the possibility of benefit. Quit rates one year after delivery were 15% in the patch group and 14% in the placebo group. Using quit rates at the final prenatal follow up did not alter the conclusions, with rates of 28% versus 25%. Possible explanations for the lack of relative benefit may have been low compliance with patch use, and the intensive cessation counselling offered to all participants. We excluded two other small trials of nicotine patch in pregnancy: Kapur 2001 had follow up only to end of treatment at 12 weeks. In this trial 0/13 in the placebo group quit compared to 4/17 (24%) in the active treatment group. Enrolment was ended early in this study because of a possible adverse event in the placebo arm. A second small study without placebo control had high rates of withdrawal and non-compliance (Hotham 2006), although 3/20 in the patch group were abstinent at delivery compared to 0/20 in the counselling

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only control. Another trial was published too late to be included in this update (Pollak 2007). A recent study measuring nicotine metabolism in smokers during their pregnancy and postpartum has suggested that nicotine is metabolised more quickly by pregnant women and that this may affect the dose of NRT required (Dempsey 2002). More studies are needed to establish whether or not NRT does aid quitting in pregnancy and what effects there are on birth outcomes (Benowitz 2000). A large trial is now underway in the UK (Coleman 2007)

Trials generally restricted recruitment to adults over the age of 18; in a small number of trials the age range was not specified. One trial in adolescents is now included (Moolchan 2005). This compared nicotine patch, gum, and double placebo. Two trials with less than six months follow up were excluded. One trial examining the effects of the nicotine patch on craving and withdrawal symptoms, safety, and compliance among 100 adolescents had 10 weeks follow up. No significant difference was detected at this point (Hanson 2003). In a second trial of the patch with 13 weeks follow up there were no quitters in either group at that point (Roddy 2006). Compliance with therapy and participant retention were both reported to be problems.

Evidence for differential treatment effects in different subgroups

We made no attempt to conduct separate analyses for any subgroups of trial participants, because subgroup results are uncommon in trial reports, and where data cannot be obtained from all studies there is a risk of bias from using incomplete data. Munafo and colleagues have reported the results of a meta-analysis of nicotine patch by sex (Munafo 2004a). They were able to include data from 11 out of 31 (35%) of eligible trials and 36% of study participants. They found no evidence that the nicotine patch was more effective for men than women as has been hypothesised, although there was a non-significant trend in that direction for outcomes at 12 months. There was also no difference in average placebo quit rates between men and women, which has been reported in some studies. In a commentary (Perkins 2004) some additional data were identified, but this did not alter the conclusions (Munafo 2004b). A second meta-analysis of any type of NRT (Cepeda-Benito 2004) reported that in women the odds ratio for cessation declined with increasing length of follow up with a non-significant difference at 12 months. Amongst males the odds ratio declined less over time and remained significant. Based on a further subgroup analysis they also reported that the decline in long-term efficacy in women was greater in trials with low intensity support than high intensity support, suggesting that the more intensive support helped prevent late relapse in women who had initially received NRT. Although there was no evidence of bias, the review could only include a subset of published studies so the finding should be regarded as hypothesis generating. All review authors agreed that trials are underpowered to identify any interaction between treatment and any type of individual characteristics, and recommended public archiving of data from studies, as well as new research specifically designed to test group by treatment interactions. At the moment there does not appear to be sufficient evidence of clinically important differences between men and women to guide treatment matching.

Pre-cessation use of NRT

When nicotine replacement therapies were first introduced there was concern that any smoking whilst using a product would increase the potential for adverse effects such as nausea and vomiting, due to nicotine overdose. However studies with higher dose products and combinations of products have found no evidence of harm from moderate increases in nicotine intake. There is some evidence that smokers who use NRT whilst not trying to alter their smoking behaviour either smoke less or reduce their nicotine from cigarettes, especially when using acute dosing types of NRT (Fagerstrom 2002). Trials have now investigated two situations in which it has been proposed that use of an NRT product can help long-term abstinence if initially used while continuing to smoke. The first of these is to begin using the nicotine patch for a short period before an abrupt quit attempt on the theoretical basis that it might diminish the reinforcing effects of cigarette smoking or reduce the dependence on inhaled nicotine (Rose 2006). Based on meta-analysis of four trials included in this review there appears to be evidence that this increases quit rates over that achieved by post-quitting NRT alone. A large trial of pre-cessation NRT use is now underway in New Zealand.

The second proposed use of NRT pre-cessation is for a period of weeks to months while people not willing or able to quit abruptly gradually reduce the number of cigarettes, before quitting completely. The use of two forms of NRT, gum and inhaler, has now been approved by licensing authorities in some European countries for this cessation approach, described variously as 'Reduce to Stop' or 'Cut Down to Quit'. Trials of this approach are included in a Cochrane review of interventions for reducing harm from continued smoking (Stead 2007). The long-term use of NRT whilst continuing to smoke smaller numbers of cigarettes cannot be supported by the evidence because it is not clear what reduction in consumption is needed for a useful health benefit.

Retreating relapsed smokers

Whilst end of treatment success rates may be quite high, many people relapse after the end of therapy. There is suggestive evidence (Gourlay 1995) that repeated use of NRT in patients who have relapsed after an initial course may produce further quitters, though the absolute effect is small. A subgroup analysis in another trial (Jorenby 1999, reported in Durcan 2002) indicated that the relative effect of treatment with nicotine patch compared to placebo was at least as high for people who had used NRT before. The authors noted that there was no way to distinguish between people who had completely failed to quit using NRT and those who had been initially successful but relapsed.

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Direct comparison and combination with non-nicotine pharmacotherapies

There is evidence from one large study (Jorenby 1999) that bupropion is more effective than nicotine patch. A combination of NRT and bupropion has not been found to be significantly more effective than bupropion alone. No trial of a direct comparison between NRT and varenicline has yet been published.

Addictive Potential of NRT

Some successful quitters continue to use NRT products beyond the recommended treatment period (Shiffman 2003), but few develop true dependence (Hughes 2004b; Hughes 2005). Although nicotine has the potential to cause harm, it is very much less harmful than tobacco smoke, so whilst complete abstinence from nicotine is preferred, the risk to health from NRT use is small compared to the risk from continued smoking.

Methodological Limitations

There are two possible methodological limitations of this overview, which need to be borne in mind: use of tabulated data predominantly derived from published reports (Stewart 1993) and publication bias (Simes 1986). We tried to partly address any shortcomings from having limited our analysis to tabulated data by approaching investigators, where necessary, to obtain additional unpublished data or to clarify areas of uncertainty. Although steps were taken to minimize publication bias by writing to the manufacturers of NRT products when this review was first prepared, the response was poor and we have not repeated this exercise. It is therefore possible that there are some unpublished trials, with less favourable results, that we have not identified despite our efforts to do so. A statistical analysis (Egger 1997, Egger personal communication) suggests that this is the case. A regression method to assess the symmetry of funnel plots showed evidence of asymmetry, and hence possible publication bias, for both nicotine gum and transdermal patches in an earlier version of this review. For the nicotine inhaler we are aware of one unpublished trial with a non-significant result. A recent meta-analysis has also demonstrated that nicotine gum and patch studies that received pharmaceutical industry funding have on average slightly higher effect sizes than other studies after controlling for some trial characteristics (Etter 2007). The practical effect of these considerations is that the magnitude of the effectiveness of nicotine replacement may be smaller than our estimates suggest.

This review excludes studies with less than six months follow up from the start of treatment; the outcome used reflects the effect of NRT after the end of active treatment. A comparison of abstinence rates during treatment and abstinence at one year (Fagerstrom 2003) suggests that the relative effect of NRT declines once active therapy stops, that is, people who quit with the help of NRT are a little more likely to relapse after they discontinue treatment than those on placebo. The relative effect of NRT could continue to decline even after a year of follow up. A meta-analysis comparing one-year and long-term outcomes in twelve NRT trials with follow up beyond one year suggested that the relative efficacy did not change, with similar relapse rates in the active and placebo groups, but further relapse does reduce the absolute difference in quit rates (Etter 2006).

AUTHORS' CONCLUSIONS

Implications for practice

1. All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation. They increase the rate of long-term quitting by approximately 50% to 70% regardless of setting. These conclusions apply to smokers who are motivated to quit and who have high levels of nicotine dependence. There is little evidence about the role of NRT for individuals smoking less than 10 to 15 cigarettes a day.

2. The choice of which form to use should reflect patient needs, tolerability, and cost considerations. Patches are likely to be easier to use than gum or nasal spray or inhaler but patches cannot be used for relief of acute cravings.

3. Eight weeks of patch therapy is as effective as longer courses and there is no evidence that tapered therapy is better than abrupt withdrawal. Wearing the patch only during waking hours (16 hours a day) is as effective as wearing it for 24 hours a day.

4. If gum is used, it may be offered on a fixed dose or ad lib basis. For highly dependent smokers, or those who have failed with 2 mg gum, 4 mg gum should be offered.

5. There is borderline evidence for a small benefit from use of the nicotine patch at doses higher than the standard dose (21 mg for 24 hours or 15 mg for 16 hours).

6. There is evidence of benefit from combining the nicotine patch with an acute dosing type (e.g. gum) to allow ad lib dosing compared to use of a single form.

7. The effectiveness of NRT in terms of the risk ratio appears to be largely independent of the intensity of additional support provided. Provision of more intensive levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT. It should be noted though that the absolute increase in success rates attributable to the use of NRT will be larger when the baseline chance of success is already raised by the provision of intensive behavioural support.

8. There is minimal evidence that a repeated course of NRT in patients who have relapsed after recent use of nicotine patches will result in a small additional probability of quitting.

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9. NRT does not lead to an increased risk of adverse cardiovascular events in smokers with a history of cardiovascular disease.

10. Nicotine patch was less effective than bupropion in one trial, but further trials are needed to confirm this. Any decision about which pharmacotherapies to use should take into account potential adverse effects as well as benefits.

Implications for research

Further research is required in several areas:

1. Direct comparisons between the various forms of NRT and between different doses and durations of treatment.

2. Use of combinations of different forms of NRT.

3. Direct comparisons between NRT and newer pharmacotherapies including varenicline

4. The effect of starting NRT use before the quit date.

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REFERENCES

References to studies included in this review

Abelin 1989 *{published data only}*

* Abelin T, Buehler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet* 1989;**1**(8628):7–10.

Abelin T, Ehrsam R, Buhler-Reichert A, Imhof PR, Muller P, Thommen A. Effectiveness of a transdermal nicotine system in smoking cessation studies. *Methods and Findings in Experimental and Clinical Pharmacology* 1989;**11**:205–14.

Muller P, Abelin T, Ehrsam R, Imhof P, Howald H, Mauli D. The use of transdermal nicotine in smoking cessation. *Lung* 1990;**168**: 445–53.

Ahluwalia 1998 *{published data only}*

Ahluwalia JS, McNagny SE, Clark WS. Smoking cessation among inner-city African Americans using the nicotine transdermal patch. *Journal of General Internal Medicine* 1998;**13**:1–8.

Ahluwalia 2006 *{published data only}*

* Ahluwalia JS, Okuyemi K, Nollen N, Choi WS, Kaur H, Pulvers K, et al.The effects of nicotine gum and counseling among African American light smokers: A 2 x 2 factorial design. *Addiction* 2006; **101**:883–91.

Nollen NL, Mayo MS, Sanderson CL, Okuyemi KS, Choi WS, Kaur H, et al.Predictors of quitting among African American light smokers enrolled in a randomized, placebo-controlled trial. *Journal of General Internal Medicine* 2006;**21**:590–5.

Okuyemi KS, Cox LS, Nollen NL, Snow TM, Kaur H, Choi W, et

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

al.Baseline characteristics and recruitment strategies in a randomized clinical trial of African-American light smokers. *American Journal of Health Promotion* 2007;**21**:183–91.

Areechon 1988 *{published data only}*
Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. *Clinical Therapeutics* 1988;**10**:183–6.

Blondal 1989 *{published data only}*
Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. *Archives of Internal Medicine* 1989;**149**:1818–21.

Blondal 1997 *{published data only}*
* Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *European Respiratory Journal* 1997;**10**:1585–90.

Blondal T, Olafsdottir I, Gunnarsdottir R, Franzon M, Westin A. Controlled trial of nicotine nasal spray as an aid to stopping smoking [abstract]. *European Respiratory Journal* 1993;**6**(Suppl 17):631S.

Blondal 1999 *{published data only}*
* Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;**318**:285–9.

Blondal T, Ludviksdottir D, Gudmundsson L, Olafsdottir I, Gustavsson G, Westin A. Efficacy of nicotine nasal spray added to transdermal nicotine patches in smoking cessation [Abstract]. Proceedings of the 10th World Conference on Tobacco or Health; Aug 24-28; Beijing, China. 1997:48.

Bohadana 2000 *{published data only}*
Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Gender differences in quit rates following smoking cessation with combination nicotine therapy: influence of baseline smoking behavior. *Nicotine & Tobacco Research* 2003;**5**(1):111–6.

* Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation - A randomized, double-blind, placebo-controlled trial. *Archives of Internal Medicine* 2000;**160**:3128–34.

Bohandana AB, Nilsson F, Martinet Y. Nicotine inhaler and nicotine patch: a combination therapy for smoking cessation [abstract]. *Nicotine & Tobacco Research* 1999;**1**(2):189.

Bolin 1999 *{published data only}*
Bolin LJ, Antonuccio DO, Follette WC, Krumpe P. Transdermal nicotine: the long and the short of it. *Psychology of Addictive Behaviors* 1999;**13**:152–6.

Br Thor Society 1983 *{published data only}*
Research Committee of the British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. Report by a subcommittee of the Research Committee of the British Thoracic Society. *British Medical Journal* 1983;**286**(6365): 595–7.

Buchkremer 1988 *{published data only}*
* Buchkremer G, Bents H, Horstmann M, Opitz K, Tolle R. Combination of behavioral smoking cessation with transdermal nicotine substitution. *Addictive Behaviors* 1989;**14**:229–38.

Buchkremer G, Bents H, Minneker E, Opitz K. Long-term effects of a combination of transdermal nicotine administration with behavior therapy for smoking cessation [Langfristige Effekte einer Kombination von transdermaler Nikotinzufuhr mit Verhaltenstherapie zur Raucherentwohnung]. *Nervenarzt* 1988;**59**:488–90.

Campbell 1987 *{published data only}*
Campbell IA, Lyons E, Prescott R. Do nicotine chewing-gum and postal encouragement add to doctors' advice. *Practitioner* 1987;**231**: 114–7.

Campbell 1991 *{published data only}*
Campbell IA, Prescott RJ, Tjeder-Burton SM. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. *Respiratory Medicine* 1991;**85**:155–7.

Campbell 1996 *{published data only}*
Burton S, Campbell IA, Prescott RJ. Nicotine patches versus placebo in 235 hospital patients [abstract 191]. Abstracts from the 8th World Conference on Tobacco or Health, Mar 30-Apr 3; Buenos Aires, Argentina. 1992.

* Campbell IA, Prescott RJ, Tjeder-Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. *Respiratory Medicine* 1996;**90**: 47–51.

CEASE 1999 *{published data only}*
Tonnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, et al.Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE trial. *European Respiratory Journal* 1999;**13**:238–46.

Cinciripini 1996 *{published data only}*
* Cinciripini PM, Cinciripini LG, Wallfisch A, Haque W. Behavior therapy and the transdermal nicotine patch: Effects on cessation outcome, affect, and coping. *Journal of Consulting and Clinical Psychology* 1996;**64**:314–23.

Cinciripini PM, Wetter DW, Fouladi RT, Blalock JA, Carter BL, Cinciripini LG, et al.The effects of depressed mood on smoking cessation: mediation by postcessation self-efficacy. *Journal of Consulting and Clinical Psychology* 2003;**71**:292–301.

Clavel 1985 *{published data only}*
Clavel F, .Benhamou S. Tobacco withdrawal. Comparison of the efficacy of various methods. Intermediate results of a comparative study [French] [Désintoxcation tabagique. Comparison de l'efficacité de differentes méthodes. Résultats intermédiaires d'une étude comparative]. *Presse Médicale* 1984;**13**:975–7.

* Clavel F, Benhamou S, Company Huertas A, Flamant R. Helping people to stop smoking: randomised comparison of groups being treated with acupuncture and nicotine gum with control group. *British Medical Journal* 1985;**291**:1538–9.

Clavel-Chapelon 1992 *{published data only}*
* Clavel-Chapelon F, Paoletti C, Benhamou S. A randomised 2 x 2 factorial design to evaluate different smoking cessation methods. *Revue d'Epidemiologie et de Sante Publique* 1992;**40**:187–90.

Cooper 2005 *{published data only}*
* Cooper TV, Klesges RC, Debon MW, Zbikowski SM, Johnson KC, Clemens LH. A placebo controlled randomized trial of the effects of phenylpropanolamine and nicotine gum on cessation rates and

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postcessation weight gain in women. *Addictive Behaviors* 2005;**30**: 61–75.

Cooper TV, Montgomery GV, Debon MW, Zbikowski SM, Klesges RC, Johnson KC. The effects of PPA and nicotine gum on cessation rates and post cessation weight gain in women [POS3-46]. Abstract Book. Society for Research on Nicotine and Tobacco 9th Annual Meeting, New Orleans, LA. 2003.

Croghan 2003 *{published data only}*

Croghan GA, Hurt RD, Croghan IT, Sloan J, Novotny P, Loprinzi C. Comparison of a 15 mg transdermal nicotine patch alone versus nicotine nasal spray alone versus both for smoking cessation. *Journal of Addictive Diseases* 1998;**17**:121.

* Croghan GA, Sloan JA, Croghan IT, Novotny P, Hurt RD, DeKrey WL, et al.Comparison of nicotine patch alone versus nicotine nasal sparay alone versus a combination for treating smokers: A minimal intervention, randomized multicenter trial in a nonspecialized setting. *Nicotine & Tobacco Research* 2003;**5**(2):181–7.

Dale 1995 *{published data only}*

* Dale LC, Hurt RD, Offord KP, Lawson GM, Croghan IT, Schroeder DR. High-dose nicotine patch therapy - percentage of replacement and smoking cessation. *JAMA* 1995;**274**:1353–8.

Dale LC, Schroeder DR, Wolter TD, Croghan IT, Hurt RD, Offord KP. Weight change after smoking cessation using variable doses of transdermal nicotine replacement. *Journal of General Internal Medicine* 1998;**13**:9–15.

Daughton 1991 *{published data only}*

* Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, et al.Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Archives of Internal Medicine* 1991; **151**:749–52.

Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, et al.Effects of transdermal nicotine as an adjunct in smoking cessation therapy. A double-blind randomized study controlled with placebo [Italian] [Effetti del rilascio transdermico di nicotina come terapia di supporto per lo svezzamento dal fumo di sigaretta. Uno studio randomizzato in doppio cieco con controlli trattati con placebo.]. *Archivio Monaldi* 1992;**47**:17–29.

Daughton 1998 *{published data only}*

Daughton D, Susman J, Sitorius M, Belenky S, Millatmal T, Nowak R, et al.Transdermal nicotine therapy and primary care. Importance of counseling, demographic, and participant selection factors on 1-year quit rates. The Nebraska Primary Practice Smoking Cessation Trial Group. *Archives of Family Medicine* 1998;**7**:425–30.

Dautzenberg 2001 *{published and unpublished data}*

Dautzenberg B, Peiffer G, Toulouse F, Yvinec MJ, Jacob N, Kienzler JL. Randomized trial assessment of nicotinell lozenge 1mg, a new oral nicotine replacement therapy. Abstract Book. Society for Research on Nicotine and Tobacco 3rd European Conference, Paris. 2001:55.

* Dautzenberg B, Ruff F, Vaucher M, Maillon P, Jacob N, Kienzler JL, et al.First demonstration of the good efficacy/safety ratio of Nicotinell 1mg Lozenge (NL 1mg), a new form of nicotine substitution, by randomised clinical trial. *European Respiratory Journal* 2001; **18 Suppl 33**:12s.

Davidson 1998 *{published data only}*

Davidson M, Epstein M, Burt R, Schaefer C, Whitworth G, McDonald A. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Archives of Family Medicine* 1998;**7**:569–74.

Ehrsam 1991 *{published data only}*

Abelin T, Ehrsam R, Imhof P Muller P, Howald H. Clinical experience with a transdermal nicotine system in healthy nicotine-dependent smokers. In: Wilhemsen L editor(s). *Smoking as a cardiovascular risk factor - new strategies for smoking cessation*. Hogrefe & Huber, 1991:35–46.

Abelin T, Ehrsam R. Buhler-Reichert A, Imhof PR, Muller P, Thommen A, et al.Effectiveness of a transdermal nicotine system in smoking cessation studies. *Methods and Findings in Experimental and Clinical Pharmacology* 1989;**11**:205–14.

* Ehrsam RE, Buhler A, Muller P, Mauli D, Schumacher PM, Howald H, et al.Weaning of young smokers using a transdermal nicotine patch [German] [Entwohnung junger Raucher mit Hilfe eines transdermalen Nikotinpflasters]. *Schweizerische Rundschau fur Medizin Praxis* 1991;**80**:145–50.

Muller P, Abelin T, Ehrsam R, Imhof P, Howald H, Mauli D. The use of transdermal nicotine in smoking cessation. *Lung* 1990;**168**: 445–53.

Fagerstrom 1982 *{published data only}*

* Fagerstrom KO. A comparison of psychological and pharmacological treatment in smoking cessation. *Journal of Behavioral Medicine* 1982;**5**:343–51.

Fagerstrom KO. Tolerance, withdrawal and dependence on tobacco and smoking termination. *International Review of Applied Psychology* 1983;**32**:29–52.

Fagerstrom 1984 *{published data only}*

Fagerstrom KO. Effects of nicotine chewing gum and follow-up appointments in physician-based smoking cessation. *Preventive Medicine* 1984;**13**:517–27.

Fee 1982 *{published data only}*

Fee WM, Stewart MJ. A controlled trial of nicotine chewing gum in a smoking withdrawal clinic. *Practitioner* 1982;**226**:148–51.

Fiore 1994A *{published data only}*

Elan Pharmaceutical Research Corp. NDA 19-983 for Approval of PROSTEP. Study 90-03 1992.

* Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 1994;**105**:524–33.

Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. *JAMA* 1994;**271**:589–94.

Fiore 1994B *{published data only}*

Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 1994;**105**:524–33.

Fortmann 1995 *{published data only}*

Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention - resuIts from a trial using pop-

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ulation-based recruitment. *Journal of Consulting and Clinical Psychology* 1995;**63**:460–8.

Garcia 1989 *{published data only}*

Quilez Garcia C, Hernando Arizaleta L, Rubio Diaz A, Estruch Riba J, Fornes Ramis MV. Treatment for smoking with nicotine gum in primary care. A double blind trial [Spanish] [Tratamiento del tabaquismo, con chicle de nicotina, en atencion primaria. Estudio a doble ciego]. *Revista Clinica Espanol* 1993;**192**(4):157–61.

* Quilez Garcia C, Hernando Arizaleta L, Rubio Diaz A, Granero Fernandez EJ, Vila Coll MA, Estruch Riba JSO. Double-blind study of the efficacy of nicotine chewing gum for smoking cessation in the primary care setting [Spanish] [Estudio doble ciego de la eficacia del chicle de nicotina en la deshabituacion tabaquica dentro del ambito de la atencion primaria]. *Atencion Primaria* 1989;**6**:719–26.

Garvey 2000 *{published data only}*

Doherty K, Militello FS, Kinnunen T, Garvey AJ. Nicotine gum dose and weight gain after smoking cessation. *Journal of Consulting and Clinical Psychology* 1996;**64**:799–807.

* Garvey AJ, Kinnunen T, Nordstrom BL, Utman CH, Doherty K, Rosner B, et al.Effects of nicotine gum dose by level of nicotine dependence. *Nicotine & Tobacco Research* 2000;**2**:53–63.

Nordstrom BL, Kinnunen T, Utman CH, Garvey AJ. Long-term effects of nicotine gum on weight gain after smoking cessation. *Nicotine & Tobacco Research* 1999;**1**:259–68.

Gilbert 1989 *{published data only}*

Gilbert JR, Wilson DM, Best JA, Taylor DW, Lindsay EA, Singer J, et al.Smoking cessation in primary care. A randomized controlled trial of nicotine-bearing chewing gum. *Journal of Family Practice* 1989; **28**:49–55.

Glavas 2003a *{published data only}*

Glavas D, Rumboldt M, Rumboldt Z. Smoking cessation with nicotine replacement therapy among health care workers: randomized double-blind study. *Croatian Medical Journal* 2003;**44**:219–24.

Glavas 2003b *{published data only}*

Glavas D, Rumboldt Z. Smoking cessation using the transdermal nicotine system [Croatian] [Odvikavanje od pusenja transdermalnim nikotinskim sustavom]. *Lijecnicki Vjesnik* 2003;**125**(1-2):8–12.

Glover 2002 *{published data only}*

Glover E, Glover P, Franzon M, Sullivan R, Cerullo C. Safety and efficacy of a nicotine sublingual tablet for smoking cessation [abstract]. Smoke Free 21st Century, 2nd European Conference on Tobacco or Health; Las Palmas de Gran Canaria. 1999.

Glover ED, Franzon M, Sullivan CR, Cerullo CL. A nicotine sublingual tablet for treating tobacco dependence [Abstract]. Society for Research on Nicotine and Tobacco 3rd Europe Conference, Paris September 2001 Abstract Book. 2001:48.

* Glover ED, Glover PN, Franzon M, Sullivan CR, Cerullo CC, Howell RM, et al.A comparison of a nicotine sublingual tablet and placebo for smoking cessation. *Nicotine & Tobacco Research* 2002;**4**: 441–50.

Glover ED, Glover PN, Franzon M, Sullivan R, Sullivan P, Howell R, et al.A nicotine sublingual tablet for smoking cessation: 6-month data [Abstract]. Proceedings of the 10th World Conference on Tobacco or Health; Aug 24-28 Beijing, China. 1997.

Goldstein 1989 *{published data only}*

Goldstein MG, Niaura R, Follick MJ, Abrams DB. Effects of behavioral skills training and schedule of nicotine gum administration on smoking cessation. *American Journal of Psychiatry* 1989;**146**:56–60.

Gourlay 1995 *{published data only}*

Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;**311**(7001):363–6.

Gross 1995 *{published data only}*

Gross J, Johnson J, Sigler L, Stitzer ML. Dose effects of nicotine gum. *Addictive Behaviors* 1995;**20**:371–81.

Hall 1985 *{published data only}*

Hall SM, Tunstall C, Rugg D, Jones R, Benowitz N. Nicotine gum and behavioral treatment in smoking cessation. *Journal of Consulting and Clinical Psychology* 1985;**53**:256–8.

Hall 1987 *{published data only}*

Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. *Journal of Consulting and Clinical Psychology* 1987;**55**:603–5.

Hall 1996 *{published data only}*

Hall SM, Munoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, et al.Mood management and nicotine gum in smoking treatment - a therapeutic contact and placebo-controlled study. *Journal of Consulting and Clinical Psychology* 1996;**64**:1003–9.

Hand 2002 *{published data only}*

Hand S, Edwards S, Campbell IA, Cannings R. Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. *Thorax* 2002;**57**:715–8.

Harackiewicz 1988 *{published data only}*

Harackiewicz JM, Blair LW, Sansone C, Epstein JA, Stuchell RN. Nicotine gum and self-help manuals in smoking cessation: an evaluation in a medical context. *Addictive Behaviors* 1988;**13**:319–30.

Hays 1999 *{published data only}*

* Hays JT, Croghan GA, Offord KP, Hurt RD, Schroeder DR, Wolter TD, et al.Over-the-counter nicotine patch therapy for smoking cessation: Results from randomized, double-blind, placebo-controlled and open label trials. *American Journal of Public Health* 1999;**89**: 1701–7.

Hays JT, Croghan GA, Offord KP, Wolter TD, Nides MA, Davidson M. Over-the-Counter (OTC) transdermal nicotine patch therapy [abstract]. *Journal of Addictive Diseases* 1997;**16**:136.

Hays JT, Croghan IT, Offord KP, Hurt RD, Schroeder DR, Wolter TD, et al.Over the counter 22mg nicotine patch therapy for smoking cessation: results from randomized double-blind placebo-controlled and open label trials. Abstract Book. Society for Research on Nicotine and Tobacco 5th Annual Meeting, San Diego (CA) 1999.

Herrera 1995 *{published data only}*

Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995;**108**:447–51.

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Hilleman 1994 *{published data only}*

Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *Journal of Clinical Pharmacology* 1994;**34**(3):222–4.

Hjalmarson 1984 *{published data only}*

Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. *JAMA* 1984; **252**:2835–8.

Hjalmarson 1994 *{published data only}*

Hjalmarson AI, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. *Archives of Internal Medicine* 1994;**154**:2567–72.

Hjalmarson 1997 *{published data only}*

Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. *Archives of Internal Medicine* 1997;**157**: 1721–8.

Huber 1988 *{published data only}*

Huber D. Combined and separate treatment effects of nicotine chewing gum and self-control method. *Pharmacopsychiatry* 1988;**21**:461–2.

Hughes 1989 *{published data only}*

Hughes JR, Gust SW, Keenan R, Fenwick JW, Skoog K, Higgins ST. Long-term use of nicotine vs placebo gum. *Archives of Internal Medicine* 1991;**151**:1993–8.

* Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. *JAMA* 1989;**261**: 1300–5.

Hughes 1990 *{published data only}*

Hughes JR, Gust SW, Keenan RM, Fenwick JW. Effect of dose on nicotine's reinforcing, withdrawal-suppression and self-reported effects. *Journal of Pharmacology and Experimental Therapeutics* 1990; **252**:1175–83.

Hughes 1991 *{published data only}*

Hughes JR, Wadland WC, Fenwick JW, Lewis J, Bickel WK. Effect of cost on the self-administration and efficacy of nicotine gum: a preliminary study. *Preventive Medicine* 1991;**20**:486–96.

Hughes 1999 *{published data only}*

Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, et al.Are higher doses of nicotine replacement more effective for smoking cessation?. *Nicotine & Tobacco Research* 1999; **1**:169–74.

Hughes 2003 *{published data only}*

Hughes JR, Novy P, Hatsukami DK, Jensen J, Callas PW. Efficacy of nicotine patch in smokers with a history of alcoholism. *Alcoholism-Clinical and Experimental Research* 2003;**27**:946–54.

Hurt 1990 *{published data only}*

Elan Pharmaceutical Research Corp. NDA 19-983 for Approval of PROSTEP. Study 88-02 1992.

* Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch-a randomized double-blind placebo-controlled trial. *Mayo Clinic Proceedings* 1990;**65**:1529–37.

Hurt 1994 *{published data only}*

Hurt RD, Dale LC, Fredrickson PA, Caldwell CC, Lee GA, Offord KP, et al.Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: One-year outcome and percentage of nicotine replacement. *JAMA* 1994;**271**:595–600.

ICRF 1994 *{published data only}*

David SP, Munafo MR, Murphy MF, Walton RT, Johnstone EC. The serotonin transporter 5-HTTLPR polymorphism and treatment response to nicotine patch: follow-up of a randomized controlled trial. *Nicotine & Tobacco Research* 2007;**9**(2):225–231.

* Imperial Cancer Research Fund General Practice research Group. Randomised trial of nicotine patches in general practice: results at one year.. *BMJ* 1994;**308**:1476–7.

Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice.. *BMJ* 1993;**306**: 1304–8.

Johnstone EC, Yudkin Pl, Hey K, Roberts SJ, Welch SJ, Murphy MF, et al.Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. *Pharmacogenetics* 2004;**14** (2):83–90.

Yudkin P, Hey K, Roberts S, Welch S, Murphy M, Walton R. Abstinence from smoking eight years after participation in randomised controlled trial of nicotine patch. *BMJ* 2003;**327**(7405):28–29.

Yudkin P, Munafo M, Hey K, Roberts S, Welch S, Johnstone E, et al.Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. *BMJ* 2004;**328**(7446):989–90.

Jamrozik 1984 *{published data only}*

Jamrozik K, Fowler G, Vessey M, Wald N. Placebo controlled trial of nicotine chewing gum in general practice. *British Medical Journal* 1984;**289**:794–7.

Jarvis 1982 *{published data only}*

Jarvis MJ, Raw M, Russell MAH, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. *British Medical Journal* 1982; **285**:537–40.

Jensen 1991 *{published data only}*

Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation. *Thorax* 1990;**45**:831–4.

Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect on smoking cessation of silver acetate, nicotine and ordinary chewing gum. Influence of smoking history. *Psychopharmacology (Berl)* 1991;**104**:470–4.

* Jensen EJ, Schmidt E, Pedersen B, Dahl R. The effect of nicotine, silver acetate, and placebo chewing gum on the cessation of smoking. The influence of smoking type and nicotine dependence. *International Journal of the Addictions* 1991;**26**:1223–31.

Jorenby 1995 *{published data only}*

Jorenby DE, Smith SS, Fiore MC, Hurt RD, Offord KP, Crogham IT, et al.Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 1995;**274**:1347–52.

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Jorenby 1999 *{published data only}*

Durcan MJ, White J, Jorenby DE, Fiore MC, Rennard SI, Leischow SJ, et al.Impact of prior nicotine replacement therapy on smoking cessation efficacy. *American Journal of Health Behaviors* 2002;**26**:213–20.

Jamerson BD, Nides M, Jorenby DE, Donahue R, Garrett P, Johnston JA, et al.Late-term smoking cessation despite initial failure: an evaluation of bupropion sustained release, nicotine patch, combination therapy, and placebo. *Clinical Therapeutics* 2001;**23**:744–52.

* Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al.A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine* 1999;**340**:685–91.

Joseph 1996 *{published data only}*

Joseph AM, Antonnucio DO. Lack of efficacy of transdermal nicotine in smoking cessation. *New England Journal of Medicine* 1999;**341**: 1157–8.

* Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al.The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *New England Journal of Medicine* 1996;**335**:1792–8.

Kalman 2006 *{published data only}*

Kalman D, Denison H, Penk W, Peer J, Kresman D, Monti P. Early findings from a treatment study of heavy smokers in alcohol recovery (PO2 34). Abstract Book. Society for Research on Nicotine and Tobacco 7th Annual Meeting March 23-23 Seattle, Washington. 2001: 61.

* Kalman D, Kahler CW, Garvey AJ, Monti PM. High-dose nicotine patch therapy for smokers with a history of alcohol dependence: 36-week outcomes. *Journal of Substance Abuse Treatment* 2006;**30**:213–7.

Kalman D, Kahler CW, Tirch D, Kaschub C, Penk W, Monti PM. Twelve-week outcomes from an investigation of high-dose nicotine patch therapy for heavy smokers with a past history of alcohol dependence. *Psychology of Addictive Behaviors* 2004;**18**:78–82.

Kalman D, Tirch D, Penk W, Denison H. An investigation of predictors of nicotine abstinence in a smoking cessation treatment study of smokers with a past history of alcohol dependence. *Psychology of Addictive Behaviors* 2002;**16**:346–9.

Kalman D, Tirch D, Penk W, Kaschub C. Preliminary findings from a treatment study of heavy smokers in alcohol recovery: end of treatment outcomes (PO2 38). Abstract Book. Society for Research on Nicotine and Tobacco 8th Annual Meeting February 20-23 Savannah, Georgia. 2002:58.

Killen 1984 *{published data only}*

Killen JD, Maccoby N, Taylor CB. Nicotine gum and self-regulation training in smoking relapse prevention. *Behavior Therapy* 1984;**15**: 234–48.

Killen 1990 *{published data only}*

Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. *JAMA* 1988;**260**:1575–80.

* Killen JD, Fortmann SP, Newman B, Varady A. Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. *Journal of Consulting and Clinical Psychology* 1990;**58**:85–92.

Killen 1997 *{published data only}*

Killen JD, Fortmann SP, Davis L, Varady A. Nicotine patch and self-help video for cigarette smoking cessation. *Journal of Consulting and Clinical Psychology* 1997;**65**:663–72.

Killen 1999 *{published data only}*

* Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy?. *Experimental and Clinical Psychopharmacology* 1999;**7**:226–33.

Kornitzer 1987 *{published data only}*

Kornitzer M, Kittel F, Dramaix M, Bourdoux P. A double blind study of 2 mg versus 4 mg nicotine-gum in an industrial setting. *Journal of Psychosomatic Research* 1987;**31**:171–6.

Kornitzer 1995 *{published data only}*

* Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Preventive Medicine* 1995;**24**:41–7.

Kornitzer M, Boutsen M, Thijs J, Gustavsson G. Efficiency and safety of combined use of nicotine patches and nicotine gum in smoking cessation: a placebo controlled double-blind trial [abstract]. *European Respiratory Journal* 1993;**6**(Suppl 17):630S.

Kralikova 2002 *{published and unpublished data}*

Kralikova E, Kozak J, Rasmussen T, Cort N. The clinical benefits of NRT-supported smoking reduction. *Nicotine & Tobacco Research* 2002;**4**:243.

Leischow 1996 *{published data only}*

Leischow SJ, Nilsson F, Franzon M, Hill A, Otte P, Merikle EP. Efficacy of the nicotine inhaler as an adjunct to smoking cessation. *American Journal of Health Behavior* 1996;**20**:364–71.

Leischow 1999 *{published data only}*

* Leischow SJ, Muramoto ML, Cook GN, Merikle EP, Castellini SM, Otte PS. OTC nicotine patch: effectiveness alone and with brief physician intervention. *American Journal of Health Behavior* 1999; **23**:61–9.

Leischow 2004 *{published data only}*

* Leischow SJ, Ranger-Moore J, Muramoto ML, Matthews E. Effectiveness of the nicotine inhaler for smoking cessation in an OTC setting. *American Journal of Health Behavior* 2004;**28**:291–301.

Leischow SJ, Ranger-Moore J, Muramoto ML, Matthews E. The safety and effectiveness of the nicotine inhaler for smoking cessation in an over-the-counter setting (POS4-78). Abstract Book. Society for Research on Nicotine and Tobacco 9th Annual Meeting, New Orleans, LA. 2003:100.

Lerman 2004 *{published data only}*

Lerman C, Jepson C, Wileyto EP, Epstein LH, Rukstalis M, Patterson F, et al.Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. *Neuropsychopharmacology* 2006;**31**(1):231–42.

* Lerman C, Kaufmann V, Rukstalis M, Patterson F, Perkins K, Audrain McGovern J, et al.Individualizing nicotine replacement ther-

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apy for the treatment of tobacco dependence: a randomized trial. *Annals of Internal Medicine* 2004;**140**:426–33.

Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, Pinto A, et al.Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clinical Pharmacology & Therapeutics* 2006;**79**:600–8.

Lerman C, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Restine S, et al.The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. *Pharmacogenomics Journal* 2004;**4**(3): 184–92.

Malaiyandi V, Lerman C, Benowitz NL, Jepson C, Patterson F, Tyndale RF. Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. *Molecular Psychiatry* 2006;**11**(4):400–409.

Patterson F, Jepson C, Kaufmann V, Rukstalis M, Audrain-McGovern J, Kucharski S, et al.Predictors of attendance in a randomized clinical trial of nicotine replacement therapy with behavioral counseling. *Drug and Alcohol Dependence* 2003;**72**:123–31.

Lewis 1998 *{published data only}*

Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: A randomized clinical trial. *Preventive Medicine* 1998;**27**(2):296–303.

Llivina 1988 *{published data only}*

Salvador Llivina T, Marin Tuya D, Gonzalez Quintana J, Iniesta Torres C, Castellvi Barrera E, Muriana Saez C, et al.Treatment of smoking: efficacy of the use of nicotine chewing gum. Double-blind study [Spanish] [Tratamiento del tabaquismo: eficacia de la utilizacion del chicle de nicotina. Estudio a doble ciego]. *Medicina Clinica Barcelona* 1988;**90**:646–50.

Malcolm 1980 *{published data only}*

Malcolm RE, Sillett RW, Turner JA, Ball KP. The use of nicotine chewing gum as an aid to stopping smoking. *Psychopharmacology Series* 1980;**70**:295–6.

Marshall 1985 *{published data only}*

Marshall A, Raw M. Nicotine chewing gum in general practice: effect of follow up appointments. *British Medical Journal* 1985;**290**:1397–8.

McGovern 1992 *{published data only}*

McGovern PG, Lando HA. An assessment of nicotine gum as an adjunct to Freedom from Smoking cessation clinics. *Addictive Behaviors* 1992;**17**:137–47.

Molyneux 2003 *{published data only}*

Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, et al.Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. *Thorax* 2003;**58**(6):484–8.

Moolchan 2005 *{published data only}*

Franken FH, Pickworth WB, Epstein DH, Moolchan ET. Smoking rates and topography predict adolescent smoking cessation following treatment with nicotine replacement therapy. *Cancer Epidemiology, Biomarkers & Prevention* 2006;**15**:154–7.

* Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al.Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics* 2005; **115**(4):e407–e414.

Robinson ML, Schroeder JR, Moolchan ET. Adolescent smokers screened for a nicotine replacement treatment trial: Correlates of eligibility and enrollment. *Nicotine & Tobacco Research* 2006;**8**:447–54.

Mori 1992 *{unpublished data only}*

Mori T, Shimao T, Yulchiro G, Namiki M, Hyachi T. A clinical trial of nicotine chewing gum for smoking cessation [abstract 428]. 8th World Conference on Tobacco or Health; Buenos Aires, Argentina 1992.

Nakamura 1990 *{unpublished data only}*

Nakamura M, Saito J, Oshima A, Miyamoto M, Matushita A, Endo S. Effect of nicotine chewing gun in smoking cessation classes. The Global War. Proceedings of the 7th World Conference on Tobacco and Health; Perth, Western Australia. Perth: Health Department of Western Australia, 1990:665–7.

Nebot 1992 *{published data only}*

Nebot M, Cabezas C. Does nurse counseling or offer of nicotine gum improve the effectiveness of physician smoking-cessation advice?. *Family Practice Research Journal* 1992;**12**:263–70.

Niaura 1994 *{published data only}*

Niaura R, Goldstein MG, Abrams DB. Matching high and low-dependence smokers to self-help treatment with or without nicotine replacement. *Preventive Medicine* 1994;**23**:70–7.

Niaura 1999 *{published data only}*

Niaura R, Abrams DB, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD. Cue exposure treatment for smoking relapse prevention: A controlled clinical trial. *Addiction* 1999;**94**(5):685–96.

Ockene 1991 *{published data only}*

* Ockene JK, Kristeller J, Goldberg R, Amick TL, Pekow PS, Hosmer D, et al.Increasing the efficacy of physician-delivered smoking interventions: a randomized clinical trial. *Journal of General Internal Medicine* 1991;**6**:1–8.

Ockene JK, Kristeller J, Pbert L, Hebert JR, Luippold R, Goldberg RJ, et al.The physician-delivered smoking intervention project: can short-term interventions produce long-term effects for a general outpatient population?. *Health Psychology* 1994;**13**:278–81.

Oncken 2007 *{published data only}*

* Oncken C, Cooney J, Feinn R, Lando H, Kranzler HR. Transdermal nicotine for smoking cessation in postmenopausal women. *Addictive Behaviors* 2007;**32**:296–309.

Oncken C, Cooney J, Lando H, Feinn R, Kranzler H. Transdermal nicotine for smoking cessation in postmenopausal women (POS1-045). Abstract Book. Society for Research on Nicotine and Tobacco 11th Annual Meeting, Prague. 2005.

Otero 2006 *{published data only}*

* Otero UB, Perez CA, Szklo M, Esteves GA, dePinho MM, Szklo AS, et al.Randomized clinical trial: effectiveness of the cognitive-behavioral approach and the use of nicotine replacement transdermal patches for smoking cessation among adults in Rio de Janeiro, Brazil [Portugese] [Ensaio clinico randomizado: efetividade da abordagem cognitivo–comportamental e uso de adesivos transdermicos

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de reposicao de nicotina, na cessacao de fumar, em adultos residentes no Municipio do Rio de Janeiro, Brasil]. *Cadernos de Saude Publica* 2006;**22**:439–49.

Page 1986 *{published data only}*

Page AR, Walters DJ, Schlegel RP, Best JA. Smoking cessation in family practice: the effects of advice and nicotine chewing gum prescription. *Addictive Behaviors* 1986;**11**:443–6.

Paoletti 1996 *{published data only}*

Paoletti P, Fornai E, Maggiorelli F, Puntoni R, Viegi G, Carrozzi L, et al.Importance of baseline cotinine plasma values in smoking cessation: results from a double blind study with nicotine patch. *European Respiratory Journal* 1996;**9**:643–51.

Perng 1998 *{published data only}*

Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. *American Journal of Respiratory and Critical Care Medicine* 1999;**159**(3SS):A735.

* Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. *Journal of the Formosan Medical Association* 1998;**97**:547–51.

Piper 2007 *{published data only}*

Piper ME, Federman EB, Bolt DM, Smith SS, Fiore MC, Baker TB. Mediators of bupropion treatment effects (PA5-6). Abstract Book. Society for Research on Nicotine and Tobacco 12th Annual Meeting, Orlando, FL. 2006:27.

* Piper ME, Federman EB, McCarthy DE, Bolt DM, Smith SS, Fiore MC, et al.Efficacy of bupropion alone and in combination with nicotine gum. *Nicotine & Tobacco Research* 2007;**9**:947–54.

Piper ME, Federman EB, Smith SS, Fiore MC, Baker TB. Efficacy of bupropion SR alone and combined with 4-mg gum (PA2-2). Abstract Book. Society for Research on Nicotine and Tobacco 10th Annual Meeting, Phoenix, AZ. 2004:18.

Pirie 1992 *{published data only}*

Pirie PL, McBride CM, Hellerstedt WL, Jeffery RW, Hatsukami DK, Allen S, et al.Smoking cessation in women concerned about weight. *American Journal of Public Health* 1992;**82**:1238–43.

Prapavessis 2007 *{published data only}*

Prapavessis H, Cameron L, Baldi JC, Robinson S, Borrie K, Harper T, et al.The effects of exercise and nicotine replacement therapy on smoking rates in women. *Addictive Behaviors* 2007;**32**:1416–32.

Puska 1979 *{published data only}*

Puska P, Bjorkqvist S, Koskela K. Nicotine-containing chewing gum in smoking cessation: a double blind trial with half year follow-up. *Addictive Behaviors* 1979;**4**:141–6.

Puska 1995 *{published data only}*

Puska P, Korhonen HJ, Vartiainen E, Urjanheimo EL, Gustavsson G, Westin A. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tobacco Control* 1995;**4**:231–5.

Richmond 1993 *{published data only}*

Richmond R, Heather N. General Practitioner interventions for smoking cessation: past results and future prospects. *Behaviour Change* 1990;**7**:110–9.

Richmond RL, Makinson RJ, Giugni AA, Webster IW. General Practitioner smoking interventions in Australia: results of studies over the past ten years. The Global War, Proceedings of the 7th World Conference on Tobacco and Health. Perth, Western Australia. Perth: Health Department of Western Australia, 1990:657–60.

* Richmond RL, Makinson RJ, Kehoe LA, Giugni AA, Webster IW. One-year evaluation of three smoking cessation interventions administered by general practitioners. *Addictive Behaviors* 1993;**18**: 187–99.

Richmond 1994 *{published data only}*

* Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Medical Journal of Australia* 1994;**161**:130–5.

Richmond RL, Kehoe L, Neto ACdA. Effectiveness of a 24-hour transdermal nicotine patch in conjunction with a cognitive behavioural programme: One year outcome. *Addiction* 1997;**92**:27–31.

Rose 1994 *{published data only}*

* Rose JE, Behm FM, Westman EC, Levin ED, Stein RM, Ripka GV. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clinical Pharmacology and Therapeutics* 1994;**56**:86–99.

Rose JE, Westman EC, Behm FM. Nicotine/mecamylamine combination treatment for smoking cessation [published erratum appears in Drug Development Research 1997;40:215]. *Drug Development Research* 1996;**38**:243–256.

Rose 1998 *{published data only}*

* Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Experimental and Clinical Psychopharmacology* 1998;**6**:331–43.

Rose JE, Westman EC, Behm FM. Nicotine/mecamylamine combination treatment for smoking cessation [published erratum appears in Drug Development Research 1997;40:215]. *Drug Development Research* 1996;**38**:243–56.

Rose 2006 *{published data only}*

Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine & Tobacco Research* 2006;**8**:89–101.

Roto 1987 *{published data only}*

Roto P, Ojala A, Sundman K, Jokinen K, Peltomakl R. Nicotine gum and withdrawal from smoking. *Suomen Laakarllehtl* 1987;**36**:3445–8.

Russell 1983 *{published data only}*

Russell MA, Merriman R, Stapleton J, Taylor W. Effect of nicotine chewing gum as an adjunct to general practitioner's advice against smoking. *British Medical Journal (Clinical Research Ed.)* 1983;**287**: 1782–5.

Sachs 1993 *{published data only}*

Sachs DPL, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Archives of Internal Medicine* 1993;**153**:1881–90.

Schneider 1985A *{published data only}*

Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *American Journal of Psychiatry* 1984;**141**:790–1.

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schneider NG, Jarvik ME. Nicotine gum vs. placebo gum: comparisons of withdrawal symptoms and success rates. *NIDA Research Monograph* 1985;**53**:83–101.

* Schneider NG, Jarvik ME, Forsythe AB, Read LL, Elliott ML, Schweiger A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. *Addictive Behaviors* 1983;**8**:253–61.

Schneider 1985B *{published data only}*

Schneider NG, Jarvik ME. Nicotine gum vs. placebo gum: comparisons of withdrawal symptoms and success rates. *NIDA Research Monograph* 1985;**53**:83–101.

* Schneider NG, Jarvik ME, Forsythe AB, Read LL, Elliott ML, Schweiger A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. *Addictive Behaviors* 1983;**8**:253–61.

Schneider 1995 *{published data only}*

Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, et al.Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995;**90**:1671–82.

Schneider 1996 *{published data only}*

* Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo controlled trial. *Addiction* 1996;**91**:1293–306.

Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: A double-blind, placebo-controlled trial [abstract]. *Addiction* 1997;**92**:630.

Schuurmans 2004 *{published data only}*

* Schuurmans MM, Diacon AH, van Biljon X, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized controlled trial. *Addiction* 2004;**99**:634–40.

Schuurmans MM, Diacon AH, van Biljon X, Westin A, Landfeldt B, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms in smokers subsequently quitting with the nicotine patch: a double-blind randomised controlled trial [https://www.ersnetsecure.org/public/prg_congres.abstract?ww_i_presentation=6711). European Respiratory Society Annual Congress, Stockholm. 2002.

Segnan 1991 *{published data only}*

* Segnan N, Ponti A, Battista RN, Senore C, Rosso S, Shapiro SH, et al.A randomized trial of smoking cessation interventions in general practice in Italy. *Cancer Causes and Control* 1991;**2**:239–46.

Senore C, Battista RN, Ponti A, Segnan N, Shapiro SH, Rosso S, et al.Comparing participants and nonparticipants in a smoking cessation trial: Selection factors associated with general practitioner recruitment activity. *Journal of Clinical Epidemiology* 1999;**52**:83–9.

Senore C, Battista RN, Shapiro SH, Segnan N, Ponti A, Rosso S, et al.Predictors of smoking cessation following physicians' counseling. *Preventive Medicine* 1998;**27**:412–21.

Shiffman 2002 (2mg) *{published data only}*

Dresler CM, Shiffman S, Strahs KR. Safety profile of the new nicotine polacrilex lozenge (PO1 36). Society for Research on Nicotine and Tobacco 8th Annual Meeting: Savannah, Georgia. 2002.

Shiffman S. Nicotine lozenge efficacy in light smokers. *Drug & Alcohol Dependence* 2005;**77**:311–4.

Shiffman S. Use of more nicotine lozenges leads to better success in quitting smoking. *Addiction* 2007;**102**:809–14.

* Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. *Archives of Internal Medicine* 2002;**162**:1267–76.

Shiffman S, Dresler CM, Rohay JM. Successful treatment with a nicotine lozenge of smokers with prior failure in pharmacological therapy. *Addiction* 2004;**99**:83–92.

Shiffman 2002 (4mg) *{published data only}*

* Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. *Archives of Internal Medicine* 2002;**162**:1267–76.

Sonderskov 1997 *{published data only}*

Sonderskov J, Olsen J, Meillier L, Overvad OK, Sabroe S. [The effect of transdermal nicotine patches in smoking cessation. A randomized trial in pharmacy customers in Denmark] [Danish]. *Ugeskrift for Laeger* 1999;**161**:593–7.

* Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: A randomized trial among over- the-counter customers in Denmark. *American Journal of Epidemiology* 1997;**145**:309–18.

Stapleton 1995 *{published data only}*

Russell MAH, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe Uet al. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993;**306**(6888):1308–12.

* Stapleton JA, Russell MAH, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, et al.Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995;**90**:31–42.

Sutherland 1992 *{published data only}*

Stapleton JA, Sutherland G, Russell MAH. How much does relapse after one year erode effectiveness of smoking cessation treatments? Long term follow up of randomised trial of nicotine nasal spray. *BMJ* 1998;**316**(7134):830–1.

* Sutherland G, Stapleton JA, Russell MAH, Jarvis MJ, Hajek P, Belcher M, et al.Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;**340**:324–9.

TNSG 1991 *{published data only}*

Daughton DM, Fortmann SP, Glover ED, Hatsukami DK, Heatley SA, Lichtenstein E, et al.The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. *Preventive Medicine* 1999;**28**:113–8.

Swan GE, Jack LM, Ward MM. Subgroups of smokers with different success rates after use of transdermal nicotine. *Addiction* 1997;**92**:207–17.

* Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation. Six-month results from two multicenter controlled clinical trials. Transdermal Nicotine Study Group. *JAMA* 1991;**266**:3133–8.

Tonnesen 1988 *{published data only}*

* Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, et al.Effect of nicotine chewing gum in combination

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

with group counseling on the cessation of smoking. *New England Journal of Medicine* 1988;**318**:15–8.

Tonnesen 1991 *{published data only}*

Mikkelsen KL, Tonnesen P, Norregaard J. Three-year outcome of two- and three-year sustained abstainers from a smoking cessation study with nicotine patches. *Journal of Smoking-Related Disorders* 1994;**5**:95–100.

Norregaard J, Tonnesen P, Petersen L. Predictors and reasons for relapse in smoking cessation with nicotine and placebo patches. *Preventive Medicine* 1993;**22**:261–71.

Tonnesen P, Norregaard J, Sawe U. Two-year outcome in a smoking cessation trial with a nicotine patch. *Journal of Smoking-Related Disorders* 1992;**3**:241–5.

* Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *New England Journal of Medicine* 1991;**325**:311–5.

Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of nicotine patches in smoking cessation [Danish] [En dobbeltblind undersogelse af nikotinplaster ved rygeafvaenning]. *Ugeskrift for Laeger* 1992;**154**:251–4.

Tonnesen 1993 *{published data only}*

Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;**269**:1268–71.

Tonnesen 2000 *{published data only}*

Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *European Respiratory Journal* 2000;**16**:717–22.

Tonnesen 2006 *{published data only}*

Pbert L. Nurse-conducted smoking cessation in patients with COPD, using nicotine sublingual tablets and behavioral support. *Chest* 2006; **130**:314–6.

* Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. *Chest* 2006;**130**:334–42.

Villa 1999 *{published data only}*

Villa RS, Alvarez ABD, Hermida JRF. Effectiveness of a multicomponent program to quit smoking with and without nicotine chewing gum [Spanish] [Eficacia de un programa multicomponente para dejar de fumar con y sin chicle de nicotina]. *Psicologia Conductual* 1999;**7**:107–18.

Wallstrom 2000 *{published data only}*

Pharmacia, Upjohn. *Nicorette Nicotine Microtab Monograph*. Chester: Adis International, 1998:Adis International, 1998.

Wallstrom M, Nilsson F, Hirsch JM. A double-blind placebo controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation [abstract]. European Respiratory Journal 1997; Vol. 10, issue Suppl 25:440S.

* Wallstrom M, Nilsson F, Hirsch JM. A randomized double-blind placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000;**95**(8):1161–71.

Westman 1993 *{published data only}*

Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation. A randomized trial with telephone counseling. *Archives of Internal Medicine* 1993;**153**:1917–23.

Wisborg 2000 *{published data only}*

* Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: A randomized controlled study. *Obstetrics & Gynecology* 2000;**96**(6):967–71.

Wong 1999 *{published data only}*

* Wong GY, Wolter TD, Croghan GA, Croghan IT, Offord KP, Hurt RD. A randomized trial of naltrexone for smoking cessation. *Addiction* 1999;**94**:1227–37.

Zelman 1992 *{published data only}*

Zelman DC, Brandon TH, Jorenby DE, Baker TB. Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. *Journal of Consulting and Clinical Psychology* 1992;**60**:943–52.

References to studies excluded from this review

Allen 2005 *{published data only}*

* Allen SS, Hatsukami D, Brintnell DM, Bade T. Effect of nicotine replacement therapy on post-cessation weight gain and nutrient intake: A randomized controlled trial of postmenopausal female smokers. *Addictive Behaviors* 2005;**30**:1273–80.

Allen SS, Hatsukami DK, Bade T, Center B. Transdermal nicotine use in postmenopausal women: does the treatment efficacy differ in women using and not using hormone replacement therapy?. *Nicotine & Tobacco Research* 2004;**6**(5):777–88.

Aubin 2006 *{published data only}*

Aubin HJ, Luthringer R, Demazieres A, Dupont C, Lagrue G. Comparison of the effects of a 24-hour nicotine patch and a 16-hour nicotine patch on smoking urges and sleep. *Nicotine & Tobacco Research* 2006;**8**:193–201.

Batra 2005 *{published data only}*

* Batra A, Klingler K, Landfeldt B, Friederich HM, Westin A, Danielsson T. Smoking reduction treatment with 4-mg nicotine gum: A double-blind, randomized, placebo-controlled study. *Clinical Pharmacology & Therapeutics* 2005;**78**:689–96.

Landfeldt B, Batra A, Friederich HM, Klingler K, Westin A. Smoking reduction with a 4 mg nicotine gum - final results from a placebo-controlled trial over 13 months. Society for Research on Nicotine and Tobacco 5th European Meeting November 20-22 2003 Padua: Abstract book. 2003.

Bolliger 2000 *{published data only}*

Bolliger CT. Practical experiences in smoking reduction and cessation. *Addiction* 2000;**95**(1 S1):S19–S24.

Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin A, et al.Influence of long-term smoking reduction on health risk markers and quality of life. *Nicotine & Tobacco Research* 2002;**4**: 433–9.

* Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin A, et al.Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ* 2000;**321** (7257):329–333.

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Bolliger 2007 *{published data only}*

Bolliger CT, van B, X, Axelsson A. A Nicotine Mouth Spray for Smoking Cessation: A Pilot Study of Preference, Safety and Efficacy. *Respiration* 2007;**74**:196–201.

Brantmark 1973 *{published data only}*

Brantmark B, Ohlin P, Westling H. Nicotine-containing chewing gum as an anti-smoking aid. *Psychopharmacologia* 1973;**31**:191–200.

Carpenter 2003 *{published data only}*

Carpenter MJ, Hughes JR, Keely JP. Effect of smoking reduction on later cessation: a pilot experimental study. *Nicotine & Tobacco Research* 2003;**5**(2):155–62.

Chou 2004 *{published data only}*

Chou KR, Chen R, Lee JF, Ku CH, Lu RB. The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. *International Journal of Nursing Studies* 2004;**41**:321–30.

Christen 1984 *{published data only}*

Christen AG, Drook C, McDonald JL, Stookey G, Olson B. Efficacy of nicotine chewing gum in facilitating smoking cessation. *Journal of the American Dental Association* 1984;**108**:594–7.

Cohen 1989a *{published data only}*

Cohen SJ, Stookey GK, Katz BP, Drook CA, Christen AG. Helping smokers quit: a randomized controlled trial with private practice dentists. *Journal of the American Dental Association* 1989;**118**:41–5.

Cohen 1989b *{published data only}*

Cohen SJ, Stookey GK, Katz BP, Drook CA, Smith DM. Encouraging primary care physicians to help smokers quit. A randomised, controlled trial. *Annals of Internal Medicine* 1989;**110**:648–52.

Croghan 2007 *{published data only}*

Clark MM, Hurt RD, Croghan I, Patten CA, Novotny P, Sloan JA, et al.The prevalence of weight concerns in a smoking abstinence clinical trial (POS2-84). Society for Research on Nicotine and Tobacco 12th Annual Meeting February 15-18, Orlando, Florida. 2006.

Croghan IT, Hurt RD, Croghan GA, Sloan JA. Comparing nicotine inhaler, bupropion and nicotine inhaler plus bupropion in treating tobacco dependence [abstract]. *Nicotine & Tobacco Research* 2005;**7**(4):680–1.

* Croghan IT, Hurt RD, Dakhil SR, Croghan GA, Sloan JA, Novotny PJ, et al.Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. *Mayo Clinic Proceedings* 2007;**82**:186–95.

Dey 1999 *{published data only}*

Dey P, Foy R, Woodman M, Fullard B, Gibbs A. Should smoking cessation cost a packet? A pilot randomized controlled trial of the cost-effectiveness of distributing nicotine therapy free of charge. *British Journal of General Practice* 1999;**49**:127–8.

Elan Pharm 88-02 *{published data only}*

Elan Pharmaceutical Research Corp. NDA 19-983 for Approval of PROSTEP. Study 88-02 1992.

Elan Pharm 90-03 *{published data only}*

Elan Pharmaceutical Research Corp. NDA 19-983 for Approval of PROSTEP. Study 90-03 1992.

Etter 2004 *{published data only}*

Dar R, Stronguin F, Etter JF. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *Journal of Consulting & Clinical Psychology* 2005;**73**:350–3.

* Etter JF, Laszlo E, Perneger TV. Postintervention effect of nicotine replacement therapy on smoking reduction in smokers who are unwilling to quit: Randomized trial. *Journal of Clinical Psychopharmacology* 2004;**24**(2):174–9.

Etter JF, Laszlo E, Zellweger JP, Perrot C, Perneger TV. Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: a randomized trial. *Journal of Clinical Psychopharmacology* 2002;**22**:487–95.

Fagerstrom 1993 *{published data only}*

Fagerstrom KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology (Berl)* 1993;**111**:271–7.

Fagerstrom 1997 *{published data only}*

* Fagerstrom KO, Tejding R, Westin A, Lunell E. Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker?. *Tobacco Control* 1997;**6**:311–6.

Fagerstrom 2000 *{published data only}*

Fagerstrom KO, Hughes JR, Rasmussen T, Callas PW. Randomised trial investigating effect of a novel nicotine delivery device (Eclipse) and a nicotine oral inhaler on smoking behaviour, nicotine and carbon monoxide exposure, and motivation to quit. *Tobacco Control* 2000;**9**:327–33.

Finland unpublished *{unpublished data only}*

Anon. Combination NRT; Improving efficacy in smoking cessation. McNeil Consumer Healthcare booklet, 2007. Short term outcomes reported on p17.

Foulds 1993 *{published data only}*

Foulds J, Stapleton J, Hayward M, Russell MA, Feyerabend C, Fleming T, et al.Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. A placebo-controlled trial. *Archives of Family Medicine* 1993;**2**:417–23.

Glover 1992 *{published data only}*

* Glover ED, Glover PN, Sullivan CR, Sullivan P, Nilsson F, Sawe U. Nicotine inhaler versus placebo in smoking cessation [abstract 237]. Abstracts from the 8th World Conference on Tobacco or Health, Buenos Aires, Argentina. 1992.

Hajek 1999 *{published data only}*

* Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine* 1999;**159**:2033–8.

West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000;**149**:198–202.

Hanson 2003 *{published data only}*

Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. *Nicotine & Tobacco Research* 2003;**5**(4):515–26.

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Haustein 2003 *{published data only}*

* Haustein KO, Batra A, Landfeldt B, Westin A. The effect of short-term or long-term reduction on smoking cessation; results from a placebo controlled smoking reduction study with the nicotine gum. *Nicotine & Tobacco Research* 2003;**5**:278.

Pfizer. Summary of Clinical Efficacy. Application for licensing of Nicorette Inhalator/Gum for smoking reduction leading to cessation. Company data NICORE-1013-273-SU.

Hotham 2006 *{published data only}*

* Hotham ED, Gilbert AL, Atkinson ER. A randomised-controlled pilot study using nicotine patches with pregnant women. *Addictive Behaviors* 2006;**31**:641–48.

Hughes 1989b *{published data only}*

Hughes JR, Gulliver SB, Amori G, Mireault GC, Fenwick JF. Effect of instructions and nicotine on smoking cessation, withdrawal symptoms and self-administration of nicotine gum. *Psychopharmacology (Berl)* 1989;**99**:486–91.

Hurt 1995 *{published data only}*

Hurt RD, Dale LC, Offord KP, Croghan IT, Hays JT, Gomez Dahl L. Nicotine patch therapy for smoking cessation in recovering alcoholics. *Addiction* 1995;**90**(11):1541–6.

Hurt 2003 *{published data only}*

Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, et al.Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *Journal of Clinical Oncology* 2003;**21**(5):914–20.

Jarvik 1984 *{published data only}*

Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *American Journal of Psychiatry* 1984;**141**:790–1.

Kapur 2001 *{published data only}*

Kapur B, Hackman R, Selby P, Klein J, Koren G. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. *Current Therapeutic Research Clinical and Experimental* 2001;**62**:274–8.

Korberly 1999 *{unpublished data only}*

Korberly B, Gustavsson G, Kruse E. Over-the-counter efficacy of a 15 mg daytime nicotine patch for smoking cessation: a randomized multicenter trial. Abstract book. Society for Research on Nicotine and Tobacco 4th European Conference October 3-5 Santander, Spain. 2002:23.

* Korberly BH, Maguire MK. An open label multicenter trial to evaluate and compare the efficacy of nicotrol 15mg as part of an OTC intervention package or as a prescription as an aid in smoking cessation. Abstract Book. Society for Research on Nicotine and Tobacco Fifth Annual Meeting, San Diego CA. 1999.

Kozak 1995 *{published data only}*

Kozak J, Fagerstrom KO, Sawe U. High-dose treatment with the nicotine patch. *International Journal of Smoking Cessation* 1995;**4**(2): 26–8.

Krumpe 1989 *{published data only}*

Krumpe P, Malani N, Adler J. Efficacy of transdermal nicotine administration as an adjunct for smoking cessation in heavily nicotine addicted smokers. *Annual Review of Respiratory Disease* 1989;**139**: A337.

Kupecz 1996 *{published data only}*

* Kupecz D, Prochazka A. A comparison of nicotine delivery systems in a multimodality smoking cessation program. *Nurse Practitioner* 1996;**21**(2):73,77–8,81.

Landfeldt 1998 *{unpublished data only}*

Landfeldt B, Kruse E, Westin A, Mattson K, Lojander J. Nicotine replacement treatment in heavy smokers: nicotine nasal spray combined with nicotine patch in a double-blind controlled study (abstract). *European Respiratory Journal* 1998;**12**(Suppl 28):154S.

Leischow 1996b *{published data only}*

Leischow SJ, Hill A, Cook G. The effects of transdermal nicotine for the treatment of hispanic smokers. *American Journal of Health Behavior* 1996;**20**:304–11.

Levin 1994 *{published data only}*

Levin ED, Westman EC, Stein RM, Carnahan E, Sanchez M, Herman S, et al.Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms, and attenuates rewarding effects of smoking. *Journal of Clinical Psychopharmacology* 1994;**14**:41–9.

Lin 1996 *{published data only}*

Lin HN. The effectiveness of nicotine patch for smoking cessation. *Chinese Psychiatry* 1996;**10**:29–38.

Marsh 2005 *{published data only}*

Marsh HS, Dresler CM, Choi JH, Targett DA, Gamble ML, Strahs KR. Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: A 12-week, randomized, open-label study. *Clinical Therapeutics* 2005; **27**(10):1571–87.

McCarthy 2006 *{published data only}*

McCarthy DE, Piasecki TM, Fiore MC, Baker TB. Life before and after quitting smoking: an electronic diary study. *Journal of Abnormal Psychology* 2006;**115**(3):454–66.

Meier 1990 *{published data only}*

Meier Lammermann E, Mayer M, Boleski PL. Combination of transdermal nicotine substitution and behavioural group therapy in smoking cessation. *European Respiratory Journal* 1990;**3**(Suppl 10):168S.

Merz 1993 *{published data only}*

* Merz PG, Keller Stanislawski B, Huber T, Woodcock BG, Rietbrock N. Transdermal nicotine in smoking cessation and involvement of non- specific influences. *International Journal of Clinical Pharmacology Therapy and Toxicology* 1993;**31**:476–82.

Millie 1989 *{published data only}*

Millie A, Berriau T, Paget D, Philardeau V, Postal MJ, Dautzenberg B, et al.Can weight gain during weaning from smoking be limited using nicotine gum? [French] [Peut–on limiter la prise de poids chez les fumeurs lors du sevrage tabagique en utilisant la gomme a la nicotine?]. *Revue de Pneumonologie Clinique* 1989;**45**:243–9.

Minneker 1989 *{published data only}*

Minneker E, Buchkremer G, Block M. The effect of different dosages of a transdermal nicotine substitution system on the success rate of smoking cessation therapy. *Methods and Findings in Experimental and Clinical Pharmacology* 1989;**11**:219–22.

Molander 2000 *{published data only}*

Molander L, Lunell E, Fagerstrom KO. Reduction of tobacco withdrawal symptoms with a sublingual nicotine tablet: a placebo controlled study. *Nicotine & Tobacco Research* 2000;**2**:187–91.

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Mooney 2005 *{published data only}*

Mooney M, Babb D, Jensen J, Hatsukami D. Interventions to increase use of nicotine gum: A randomized, controlled, single-blind trial. *Nicotine & Tobacco Research* 2005;**7**(4):565–79.

Mulligan 1990 *{published data only}*

Mulligan SC, Masterson JG, Devane JG, Kelly JG. Clinical and pharmacokinetic properties of a transdermal nicotine patch. *Clinical Pharmacology and Therapeutics* 1990;**47**:331–7.

Okuyemi 2007 *{published data only}*

Okuyemi KS, James AS, Mayo MS, Nollen N, Catley D, Choi WS, et al.Pathways to health: a cluster randomized trial of nicotine gum and motivational interviewing for smoking cessation in low-income housing. *Health Education & Behavior* 2007;**34**:43–54.

Pomerleau 2003 *{published data only}*

Lerman C, Audrain J, Patterson F, Kaufmann V, Rukstalis M, Wileyto EP, et al.Differential response to nicotine replacement therapies in obese and non-obese women (PA2-6). Abstract Book. Society for Research on Nicotine and Tobacco 9th Annual Meeting, New Orleans, LA. 2003.

* Pomerleau OF, Pomerleau CS, Marks JL, Snedecor SM, Mehringer AM, Namenek-Brouwer RJ, et al.Prolonged nicotine patch use in quitters with past abstinence-induced depressed mood. *Journal of Substance Abuse Treatment* 2003;**24**(1):13–18.

Rennard 2006 *{published data only}*

Rennard SI, Glover E, Leischow S, Daughton DM, Glover P, Muramoto M. Efficacy of nicotine inhaler in smoking reduction. *Nicotine & Tobacco Research* 2002;**4**:380.

* Rennard SI, Glover ED, Leischow S, Daughton DM, Glover PN, Muramoto M, et al.Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. *Nicotine & Tobacco Research* 2006;**8**:555–64.

Roddy 2006 *{published data only}*

Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. *Tobacco Control* 2006;**15**:373–6.

Rose 1990 *{published data only}*

Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. *Clinical Pharmacology and Therapeutics* 1990;**47**:323–30.

Sachs 1995 *{published data only}*

Sachs DPL. Effectiveness of the 4-mg dose of nicotine polacrilex for the initial treatment of high-dependent smokers. *Archives of Internal Medicine* 1995;**155**:1973–80.

Shiffman 2000a *{published data only}*

Shiffman S, Khayrallah M, Nowak R. Efficacy of the nicotine patch for relief of craving and withdrawal 7-10 weeks after cessation. *Nicotine & Tobacco Research* 2000;**2**:371–8.

Shiffman 2000b *{published data only}*

Shiffman S, Elash CA, Paton SM, Gwaltney CJ, Paty JA, Clark DB, et al.Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 2000;**95**(8):1185–95.

Shiffman 2002a *{published data only}*

Shiffman S, Dresler CM, Gorsline J, Dimarino ME. The efficacy of nicotine patch in an over-the-counter environment: results from a randomized, double-blind, placebo-controlled trial (PO130). Abstract book, 11th World Conference on Tobacco or Health, 6-11 August, Chicago, Illinois. 2000; Vol. 1.

* Shiffman S, Gorsline J, Gorodetzky CW. Efficacy of over-the-counter nicotine patch. *Nicotine & Tobacco Research* 2002;**4**:477–83.

Shiffman 2002b *{published data only}*

Shiffman S, Rolf CN, Hellebusch SJ, Gorsline J, Gorodetzky CW, Chiang YK, et al.Real-world efficacy of prescription and over-the-counter nicotine replacement therapy. *Addiction* 2002;**97**:505–16.

Shiffman 2006 *{published data only}*

Ferguson SG, Shiffman S, Gwaltney CJ. Does reducing withdrawal severity mediate nicotine patch efficacy? A randomized clinical trial. *Journal of Consulting and Clinical Psychology* 2006;**74**:1153–61.

Shiffman S, Ferguson SG, Gwaltney CJ. Immediate hedonic response to smoking lapses: Relationship to smoking relapse, and effects of nicotine replacement therapy. *Psychopharmacology* 2006;**184**(3-4): 608–18.

Shiffman S, Ferguson SG, Gwaltney CJ, Balabanis MH, Shadel WG. Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology* 2006;**184**(3-4):637–44.

* Shiffman S, Scharf DM, Shadel WG, Gwaltney CJ, Dang Q, Paton SM, et al.Analyzing milestones in smoking cessation: illustration in a nicotine patch trial in adult smokers. *Journal of Consulting & Clinical Psychology* 2006;**74**:276–85.

Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. Attentional bias predicts outcome in smoking cessation. *Health Psychology* 2003;**22**:378–87.

Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. Cue-provoked craving and nicotine replacement therapy in smoking cessation. *Journal of Consulting and Clinical Psychology* 2004; **72**(6):1136–43.

Sutherland 1999 *{published data only}*

Anon. Combination NRT; Improving efficacy in smoking cessation. McNeil Consumer Healthcare booklet. Short term outcomes reported on p18.

* Sutherland G. A placebo-controlled double-blind combination trial of nicotine spray and patch [abstract]. *Nicotine & Tobacco Research* 1999;**1**:186.

Sutherland 2005 *{published data only}*

Sutherland G, Stapleton JA, Russell MA. Randomized placebo-controlled trial of nicotine nasal spray in general practice. *Nicotine & Tobacco Research* 2005;**7**(4):686.

Sutton 1987 *{published data only}*

Sutton S, Hallett R. Randomized trial of brief individual treatment for smoking using nicotine chewing gum in a workplace setting. *American Journal of Public Health* 1987;**77**:1210–1. [MEDLINE: 87296451]

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sutton 1988 *{published data only}*

Sutton S, Hallett R. Smoking intervention in the workplace using videotapes and nicotine chewing gum. *Preventive Medicine* 1988;**17**: 48–59.

Thorsteinsson 2001 *{published data only}*

Thorsteinsson HS, Gillin JC, Patten CA, Golshan S, Sutton LD, Drummond S, et al.The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. *Neuropsychopharmacology* 2001;**24**(4):350–8.

Tzivoni 1998 *{published data only}*

Tzivoni D, Keren A, Meyler S, Khoury Z, Lerer T, Brunel P. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovascular Drugs and Therapy* 1998;**12**:239–44.

Uyar 2005 *{unpublished data only}*

Uyar M, Bayram N, Filiz A, Elbek O, Topçu A, Dikensoy O, et al.Comparison of nicotine patch and bupropion in treating tobacco dependence. *European Respiratory Journal* 2005;**26**(Suppl 49):388s.

Velicer 2006 *{published data only}*

* Velicer WF, Friedman RH, Fava JL, Gulliver SB, Keller S, Sun X, et al.Evaluating nicotine replacement therapy and stage-based therapies in a population-based effectiveness trial. *Journal of Consulting & Clinical Psychology* 2006;**74**:1162–72.

Velicer WF, Keller S, Friedman RH, Fava JL, Gulliver SB, Ward RM, et al.Comparing participants and nonparticipants recruited for an effectiveness study of nicotine replacement therapy. *Annals of Behavioral Medicine* 2005;**29**:181–91.

Vial 2002 *{published data only}*

Vial RJ, Jones TE, Ruffin RE, Gilbert AL. Smoking cessation program using nicotine patches linking hospital to the community. *Journal of Pharmacy Practice and Research* 2002;**32**(1):57–62.

Warner 2005 *{published data only}*

Warner DO, Patten CA, Ames SC, Offord KP, Schroeder DR. Effect of nicotine replacement therapy on stress and smoking behavior in surgical patients. *Anesthesiology* 2005;**102**(6):1138–46.

Wennike 2003 *{published data only}*

Wennike P, Danielsson T, Landfeldt B, Westin A, Tonnesen P. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction* 2003;**98**(10):1395–402.

Wiseman 2005 *{published data only}*

Wiseman EJ, Williams DK, McMillan DE. Effectiveness of payment for reduced carbon monoxide levels and noncontingent payments on smoking behaviors in cocaine-abusing outpatients wearing nicotine or placebo patches. *Experimental and Clinical Psychopharmacology* 2005;**13**(2):102–10.

Working Group 1994 *{published data only}*

Working Group for the Study of Transdermal Nicotine. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease. *Archives of Internal Medicine* 1994;**154**:989–95.

References to studies awaiting assessment

Garvey 2006 *{unpublished data only}*

* Garvey AJ, Hoskinson RA, Wadler BM, Kinnunen T, Sachs DPL. Individualising nicotine patch dose to match smokers' usual nicotine intake levels (PA9-4). Society for Research on Nicotine and Tobacco 12th Annual Meeting February 15-18, Orlando, Florida. 2006:32.

Mustonen TK, Spencer SM, Hoskinson RA, Sachs DPL, Garvey AJ. The influence of gender, race, and menthol content on tobacco exposure measures. *Nicotine & Tobacco Research* 2005;**7**:581–90.

Hoch 2006 *{published data only}*

* Hoch E, Wittchen HU. Population health perspective on smoking cessation: A randomized controlled trial of different methods in primary health care (RPOS 3-71). Society for Research on Nicotine and Tobacco 12th Annual Meeting February 15-18, Orlando, Florida. 2006.

Sonntag H, Hoch E, Jahn B, Spiegel B, Pfister H, Wittchen HU. Smoking cessation in primary care: implementation effectiveness and optimized allocation. *Suchtmedizin in Forschung und Praxis* 2003;**5** (2):137–41.

Pollak 2007 *{published data only}*

Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, et al.Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *American Journal of Preventive Medicine* 2007; **33**:297–305.

Vikhireva 2003 *{published data only}*

* Vikhireva O, Shalnova S, Deev A. Nicotine replacement therapy in Russia: old wine in new skins? Randomized parallel study of nicotine gum/inhaler in smoking cessation/reduction. Abstract book. Society for Research on Nicotine and Tobacco. Fifth European Conference. November 20-22nd, Padua, Italy. 2003.

Vikhireva O, Shalnova S, Deev A, Levshin V, Radkevich N, Kalinina A. NRT-assisted cessation in Russia: individual and population level benefits. Society for Research on Nicotine and Tobacco 11th Annual Meeting, 20-23 March 2005; Prague, Czech Republic. 2005.

References to ongoing studies

Coleman 2007 *{published data only}*

Coleman T, Thornton J, Britton J, Lewis S, Watts K, Coughtrie MWH, et al.Protocol for the Smoking, Nicotine and Pregnancy (SNAP) trial: Double-blind, placebo-randomised, controlled trial of nicotine replacement therapy in pregnancy. *Bmc Health Services Research* 2007;**7**:2.

Additional references

Altman 2002

Altman DG, .Deeks JJ. Meta-analysis, Simpson's paradox, and the number needed to treat. *BMC Medical Research Methodology* 2002; **2**:3.

Altman 2004

Altman DG, Schulz KF, Moher D. Turning a blind eye: testing the success of blinding and the CONSORT statement. *BMJ* 2004;**328** (7448):1135.

Benowitz 2000

Benowitz NL, Dempsey DA, Goldenberg RL, Hughes JR, Dolan-Mullen P, Ogburn PL, et al.The use of pharmacotherapies for smoking cessation during pregnancy. *Tobacco Control* 2000;**9**:91–4.

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Cahill 2007
Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD006103.pub2]

Cepeda-Benito 2004
Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women. *Journal of Consulting and Clinical Psychology* 2004;**72**:712–22.

CONSORT 1996
Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al.Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *Journal of the American Medical Association* 1996;**276**:637–9.

Cummings 2005
Cummings KM, Hyland A. Impact of nicotine replacement therapy on smoking behavior. *Annual Review of Public Health* 2005;**26**:583–99.

D'Orlando 2004
D'Orlando K, Fox B. Tolerability and pharmacokinetics of single and repeated doses of nicotine with The Straw, a novel nicotine replacement product. *Nicotine & Tobacco Research* 2004;**6**:63–70.

Deeks 2005
Deeks J, Higgins JPT, Altman DG. In: Higgins JPT, Green S, editors. Analysing and presenting results: Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]; Section 8. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 30th October 2007).

Dempsey 2002
Dempsey D, Jacob P, Benowitz L. Accelerated metabolism of nicotine and cotinine in pregnant smokers. *Journal of Pharmacology and Experimental Therapeutics* 2002;**301**:594–8.

Durcan 2002
Durcan MJ, White J, Jorenby DE, Fiore MC, Rennard SI, Leischow SJ, et al.Impact of prior nicotine replacement therapy on smoking cessation efficacy. *American Journal of Health Behaviors* 2002;**26**:213–20.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder CE. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

Etter 2006
Etter JF, Stapleton JA. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. *Tobacco Control* 2006;**15**:280–5.

Etter 2007
Etter JF, Burri M, Stapleton J. The impact of pharmaceutical company funding on results of randomized trials of nicotine replacement therapy for smoking cessation: a meta-analysis (PA9-6). *Addiction* 2007;**102**:815–22.

Fagerstrom 2002
Fagerstrom KO, .Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. *Nicotine & Tobacco Research* 2002;**4**(Suppl 2):S73–S79.

Fagerstrom 2003
Fagerstrom KO. Clinical treatment of tobacco dependence: The endurance of pharmacologic efficacy. *Journal of Clinical Psychiatry Monograph* 2003;**18**:35–40.

Fiore 1992
Fiore MC, Jorenby DE, Baker TB, Kenford SL. Tobacco dependence and the nicotine patch. Clinical guidelines for effective use. *JAMA* 1992;**268**:2687–94.

Fiore 2000
Fiore MC, Bailey WC, Cohen SJ, et al.*Treating Tobacco Use and Dependence. A Clinical Practice Guideline*. Rockville, MD: US Dept of Health and Human Services: AHRQ publication No. 00-0032, 2000.

Franzon 2002
Franzon M, Gustavsson G, Korberly BH. Effectiveness of over-the-counter nicotine replacement therapy. *JAMA* 2002;**288**:3109–10.

Greenland 1998
Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998;**18**:297–308.

Henningfield 2005
Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. *CA Cancer Journal for Clinicians* 2005;**55**:281–99.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557–60.

Hughes 1995
Hughes JR. Treatment of nicotine dependence. Is more better?. *JAMA* 1995;**274**:1390–1.

Hughes 2001
Hughes JR. The effectiveness of over-the-counter nicotine replacement: a rebuttal. *Drug and Alcohol Review* 2001;**20**:319–22.

Hughes 2004a
Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;**99**:29–38.

Hughes 2004b
Hughes JR, Pillitteri JL, Callas PW, Callahan R, Kenny M. Misuse of and dependence on over-the-counter nicotine gum in a volunteer sample. *Nicotine & Tobacco Research* 2004;**6**:79–84.

Hughes 2005
Hughes JR, Adams EH, Franzon MA, Maguire MK, Guary J. A prospective study of off-label use of, abuse of, and dependence on nicotine inhaler. *Tobacco Control* 2005;**14**:49–54.

Hughes 2007
Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD000031.pub3]

Hyland 2005
Hyland A, Rezaishiraz H, Giovino G, Bauer JE, Cummings KM. Over-the-counter availability of nicotine replacement therapy and smoking cessation. *Nicotine & Tobacco Research* 2005;**7**:547–55.

Ikinci 2006
Ikinci G, Senel S, Tokgozoglu L, Wilson CG, Sumnu M. Development and in vitro/in vivo evaluations of bioadhesive buccal tablets for nicotine replacement therapy. *Pharmazie* 2006;**61**:203–7.

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Italy ISS 2004
Osservatorio Fumo, Alcol e Droga. *Linee guida cliniche per promuovere la cessazione dellabitudine al fumo*. Rome: Istituto Superiore di Sanita, 2004.

Joseph 2003
Joseph AM, Fu SS. Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. *Progress in Cardiovascular Diseases* 2003;**45**:429–41.

Lancaster 2000
Lancaster T, Silagy C, Fowler G. Training health professionals in smoking cessation. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD000214.]

Le Foll 2005
Le Foll B, Melihan-Cheinin P, Rostoker G, Lagrue G. Smoking cessation guidelines: evidence-based recommendations of the French Health Products Safety Agency. *European Psychiatry* 2005;**20**:431–41.

McClure 2006
McClure JB, Swan GE. Tailoring nicotine replacement therapy: rationale and potential approaches. *Central Nervous System Drugs* 2006; **20**:281–91.

Meine 2005
Meine TJ, Patel MR, Washam JB, Pappas PA, Jollis JG. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *American Journal of Cardiology* 2005;**95**: 976–8.

Mooney 2004
Mooney M, White T, Hatsukami D. The blind spot in the nicotine replacement therapy literature: assessment of the double-blind in clinical trials. *Addictive Behaviors* 2004;**29**(4):673–84.

Munafo 2004a
Munafo M, Bradburn M, Bowes L, David S. Are there sex differences in transdermal nicotine replacement therapy patch efficacy? A meta-analysis. *Nicotine & Tobacco Research* 2004;**6**:769–76.

Munafo 2004b
Munafo M, Bradburn M, Bowes L, David S. Investigating subgroups in smoking cessation treatment response: Response to Perkins. *Nicotine & Tobacco Research* 2004;**6**:865–7.

NZ NACHD 2002
National Advisory Committee on Health and Disability. *Guidelines for smoking cessation: revised 2002*. Wellington, New Zealand: National Health Committee, 2002.

Palmer 1992
Palmer KJ, Buckley MM, Faulds D. Transdermal Nicotine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. *Drugs* 1992;**44**:498–529.

Park 2002
Park CR, Munday DL. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. *International Journal of Pharmaceutics* 2002;**237**(1-2):215–26.

Perkins 2004
Perkins KA. Obstacles to determining individual differences in the efficacy of smoking cessation medications. *Nicotine & Tobacco Research* 2004;**6**:765–7.

Pierce 2002
Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA* 2002;**288**: 1260–4.

Schneider 2004
Schneider NG, Olmstead RE, Nides M, Mody FV, Otte Colquette P, Doan K, et al.Comparative testing of 5 nicotine systems: initial use and preferences. *American Journal of Health Behavior* 2004;**28**: 72–86.

Shiffman 2003
Shiffman S, Hughes JR, Pillitteri JL, Burton SL. Persistent use of nicotine replacement therapy: an analysis of actual purchase patterns in a population based sample. *Tobacco Control* 2003;**12**:310–6.

Shiffman 2005
Shiffman S, Di Marino ME, Sweeney CT. Characteristics of selectors of nicotine replacement therapy. *Tobacco Control* 2005;**14**:346–55.

Simes 1986
Simes RJ. Publication bias: the case for an international registry of clinical trials. *Journal of Clinical Oncology* 1986;**4**(10):1529–41.

Stead 2002
Stead LF, Davis RM, Fiore MC, Hatsukami DK, Raw M, West R. Effectiveness of over-the-counter nicotine replacement therapy. *JAMA* 2002;**288**:3109–10.

Stead 2007
Stead LF, Lancaster T. Interventions to reduce harm from continued tobacco use. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD005231.pub2]

Stewart 1993
Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference?. *Lancet* 1993;**341**(8842): 418–22.

Sweeney 2001
Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. *CNS Drugs* 2001;**15**:453–67.

TNWG 1994
Transdermal Nicotine Working Group. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. *Archives of Internal Medicine* 1994;**154**:989–95.

Wallstrom 1999
Wallstrom M, Sand L, Nilsson F, Hirsch JM. The long-term effect of nicotine on the oral mucosa. *Addiction* 1999;**94**:417–23.

Walsh 2000
Walsh RA, Penman AG. The effectiveness of nicotine replacement therapy over-the-counter. *Drug and Alcohol Review* 2000;**19**:243–7.

Walsh 2001
Walsh RA, .Penman AG. The effectiveness of over-the-counter nicotine replacement: reply to Hughes. *Drug and Alcohol Review* 2001; **20**:322–4.

Walsh 2007
Walsh RA, Stead L, Lancaster T. The Cochrane review on nicotine replacement therapy: incorrect or uncertain classifications of addi-

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tional support levels & Authors' response. *Tobacco Control* 2007;**16**: 215–6.

West 2000
West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;**55**:987–99.

West 2001
West R, .Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology Berl* 2001;**155**:115–22.

West 2007
West R, Zhou X. Is nicotine replacement therapy for smoking cessation effective in the "real world"? Findings from a prospective multinational cohort study. *Thorax* 2007;**62**:998–1002.

Woolacott 2002
Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, et al.The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation. *Health Technology Assessment* 2002; **6**:1–245.

Zwar 2004
Zwar N, Richmond R, Borland R, Stillman S, Cunningham N, Litt J. *Smoking cessation guidelines for Australian General Practice*. Guideline Development Group, 2004.

References to other published versions of this review

Silagy 1994a
Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994; **343**:139–42.

Silagy 1994b
Silagy C, Mant D, Fowler G, Lancaster T. The effectiveness of nicotine replacement therapies in smoking cessation. *Online Journal of Current Clinical Trials* 1994;**Doc No**:113.

Silagy 1996
Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 1996, Issue 2.[Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub3]

Silagy 2001
Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD000146]

Silagy 2002
Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD000146]

Silagy 2004
Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000146.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abelin 1989

Methods	Country: Switzerland Recruitment: 21 Primary care clinics Randomization: method not stated
Participants	199 primary care patients 40% F, av.age 41, av.cpd 27
Interventions	1. Nicotine patch, 24hr, 12 wk with weaning; 21mg smokers of >20 cpd, 14 mg for <20 cpd 2. Placebo patch Level of support: low (number of visits unclear)
Outcomes	Sustained abstinence at 12m (0-3 cigs/wk) Validation: expired CO
Notes	Methods in Lancet paper, Final follow up in Muller 1990

Risk of bias

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Reference #9

Fiore M, Jaen CR, Baker TB, *et al*. Clinical practice guideline treating tobacco use and dependence: 2008 update. A U.S. Public Health Service Report. *Am J Prev Med*. 2008; 35(2): 158-176.

The full report is available online at:

http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

Review

The Effectiveness of the Nicotine Patch for Smoking Cessation

A Meta-analysis

Michael C. Fiore, MD, MPH; Stevens S. Smith, PhD; Douglas E. Jorenby, PhD; Timothy B. Baker, PhD

Objective—To estimate the overall efficacy and optimal use of the nicotine patch for treating tobacco dependence.

Data Sources.—Nicotine patch efficacy studies published through September 1993, identified through MEDLINE, Psychological Abstracts, and Food and Drug Administration new drug applications.

Study Selection.—Double-blind, placebo-controlled nicotine patch studies of 4 weeks or longer with random assignment of subjects, biochemical confirmation of abstinence, and subjects not selected on the basis of specific diseases (eg, coronary artery disease).

Data Extraction.— Pooled abstinence rates and combined odds ratios (ORs) at end of treatment and 6-month follow-up were examined overall and in terms of patch type (16-hour vs 24-hour), patch treatment duration, dosage reduction (weaning), counseling format (individual vs group), and intensity of adjuvant behavioral counseling.

Data Synthesis.—Across 17 studies (n=5098 patients) meeting inclusion criteria, overall abstinence rates for the active patch were 27% (vs 13% for placebo) at the end of treatment and 22% (vs 9% for placebo) at 6 months. The combined ORs for efficacy of active patch vs placebo patch were 2.6 at the end of treatment and 3.0 at 6 months. The active patch was superior to the placebo patch regardless of patch type (16-hour vs 24-hour), patch treatment duration, weaning, counseling format, or counseling intensity. The 16-hour and 24-hour patches appeared equally efficacious, and extending treatment beyond 8 weeks did not appear to increase efficacy. The pooled abstinence data showed that intensive behavioral counseling had a reliable but modest positive impact on quit rates.

Conclusions.—The nicotine patch is an effective aid to quitting smoking across different patch-use strategies. Active patch subjects were more than twice as likely to quit smoking as individuals wearing a placebo patch, and this effect was present at both high and low intensities of counseling. The nicotine patch is an effective smoking cessation aid and has the potential to improve public health significantly.

(*JAMA*. 1994;271:1940-1947)

THE NICOTINE patch, a relatively new treatment for tobacco dependence,[1-4] became available via prescription in the United States in December 1991. The patch has been an extremely popular product; to date, more than 4 million Americans have received prescriptions for the nicotine patch.

Research has not kept pace with the widespread use of the nicotine patch, resulting in many unanswered, but important, questions. For instance, little is known about the optimal duration of patch treatment. While different studies have used different durations of patch treatment, none has systematically varied treatment duration in the same clinical trial. Similarly, no studies have directly compared different brands of patches. Patch marketers have recommended prolonged patch treatments ranging from 8 to 18 weeks.[5-8] Besides having obvious clinical significance, this issue (optimal treatment duration) is of great economic importance given that 1993 patch sales are estimated at $300 million (written communication, Jeff Hoyak, Lederle Laboratories, Wayne, NJ, September 1993). If research demonstrates no added therapeutic benefit for treatment beyond 6 to 8 weeks, this finding would have the potential to decrease significantly the cost of this intervention.

Other important questions concern whether the 16-hour patch and 24-hour patch differ in effectiveness, whether patch effectiveness varies with type or intensity of adjuvant behavioral counseling, whether weaning to a lower-strength nicotine patch enhances efficacy, and whether particular attributes of adjuvant counseling are especially effective when paired with the nicotine patch. As with the issue of treatment duration, these questions are of vital clinical and public health importance but have not yet been addressed adequately in individual studies.[9,10]

The role of adjuvant behavioral counseling is of particular importance, since many third-party payers require that patients who use the patch also attend a behavioral smoking cessation program.[11] In addition, the Food and Drug Administration (FDA) has encouraged this approach by mandating that the four licensed nicotine patch manufacturers in the United States include a clear statement in all package inserts and advertising material that this product should only be prescribed as "part of a comprehensive behavioral smoking cessation program."[5,6]

Research on nicotine gum suggests that its effectiveness is highly dependent on the intensity of the adjuvant counseling with which it is paired.[12-14] When the gum is paired with brief, less intensive behavioral counseling, it has little effect on long-term abstinence rates; when the gum is used with intensive counseling, it can double success rates. If the same findings are obtained with the nicotine patch, the patch's usefulness may be limited because most smokers appear to be unable or unwilling to go through intensive cessation

From the Center for Tobacco Research and Intervention (Drs Fiore, Smith, Jorenby, and Baker) and the Division of General Internal Medicine, Department of Medicine (Drs Fiore and Jorenby), University of Wisconsin Medical School, and the University of Wisconsin Department of Psychology (Drs Smith and Baker), Madison. Drs Fiore, Smith, Jorenby, and Baker have conducted research funded in part by Elan Pharmaceuticals Ltd, Gainesville, Ga, CIBA-GEIGY Corp, Edison, NJ, and Lederle Laboratories, Wayne, NJ. Dr Fiore has also received honoraria for educational activities from CIBA-GEIGY Corp, Marion Merrell Dow Inc, Kansas City, Mo, and Lederle Laboratories.

Reprint requests to the Center for Tobacco Research and Intervention, University of Wisconsin Medical School, 7275 Medical Sciences Center, 1300 University Ave, Madison, WI 53706-1532 (Dr Fiore).

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therapy.[4-9] Conversely, if the nicotine patch is found to be efficacious with minimal or no adjuvant counseling, this would have significant public health importance, and the total cost of this smoking cessation intervention would be markedly reduced. In addition to determining whether the patch is effective with minimal counseling such as might be provided in the typical clinical practice setting, it is important to determine the characteristics of adjuvant behavioral counseling (eg, length and frequency of sessions) that work best with the nicotine patch.

While there is mounting evidence that the nicotine patch increases quit rates over those produced by placebo treatment,[1,2,17] the size of this effect across different settings, treatment characteristics, and populations of smokers has not been determined. It is important to estimate the effectiveness of nicotine patch treatment across diverse settings and populations so that comparisons with other interventions and cost-benefit analyses can be conducted.

This article describes a meta-analysis conducted on all available nicotine patch studies that met specific inclusion criteria (eg, double-blind, placebo-controlled nicotine patch treatment of 4 weeks' duration or longer) as of September 1993. Meta-analysis is a statistical technique that permits the estimation of the impact of variables or treatments across a set of related investigations.[18-20] In this article, we report the results of a meta-analysis that was conducted to evaluate the following issues in relation to the effectiveness of the nicotine patch: (1) overall effectiveness of the nicotine patch at the end of patch treatment and at 6-month follow-up; (2) patch effectiveness as a function of patch type (16-hour vs 24-hour); (3) duration of patch treatment (≤8 weeks vs >8 weeks); (4) weaning (abrupt termination of patch treatment vs dosage reduction); (5) counseling format (individual vs group); and (6) intensity of adjuvant behavioral counseling (low intensity vs high intensity).

METHODS

Studies Included

Nicotine patch efficacy studies published through September 1993 were located by means of computerized searches of MEDLINE (National Library of Medicine, Bethesda, Md) and Psychological Abstracts (American Psychological Association, Washington, DC). In addition, unpublished studies were located by requesting applications submitted to the FDA by the four pharmaceutical companies (CIBA-GEIGY Corp, Edison, NJ; Elan Pharmaceutical Research Corp/Lederle Laboratories; Alza Corporation/Marion Merrell Dow, Kansas City, Mo; and Kabi Pharmacia/Parke-Davis, Morris Plains, NJ) seeking approval to market the nicotine patch. Some published studies were also described in FDA applications; all sources of information about each clinical trial were included for review.

Two raters independently evaluated a total of 23 separate clinical trials. For inclusion in the meta-analysis, each study had to display the following characteristics: (1) random assignment of subjects to active or placebo patch conditions, (2) double-blind, (3) placebo-controlled, (4) 4 or more weeks of patch therapy, (5) biochemical confirmation of abstinence, and (6) subjects not selected on the basis of specific diseases (eg, psychiatric patients or patients with coronary artery disease). Rater agreement exceeded 99% (one disagreement out of 138 individual criterion ratings); a consensus decision was made for the one disagreement. Studies satisfying all inclusion criteria are listed in Table 1 with annotations concerning the source of data (published study and/or FDA application) used in the meta-analysis; studies failing to meet one or more inclusion criteria are listed in Table 2.

Two studies included in the meta-analysis[27,42] each consisted of two separate clinical trials. Daughton et al[27] tested two versions of the patch (16-hour vs 24-hour), and the Transdermal Nicotine Study Group[42] reported two separate trials to provide independent confirmation of the results. For purposes of the meta-analysis, the two trials from each of these studies were evaluated separately. In addition, Fiore et al[21] report results for two independent and procedurally different clinical trials, although only one trial (study 2) was included in the meta-analysis as a separate clinical trial. The other clinical trial (study 1) reflected data collected at one site as part of a four-site, multicenter trial. End-of-treatment (EOT) (but not 6-month) data for the complete four-center trial (including the Fiore et al/Wisconsin site) were available in an FDA application by Elan Pharmaceutical Research Corporation,[30] and these data were used in the meta-analysis. Overall, 17 separate clinical trials were included in the meta-analysis (Table 1); all 17 trials reported abstinence results at the end of patch treatment, whereas only 13 of the trials reported 6-month follow-up data. Six studies failed to meet inclusion criteria and were excluded (Table 2).

Abstinence Data

For each trial, EOT and 6-month abstinence rates in the active patch and placebo patch groups were recorded by two independent raters, and any disagreements were resolved. All EOT and 6-month abstinence rates were based on intent to treat. Six-month data were selected to evaluate long-term efficacy because 13 of the 17 clinical trials reported 6-month data, whereas only seven trials reported 1-year data, and the relapse curve for smoking cessation is relatively flat after 6 months.[32]

All abstinence data included in the meta-analysis were based on biochemically verified abstinence: two studies[21,23] allowed minimal lapses (up to three cigarettes per week), whereas data for all other studies were based on abstinence rates that required total abstinence (no cigarettes smoked, typically not even a puff) in order to count a subject as abstinent. Abstinence data were reported in the 17 clinical trials as a point-prevalence measure (abstinence during a standard-length period, typically a 1- to 2-week period preceding EOT or the 6-month follow-up) or a continuous-prevalence measure (abstinence through most or all of the assessment period; eg, total abstinence from week 1 of patch treatment to the 6-month follow-up) or both. Seven studies reported continuous-prevalence rates, and 10 studies reported point-prevalence rates. Interrater agreement for type of prevalence reported was 88.2%.

Two trials reported by the Transdermal Nicotine Study Group[42] tested more than one starting dose in the active patch groups (21 mg, 14 mg, or 7 mg in trial 1; and 21 mg or 14 mg in trial 2). Among active patch subjects in these two trials, only the 21-mg active patch groups were included in the meta-analysis.

Study Characteristics Examined

Two independent raters evaluated study characteristics. Rater agreement for each study characteristic was determined as percentage agreement (across all 17 trials). In all instances of disagreement, consensus was reached through discussion after independent ratings were made. Thus, for each clinical trial satisfying the meta-analysis inclusion criteria, the following study characteristics were rated:

1. Daily patch duration (ie, 16-hour vs 24-hour): Independent rater agreement was 100%. There were more 24-hour patch trials (n=13) than 16-hour patch trials (n=4).

2. Patch treatment duration (ie, length of patch treatment, including any planned dosage reduction and any period of time that the patch was available to subjects; coded as ≤8 weeks vs >8 weeks): Independent rater agreement was 88.2%. The 8-week cutoff was selected because there were nine studies with patch duration up to 8 weeks vs eight studies with patch duration more than 8 weeks.

3. Weaning or dosage reduction

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Table 1.—Randomized, Double-blind, Placebo-Controlled Nicotine Patch Clinical Trials Included in the Meta-analysis

Investigators and Clinical Trials	Abstinence Data*
Abelin et al *Lancet*[1,2,4]	End of treatment
FDA application 020076[5,6,8,11]	6 months
Abelin et al *Methods Find Exp Clin Pharmacol*[3,9,10,12]	End of treatment
FDA application 020076[4,7,8,11]	6 months
Buchkremer et al *Addict Behav*[13,14,15,16]	End of treatment
Nervenarzt[17,18,19,20]	6 months
Daughton et al 16 h[21,22,23,24,25,26,27,28]	End of treatment
24 h[21,22,23,24,25,26,27,28]	6 months
Elan Pharmaceutical Research Corp NDA 19-983[29,30,31]	End of treatment 6 months: not available
Mayo Clin Proc[32]	...
Elan Pharmaceutical Research Corp NDA 19-983[29,30,31]	End of treatment 6 months: not available
Chest[33]	...
Fiore et al *Chest*,[34,35,36,37,38] study 2 only	End of treatment 6 months
Hurt et al *JAMA*[39,40,41,42,43,44]	End of treatment 6 months
NDA 19-983[30]	...
Imperial Cancer Research Fund General Practice Research Group *BMJ*[45,46,47,48,49]	End of treatment 6 months: not available
Mulligan et al *Clin Pharmacol Ther*[50,51,52,53]	End of treatment 6 months: not available
NDA 19-983[30]	...
Russell et al *BMJ*[54,55,56,57,58]	End of treatment 6 months
Sachs et al *Arch Intern Med*[59,60,61,62,63]	End of treatment 6 months
FDA application 020150[59]	...
Tonnesen et al† *N Engl J Med*[64]	...
FDA application 020150[61,65,66]	End of treatment 6 months
Transdermal Nicotine Study Group, trial 1‡ *JAMA*[67]	...
FDA application 020165[68,69,70]	End of treatment 6 months
Transdermal Nicotine Study Group, trial 2‡ *JAMA*[67]	...
FDA application 020165[68,69,70]	End of treatment 6 months
Westman et al *Arch Intern Med*[71,72,73,74]	End of treatment 6 months

*Some published and unpublished studies were submitted to the US Food and Drug Administration (FDA) by pharmaceutical companies seeking approval to market the nicotine patch. In cases where published data and FDA data were available for the same study, raters extracted data from the source that provided intent-to-treat results and/or more complete data (eg, some published studies did not report 6-month outcomes whereas the FDA application did report it). All sources of data for each study (published study and/or FDA applications) are listed above for informational purposes.

†There was a slight discrepancy in end-of-treatment data for one study reported both in a published study (Tonnesen et al[64]) and in a corresponding FDA application (Kabi study 1[61]); data for this study were extracted from the FDA application because it provided a more conservative odds ratio and had 6-month data available that were based on complete abstinence (whereas the 6-month abstinence rate reported by Tonnesen et al allowed lapses).

‡The Transdermal Nicotine Study Group[67] reported two separate, although similar, trials that for purposes of the meta-analysis were treated as separate studies because quit rates differed significantly for the two trials. Also, data reported for the Transdermal Nicotine Study Group studies were extracted from the Marion Merrell Dow FDA application 020165 (studies 010[68] and 011[69]) because the FDA application provided more complete abstinence data on the individual trials than the published study.

coded as yes or no. Independent rater agreement was 82.4%. There were 11 trials that provided dosage reduction vs six trials that did not.

4. Individual counseling vs group counseling: Once raters decided that some counseling had occurred in a study, they rated whether an individual or group format was used in such counseling (independent rater agreement was 100%). Of the 17 studies, only three were judged to contain no significant counseling.[21,22,24] When the remaining studies were categorized for counseling format, eight were judged to involve individual counseling, and six were judged to involve group counseling.

5. Intensity of behavioral counseling: Each trial was evaluated on four behavioral counseling criteria that were determined on an a priori basis: (1) whether counseling was an intended, primary goal of meetings (0=no, 1=yes; independent rater agreement was 88.2%); (2) frequency of meetings in the first 4 weeks of patch treatment (0=less often than weekly meetings or not stated, 1=weekly or more frequent meetings; independent rater agreement was 76.5%); (3) total number of meetings in the first 12 weeks (0=fewer than seven meetings or not stated, 1=seven or more meetings; independent rater agreement was 94.1%); and (4) length of meetings (0=≤40 minutes or not stated, 1=>40 minutes; independent rater agreement was 100%). Consensus ratings for each of the four criteria were summed to form a counseling intensity index that could range from 0 to 4. Eleven trials that were rated 2 or less were assigned to the low-intensity counseling group, and six trials that were rated 3 or higher were assigned to the high-intensity counseling group. The correlation between the two raters for the counseling intensity index was .91, and percentage agreement between the raters for which trials fell into low-intensity and high-intensity counseling groups was 100%. Group counseling vs individual counseling format was not included in the counseling intensity index because we did not view this format dimension as having an unambiguous relation with intensity.

When the studies were examined in terms of the actual counseling information provided to patients, insufficient data were available to systematically examine this variable. However, components of counseling frequently included techniques such as skills training, social support, and relapse prevention.

Each rater also recorded the following sample information for each trial: (1) number of weeks of down titration; (2) percentage of females; (3) mean age; (4) mean number of cigarettes per day at baseline; (5) total number of active patch subjects; and (6) total number of placebo patch

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subjects. Disagreements were minimal and were resolved by the raters.

Statistical Analyses

To provide information about the magnitude of the effect of the nicotine patch on smoking cessation success, abstinence rates were combined for active groups and placebo groups (separately) at both EOT and at 6-month follow-up. To account for differences in sample sizes between studies, abstinence rates from individual trials were pooled such that each study was weighted by its sample size, and overall rates of abstinence were computed. In addition, a 95% confidence interval (CI) for each resulting pooled proportion was computed.[32] These proportions must be interpreted cautiously because of the wide range of sample sizes for individual trials included in the computation of the common abstinence rates. However, these proportions provide a means for estimating the magnitude of abstinence rates for comparisons of interest.

In contrast to pooled abstinence rates, individual and common odds ratios (ORs) provide a measure of relative effect size of the active patch vs placebo patch. To assess this measure, for each study, frequencies of abstinent subjects and nonabstinent subjects in active patch and placebo patch groups at EOT (and at 6-month follow-up, if available) were tabled as 2×2 cross-tabulations from which ORs for each trial were computed. The OR provides a measure of the effect on abstinence of the active nicotine patch relative to the placebo patch. In order to estimate a common OR (ie, an OR that reflects the statistical combination of ORs from independent studies) for various comparisons of interest (eg, comparing all 16-hour patch trials vs all 24-hour patch trials), the Mantel-Haenszel method[34] for combining ORs was used. In addition, a test-based 95% CI[35] for each common OR was computed. The Breslow-Day Test[36] for homogeneity of the common OR was computed to test for heterogeneity of ORs. In cases where statistically significant heterogeneity ($P<.10$) of ORs was detected, outlier ORs were deleted until homogeneity criteria were satisfied. In all cases, one particular study (Tonnesen et al[40]) accounted for heterogeneity of ORs.

RESULTS

Characteristics of Individual Studies

Table 3 provides study and sample characteristics for each of the 17 studies included in the meta-analysis. These studies, comprising 5098 patients, were diverse on most rated dimensions. Table 4 provides abstinence rates and ORs for each of the 17 studies. At EOT, abstinence rates ranged from 14.4% to 69.0% and from 4.9% to 51.2% for active groups and placebo groups, respectively. At the 6-month follow-up, abstinence rates ranged from 12.5% to 33.6% and from 2.5% to 20.9% for the active groups and placebo groups, respectively. The ORs for individual trials ranged from 1.8 to 8.3 at EOT and from 1.9 to 10.1 at the 6-month follow-up (Table 4).

Percentage of Subjects Abstinent

Table 5 presents the percentage of subjects abstinent at EOT and at 6-month follow-up for both the active groups and placebo groups. Whereas ORs reflect the success of active patch subjects relative to that of placebo subjects, this analysis displays the success of each treatment group (active and placebo) separately. The overall abstinence rates (percentage not smoking) for active patch and placebo patch groups at EOT and 6 months agree well with the OR analysis in suggesting that the active patch more than doubles a subject's chances of abstinence.

The 16-hour and 24-hour patch studies yielded roughly equivalent outcomes at EOT, while the 24-hour patch is associated with slightly better outcomes at 6 months (Table 5). Also, there seemed to be no advantage to extending patch treatment beyond 8 weeks. Studies that did

Table 2.—Nicotine Patch Clinical Trials Not Included in the Meta-analysis

Source, y	Reason(s) for Exclusion From Meta-analysis
Foulds et al,[44] 1992	1. Patch treatment <4 wk 2. Cross-over design
Hartman et al,[47] 1991	1. Patch treatment <4 wk 2. Subjects were psychiatric patients
Krumpe et al,[48] 1989	1. Patch treatment duration not specified 2. Patch group sizes not specified
Meier-Lammerman et al,[49] 1990	1. No placebo patch group 2. Patch treatment duration not specified
Rennard et al,[50] 1991	1. Subjects were coronary artery disease patients
Rose et al,[51] 1990	1. Patch treatment <4 wk

Table 3.—Double-blind, Placebo-Controlled Clinical Trials of the Nicotine Patch: Study Characteristics

Clinical Trials	Patch Type, h	Total Weeks of Patch Treatment	Weeks of Weaning	Female, %	Mean Age, y	Mean No. of Cigarettes/d	Total No. Using Active Patch	Total No. Using Placebo Patch
Abelin et al,[21] 1989	24	12	6	40.2	41.6	27.5	100	99
Abelin et al,[23] 1989	24	9	6	26.8	24.0	23.0	56	56
Buchkremer et al,[25] 1989	24	7	1	50.4	35.3	29.3	42	43
Daughton et al,[27] 1991 (16 h)	16	4	0	53.2	41.8	32.9	55	52
Daughton et al,[27] 1991 (24 h)	24	4	0	53.2	41.8	32.9	51	52
Elan Pharmaceutical Research Corp[28]	24	6	0	58.4	41.3	30.8	165	164
Elan Pharmaceutical Research Corp[29]	24	8	0	64.5	41.3	29.3	139	137
Fiore et al,[31] 1994 (study 2)	24	6	2	67.9	43.6	30.3	57	55
Hurt et al,[33] 1994	24	8	0	53.8	43.2	28.6	120	120
Imperial Cancer Research Fund General Practice Research Group,[34] 1993	24	12	6	55.1	43.7	24.4	842	844
Mulligan et al,[36] 1990	24	6	0	52.5	36.9	25.1	40	40
Russell et al,[37] 1993	16	16	6	61.2	39.5	23.5	400	200
Sachs et al,[38] 1993	16	18	6	59.1	47.6	28.0	113	107
Tonnesen et al,[40] 1991	16	16	4	70.0	45.2	21.5	145	144
Transdermal Nicotine Study Group,[42] 1991 (trial 1)	24	12	6	60.3	43.3	31.2	121	124
Transdermal Nicotine Study Group,[42] 1991 (trial 2)	24	12	6	62.7	43.1	30.5	128	129
Westman et al,[46] 1993	24	6	2	56.6	41.8	41.8	78	80
Median	...	...	...	57	42	29	...	...
Total	...	...	...	...	...	...	2652	2446

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...e 4.—Double-blind Placebo-Controlled Clinical Trials of the Nicotine Patch*

Clinical Trials	Prevalence Type	End of Treatment: Active Abstinent, No. (%)	End of Treatment: Placebo Abstinent, No. (%)	End of Treatment: OR (95% CI)†	6 Months: Active Abstinent, No. (%)	6 Months: Placebo Abstinent, No. (%)	6 Months: OR (95% CI)†
Abelin et al[21] 1989	Point	36/100 (36.0)	22/99 (22.2)	2.0 (1.1-3.7)	22/100 (22.0)	12/99 (12.1)	2.1 (1.0-4.4)
Abelin et al[22] 1989	Point	22/56 (39.3)	11/56 (19.6)	2.7 (1.1-6.2)	13/56 (23.2)	4/56 (7.1)	3.9 (1.2-12.9)
Buchkremer et al.[23] 1989	Point	29/42 (69.0)	22/43 (51.2)	2.1 (0.9-5.2)	14/42 (33.3)	9/43 (20.9)	1.9 (0.7-5.0)
Daughton et al.[27] 1991 (16 h)	Point	19/55 (34.5)	7/52 (13.5)	3.4 (1.3-9.0)	17/55 (30.9)	4/52 (7.7)	5.4 (1.7-17.3)
Daughton et al.[27] 1991 (24 h)	Point	20/51 (39.2)	7/52 (13.5)	4.2 (1.6-11.0)	11/51 (21.6)	4/52 (7.7)	3.3 (1.0-11.2)
Elan Pharmaceutical Research Corp[28]‡	Point	48/165 (29.1)	22/164 (13.4)	2.7 (1.5-4.6)	...	...	...
Elan Pharmaceutical Research Corp[28]‡	Point	48/139 (34.5)	30/137 (21.9)	1.9 (1.1-3.2)	...	...	...
Fiore et al.[31] 1994 (study 2)	Point	21/57 (36.8)	11/55 (20.0)	2.3 (1.0-5.5)	10/57 (17.5)	4/55 (7.3)	2.7 (0.8-9.2)
Hurt et al.[32] 1994	Point	56/120 (46.7)	24/120 (20.0)	3.5 (2.0-6.2)	35/120 (29.2)	18/120 (15.0)	2.3 (1.2-4.4)
Imperial Cancer Research Fund General Practice Research Group.[34] 1993‡	Continuous	121/842 (14.4)	73/844 (8.6)	1.8 (1.3-2.4)	...	...	...
Mulligan et al.[35] 1990‡	Point	19/40 (47.5)	6/40 (15.0)	5.1 (1.8-14.9)	...	...	...
Russell et al.[37] 1993	Continuous	70/400 (17.5)	15/200 (7.5)	2.6 (1.5-4.7)	50/400 (12.5)	13/200 (6.5)	2.1 (1.1-3.9)
Sachs et al.[38] 1993	Continuous	46/113 (40.7)	17/107 (15.9)	3.6 (1.9-6.9)	38/113 (33.6)	13/107 (12.1)	3.7 (1.8-7.4)
Tonnesen et al.[40] 1991	Continuous	43/145 (29.7)	7/144 (4.9)	8.3 (3.6-19.1)	28/145 (19.3)	4/144 (2.8)	8.4 (2.9-24.5)
Transdermal Nicotine Study Group,[42] 1991 (trial 1)	Continuous	61/121 (50.4)	29/124 (23.4)	3.3 (1.9-5.8)	40/121 (33.1)	22/124 (17.7)	2.3 (1.3-4.2)
Transdermal Nicotine Study Group,[42] 1991 (trial 2)	Continuous	37/128 (28.9)	11/129 (8.5)	4.4 (2.1-9.0)	25/128 (19.5)	9/129 (7.0)	3.2 (1.5-7.3)
Westman et al.[43] 1993	Continuous	23/78 (29.5)	7/80 (8.8)	4.4 (1.8-10.9)	16/78 (20.5)	2/80 (2.5)	10.1 (2.2-45.4)

*One-year data were available for seven studies only; for each study, the following data are provided: active patch, percentage abstinent; placebo patch, percentage abstinent; and odds ratio (OR). Abelin et al[21]: 17.0%, 11.1%, 1.64; Abelin et al[22]: 16.1%, 5.4%, 3.38; Buchkremer et al[23]: 26.2%, 20.9%, 1.34; Hurt et al[32]: 27.5%, 14.2%, 2.30; Russell et al[37]: 9.3%, 5.0%, 1.94; Sachs et al[38]: 24.8%, 9.4%, 3.20; and Tonnesen et al[40]: 12.4%; 2.8%, 4.96.
†CI indicates confidence interval.
‡These studies did not report 6-month outcomes.

Table 5.—Percentage Abstinent in Active Groups and Placebo Groups*

Comparison of Studies	End of Treatment: Active Patch, % (95% CI)	End of Treatment: Placebo Patch, % (95% CI)	6 Months: Active Patch, % (95% CI)	6 Months: Placebo Patch, % (95% CI)
All patch studies	27.1 (25.4-28.8) (n=17)	13.1 (11.8-14.5) (n=17)	21.8 (19.7-23.9) (n=13)	9.4 (7.8-11.0) (n=13)
Patch				
16 h	25.0 (21.9-28.2) (n=4)	9.1 (6.8-11.9) (n=4)	18.7 (15.9-21.6) (n=4)	6.8 (4.8-9.2) (n=4)
24 h	27.9 (25.9-29.9) (n=13)	14.2 (12.6-15.7) (n=13)	24.7 (21.7-27.8) (n=9)	11.1 (9.0-13.4) (n=9)
Patch treatment				
≤8 wk	37.9 (34.4-41.3) (n=9)	18.3 (15.6-21.2) (n=9)	25.6 (21.4-29.9) (n=6)	10.2 (7.5-13.4) (n=6)
>8 wk	22.9 (21.0-24.8) (n=8)	10.9 (9.4-12.4) (n=8)	20.3 (18.0-22.8) (n=7)	9.0 (7.2-11.0) (n=7)
Weaning				
No	36.8 (32.9-40.8) (n=6)	17.0 (14.0-20.2) (n=6)	27.9 (22.2-38.1) (n=3)	11.6 (7.9-16.2) (n=3)
Yes	24.4 (22.6-25.3) (n=11)	12.0 (10.5-13.5) (n=11)	20.6 (18.4-22.9) (n=10)	8.9 (7.2-10.7) (n=10)
Counseling format				
Individual	26.8 (26.2-31.4) (n=8)	11.9 (9.9-14.1) (n=8)	20.0 (17.6-22.6) (n=7)	7.7 (5.9-9.7) (n=7)
Group	41.4 (36.8-45.3) (n=6)	20.0 (16.7-23.5) (n=6)	26.3 (21.8-31.1) (n=4)	12.6 (9.4-16.4) (n=4)
Counseling intensity				
Low	22.8 (21.0-24.7) (n=11)	10.6 (9.2-12.0) (n=11)	19.5 (17.2-22.1) (n=8)	7.1 (5.4-9.0) (n=8)
High	41.5 (37.6-45.4) (n=6)	20.9 (17.8-24.2) (n=6)	26.5 (22.6-30.6) (n=5)	13.2 (10.3-16.4) (n=5)

*CI indicates confidence interval.

not use a weaning procedure tended to yield higher abstinence rates than studies using weaning. However, this outcome is potentially confounded because there were no "no-weaning" studies with continuous-prevalence data. Therefore, the apparent lower abstinence rate created by weaning is probably due to the relatively lower abstinence rates obtained with the more conservative continuous-prevalence measure.

At EOT, higher abstinence rates were noted among studies using a group-counseling format; this difference, however, was much reduced at 6 months as indicated by overlapping CIs (Table 5). Table 5 also shows that at EOT, more intensive behavioral counseling had a significant effect on outcome rates: it almost doubled the likelihood of quitting successfully relative to less intensive counseling. However, the benefit of intensive counseling was more modest at 6 months, especially among those receiving active patch treatment.

Combined ORs

Table 6 presents combined ORs and 95% CIs. When all analyzable patch studies were combined, the odds of active patch subjects being abstinent at the EOT were about 2.5 times that of placebo subjects, and at 6 months, the odds were about three times that of placebo subjects. When studies reporting point-prevalence and continuous-prevalence data were considered separately, the continuous-prevalence studies yielded higher ORs (3.8 at EOT and 3.2 at 6 months) than did the point-prevalence studies (2.6 at EOT and 2.6 at 6 months). Thus, regardless of type of outcome data, the odds of active patch subjects being abstinent were at least 2.5 times that of placebo subjects at EOT and 6 months.

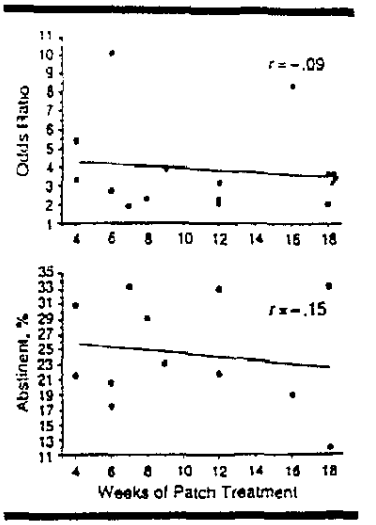
In addition to overall ORs, Table 6 presents ORs for subcategories of patch studies. These subcategories include both continuous-prevalence and point-prevalence studies analyzed at EOT and 6 months. To limit the number of analyses presented, we will discuss the separate analysis of continuous-prevalance and point-prevalence studies only when such analyses

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Table 6.—Efficacy Meta-analyses' Benefit of Active Patch Over Placebo Patch as Measured by Combined Odds Ratios (ORs)*

Comparison of Studies	End of Treatment		6 Months	
	No. of Studies	OR (95% CI)	No. of Studies	OR (95% CI)
All patch studies	16†	2.6 (2.2-3.0)	13	3.0 (2.4-3.7)
Patch				
16 h	4	3.8 (2.7-5.3)	4	3.5 (2.4-5.1)
24 h	13	2.5 (2.1-2.9)	9	2.7 (2.0-3.6)
Patch treatment				
≤8 wk	9	2.9 (2.2-3.6)	6	3.1 (2.1-4.6)
>8 wk	7†	2.4 (2.0-2.9)	7	2.9 (2.2-3.8)
Weaning				
No	6	2.9 (2.2-3.8)	3	3.0 (1.8-4.8)
Yes	10†	2.4 (2.0-2.9)	10	3.0 (2.3-3.8)
Counseling format				
Individual	8	3.4 (2.7-4.3)	7	3.4 (2.5-4.5)
Group	6	3.0 (2.3-3.9)	4	2.5 (1.7-3.6)
Counseling intensity				
Low	10†	2.5 (2.0-3.0)	8	3.5 (2.6-4.7)
High	6	2.8 (2.2-3.7)	5	2.4 (1.7-3.4)

*CI indicates confidence interval.
†The study of Tonnesen et al[44] was omitted in order to reduce statistically significant heterogeneity of the ORs.



Treatment duration (in weeks). Nicotine patch efficacy (expressed as odds ratios) (top) and percentage abstinent (bottom) for all studies at 6-month follow-up.

provide different information from that provided by the combined analysis.

The 16-hour patch studies appeared to produce higher ORs at both EOT and 6 months than did the 24-hour patch studies (Table 6). However, the 95% CIs for the ORs overlap at both follow-up points. Moreover, there was confounding of patch type with type of prevalence measure: three of four 16-hour patch studies used continuous prevalence whereas nine of thirteen 24-hour patch studies used point prevalence. As noted herein, continuous-prevalence studies tended to have higher ORs than point-prevalence studies. Examination of combined ORs at EOT and 6 months for the subset of studies using continuous prevalence failed to reveal superiority for either patch. A similar analysis of the subset of point-prevalence studies was not feasible because there was only one 16-hour patch study in this group.

The results for patch duration (studies lasting ≤8 weeks vs studies lasting >8 weeks) suggest that there is no apparent advantage to extending patch treatment beyond 8 weeks (Figure). Similarly, no discernible advantage could be attributed to weaning patients off the nicotine patch or based on counseling format (individual vs group) (Table 6).

Table 6 also reveals ORs greater than 2 for both low-intensity and high-intensity behavioral counseling comparisons at EOT and 6 months. There was no indication that low-intensity or high-intensity counseling resulted in greater efficacy of the nicotine patch in relation to placebo patch as evidenced by the considerable overlap of the 95% CIs for combined ORs at EOT and 6 months. This pattern was consistent across both continuous-prevalence and point-prevalence outcome measures. However, clinical trials typically involve significant patient monitoring that may have attenuated differences in outcome between low-intensity and high-intensity counseling.

Counseling Characteristics

To explore further the effect of counseling on outcomes, studies were contrasted on the basis of the individual counseling dimensions that constituted the counseling intensity index. The results of these analyses are depicted in Table 7 for active subjects and placebo subjects. Table 7 shows that three of the counseling dimensions seem to be especially important in determining outcomes. Subjects were more likely to become abstinent if counseling was a major, intended reason for patient contacts or sessions, if there were at least weekly patient meetings in the first 4 weeks of treatment, and if there were at least seven meetings in the first 12 weeks of treatment. These effects were greater at EOT than at the 6-month follow-up.

COMMENT

This meta-analysis provides compelling evidence that the nicotine patch is a consistently effective aid to smoking cessation. Individuals wearing the active nicotine patch were more than twice as likely to quit smoking as were individuals wearing a placebo patch. This relative advantage was maintained at EOT and at 6-month follow-up for point-prevalence and continuous-prevalence measures of outcome, for the 16-hour and 24-hour delivery systems, for relatively brief (≤8 weeks) and longer (>8 weeks) patch treatment durations, and for studies in which patch dosage was gradually reduced (weaning) and terminated abruptly. The consistent benefit of the active nicotine patch across all of these treatment and assessment dimensions points to the robustness of the patch's clinical efficacy. Overall, mean abstinence rates for active patch users were about 27% at EOT and 22% at 6 months compared with 13% and 9%, respectively, for placebo patch users.

Although intensive counseling enhanced clinical success with the patch, there was compelling evidence that the patch was also effective with minimal adjuvant therapy. This finding is different from that obtained with nicotine gum; there is substantial evidence that nicotine gum is not an effective long-term cessation aid when not accompanied by substantial adjuvant therapy.[12,13] In the absence of more intensive counseling, the patch may be more effective than gum because it is easier to use and thus may boost compliance and result in more stable nicotine serum levels.

The FDA requires that patch marketers state in package inserts that the nicotine patch should be used only as part of a comprehensive behavioral smoking-cessation program. It is clear from the results of this meta-analysis that the efficacy of the nicotine patch, relative to the placebo patch, was essentially unrelated to adjuvant intensity. Importantly, two of the studies included in the meta-analysis[34,37] were conducted in primary care settings and appear fairly representative of typical clinical office practice. Although these studies offered minimal behavioral counseling, both showed the active patch to be superior to the placebo patch.

Because the nicotine patch appears to be effective with minimal counseling, it may be ideal for use in a "stepped-care" approach to smoking cessation.[47] In such an approach, the nicotine patch might be

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Table 7.—Counseling Characteristics in Relation to Achieved Abstinence Rates*

Comparison of Studies	End of Treatment		6 Months	
	Active Patch, % (95% CI)	Placebo Patch, % (95% CI)	Active Patch, % (95% CI)	Placebo Patch, % (95% CI)
Counseling				
Not a major reason for meeting	21.2 (19.4-23.1) (n=7)	10.3 (8.9-11.9) (n=7)	18.6 (15.0-21.3) (n=5)	7.6 (5.7-9.9) (n=5)
Is a major reason for meeting	40.1 (36.7-43.4) (n=10)	18.5 (16.0-21.2) (n=10)	25.8 (22.5-29.2) (n=8)	11.0 (8.8-13.5) (n=8)
Frequency of meetings in first 4 weeks				
<Weekly	19.5 (17.6-21.4) (n=6)	9.7 (8.2-11.3) (n=6)	17.2 (14.6-20.0) (n=5)	6.7 (4.6-9.0) (n=5)
≥Weekly	38.7 (35.8-41.6) (n=11)	17.7 (15.5-20.1) (n=11)	26.6 (23.4-29.9) (n=8)	11.4 (9.2-13.9) (n=8)
No. of meetings in first 12 weeks				
≤6	22.8 (21.0-24.7) (n=11)	10.6 (9.2-12.0) (n=11)	19.5 (17.2-22.1) (n=8)	7.1 (5.4-9.0) (n=8)
>6	41.5 (37.5-45.4) (n=6)	20.9 (17.8-24.2) (n=6)	26.5 (22.6-30.6) (n=5)	13.2 (10.3-16.4) (n=5)
Duration of meetings				
≤40 min	25.3 (23.5-27.1) (n=14)	12.2 (10.8-13.7) (n=14)	20.9 (18.6-23.2) (n=11)	8.6 (7.0-10.5) (n=11)
>40 min	37.8 (32.8-42.4) (n=3)	17.9 (14.3-21.9) (n=3)	26.1 (20.9-31.7) (n=2)	12.3 (8.6-16.6) (n=2)

*CI indicates confidence interval.

offered first with minimal assistance during an initial quit attempt with a clinician. Should this effort prove unsuccessful and retreatment be necessary, the patch might be used with an intermediate-intensity adjuvant, such as support and follow-up provided via telephone[45] or with a clinician using the National Cancer Institute's manual, *How to Help Your Patients Stop Smoking*.[58] The next level of retreatment in this stepped-care approach would be a combination of the patch and intensive group counseling comprising support, skill training, and education.[1,59]

The absolute effectiveness of patch treatment in terms of percentage of patients abstinent was, however, influenced by the intensity of adjuvant behavioral counseling therapy.[60] In particular, there were increases in abstinence rates when counseling was a major reason for patients to attend meetings, when there were weekly or more frequent meetings in the first 4 weeks of treatment, and when there were seven or more meetings over the course of treatment. Among subjects using the active nicotine patch, those who received more intensive behavioral counseling were about twice as likely to be abstinent at the EOT compared with patients receiving less intensive counseling. This finding is consistent with earlier work by Kottke et al,[61] noting higher smoking cessation rates with more intensive interventions. Intensive counseling also boosted outcomes at 6-month follow-up, although to a smaller degree.

While our data suggest that intensive counseling may boost outcomes with the patch, these findings do not, by themselves, support the routine use of intensive counseling. First, the great majority of smokers may be unwilling to undergo intensive counseling,[16] and this would reduce its utility. Second, it is unclear whether the modest benefits of counseling at long-term follow-up would outweigh its costs.

This meta-analysis calls into question some common clinical practices and recommendations by patch marketers. For instance, the marketers of three of the four nicotine patches recommend patch treatment durations from 10 to 18 weeks. Although there may be an advantage to long-term nicotine patch treatment (>8 weeks) in some instances, the results of this meta-analysis provide no support for this as a general practice. A shorter duration of patch treatment could reduce the cost by a third or more. For example, given the average retail cost of $4 per patch, an 8-week course and 12-week course of therapy would cost about $224 and $336, respectively. Given projected sales figures of $300 million in 1993, limiting patch treatment to 8 weeks or less may result in a public health savings of up to $100 million. Of course, our conclusions regarding treatment duration must be tempered by the fact that longer treatment durations might have benefits not appraised in this meta-analysis (eg, reduced craving late in the quitting process), might enhance clinical outcomes in a subpopulation of smokers (eg, those with high pretreatment nicotine levels),[62] or might be revealed in treatment extending beyond 18 weeks, the duration of longest patch regimen included in the reviewed studies.

The meta-analysis results also challenge the utility of a second aspect of clinical practice: the weaning or reduction of patch dosage prior to treatment termination. Weaning is strongly encouraged by most of the marketers, yet the data evaluated in the current research did not show weaning to have an added beneficial effect. Of course, weaning might have important effects other than on efficacy, such as reducing patients' worry about abrupt withdrawal from nicotine, or it might be important for some subtypes of smokers.

Perhaps the biggest difference among all the commercially available patches in the United States is that one is intended for 16-hour use, and the rest are intended for 24-hour use. As we noted in the "Results" section, there was no evidence that either use pattern was consistently better than the other in producing abstinence. However, differences between the 16-hour and 24-hour patches might appear in other areas, such as differences in sleep disturbance or morning craving and relapse.

The findings of this meta-analysis must be evaluated with respect to some important caveats. First, all of the comparisons reported were made on the basis of a single type of outcome (abstinence rates), and these comparisons were limited to two time points: EOT and 6 months after initiation of treatment. A different pattern of results might have been obtained if the nicotine patches were evaluated in terms of other effects (eg, withdrawal suppression) or if 1-year data were available for all comparisons. Second, the contrasted studies differed from one another on numerous dimensions. This made it difficult to examine the effects of a single study dimension independent of other dimensions with which it might co-occur. For instance, the occurrence of dosage weaning was related to duration of patch treatment: those treatments that included weaning tended to be longer than those with abrupt dosage termination. Third, because these findings were based on clinical research trials often using highly motivated and monitored subjects, it will be important to confirm and extend these findings with population-based studies.

Confounding is especially likely in comparisons of abstinence percentages (eg, Tables 5 and 7). This is because, in contrast to ORs, abstinence rates in one group are not referenced to control (placebo) group outcomes from the same study (ie, as a ratio of active to placebo abstinence rates). As a result, a host of treatment context and population variables may be correlated with the treatment elements ostensibly being compared. For instance, our analysis suggested that intensive counseling boosts abstinence rates. It is possible that counseling per se has little effect on outcome, but instead it might be that only highly motivated subjects volunteer for studies using intensive counseling. This particular hypothesis is only illustrative of the sorts of confounders that are possible.

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Most importantly, the results of this meta-analysis can help the clinician in assisting patients who want to quit smoking. The following observations may be particularly important in guiding clinicians: (1) The nicotine patch is an effective aid to smoking cessation, resulting in abstinence rates about two to three times those observed with placebo patches. This does not mean that every smoker should receive the nicotine patch when trying to quit, but it does suggest that the patch should be a principal weapon in the physician's pharmacopeia. (2) Even when patients are given the nicotine patch, only about 22% are abstinent after 6 months, averaging across diverse studies (Table 5). Therefore, while clinicians can treat cigarette smoking successfully, they should also realize that smoking is a chronic disease with a substantial rate of relapse. As such, the clinician should be prepared to reassess and treat the smoker on a repeated basis. (3) Unlike nicotine gum, the nicotine patch appears to be effective in the primary care setting when offered without lengthy or sophisticated adjuvant counseling. (4) Although intensive adjuvant counseling appears to improve overall rates of smoking cessation, such counseling is not critical to ensuring acceptable levels of efficacy. This suggests that a stepped-care approach may be appropriate for smoking similar to that used for hyperlipidemia and hypertension. In such an approach, the patch might be accompanied by little or no adjuvant counseling in its initial use and with increasing amounts of counseling in re-treatments. (5) The nicotine patch is effective across diverse styles of administration. For example, the patch appears to be effective with or without dosage weaning, across great variation in patch-use durations, with both a 16-hour and 24-hour daily wearing period, and with or without intensive counseling.

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References

1. Fiore MC, Jorenby DE, Baker TB, Kenford SL. Tobacco dependence and the nicotine patch: clinical guidelines for effective use. *JAMA*. 1992;268:2687-2694.
2. Palmer KJ, Buckley MM, Faulds D. Transdermal nicotine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. *Drugs*. 1992;44:498-529.
3. McKenna JP, Cox JL. Transdermal nicotine replacement and smoking cessation. *Am Fam Phys*. 1992;45:2595-2601.
4. Orleans CT, Resch N, Noll E, et al. Use of transdermal nicotine in a state-level prescription plan for the elderly: a first look at 'real-world' patch users. *JAMA*. 1994;271:601-607.
5. CIBA-GEIGY Corp. *Habitrol (Nicotine Transdermal Therapeutic System) Prescribing Information*. Edison, NJ: CIBA-GEIGY Corp; 1992.
6. Lederle Laboratories. *PROSTEP (Nicotine Transdermal System) Prescribing Information*. Wayne, NJ: Lederle Laboratories; 1992.
7. Marion Merrell Dow Inc. *Nicoderm (Nicotine Transdermal System) Prescribing Information*. Kansas City, Mo: Marion Merrell Dow Inc; 1991.
8. Parke-Davis. *Nicotrol (Nicotine Transdermal System) Prescribing Information*. Morris Plains, NJ: Parke-Davis; 1992.
9. Glover ED. What can we expect from the nicotine transdermal patch? a theoretical/practical approach. *Health Values*. 1993;17:69-79.
10. Benowitz NL. Nicotine replacement therapy: what has been accomplished—can we do better? *Drugs*. 1993;45:157-170.
11. McAfee T. Transdermal nicotine: clarifications, side effects, and funding. *JAMA*. 1993;269:1939-1940.
12. Cepeda-Benito A. A meta-analytical review of the efficacy of nicotine chewing gum. *J Consult Clin Psychol*. 1993;61:822-830.
13. Hughes JR. Pharmacotherapy for smoking cessation: unvalidated assumptions, anomalies, and suggestions for future research. *J Consult Clin Psychol*. 1993;61:751-760.
14. Lam W, Sze PC, Sacks HS, Chalmers TC. Meta-analysis of randomised controlled trials of nicotine chewing-gum. *Lancet*. 1987;2:27-30.
15. Fiore MC, Novotny TE, Pierce JP, et al. Methods used to quit smoking in the United States: do cessation programs help? *JAMA*. 1990;263:2760-2765.
16. Lichtenstein E, Hollis J. Patient referral to a smoking cessation program: who follows through? *J Fam Pract*. 1992;34:739-744.
17. Hughes JR, Glaser M. Transdermal nicotine for smoking cessation. *Health Values*. 1993;17:25-31.
18. Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. *Epidemiol Rev*. 1992;14:154-176.
19. Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. Orlando, Fla: Academic Press; 1985.
20. Mosteller F, Chalmers TC. Some progress and problems in meta-analysis of clinical trials. *Stat Sci*. 1992;7:227-236.
21. Abelin T, Buehler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet*. 1989;1:7-10.
22. CIBA-GEIGY Corp. *FDA Application 020076 for Approval of Habitrol: Study 30-87*. Edison, NJ: CIBA-GEIGY Corp; 1992.
23. Abelin T, Ehrsam R, Buhler-Reichert A, et al. Effectiveness of a transdermal nicotine system in smoking cessation studies. *Methods Find Exp Clin Pharmacol*. 1989;11:205-214.
24. CIBA-GEIGY Corp. *FDA Application 020076 for Approval of Habitrol: Study 7-87*. Edison, NJ: CIBA-GEIGY Corp; 1992.
25. Buchkremer G, Benta H, Horstmann M, Opitz K, Talla R. Combination of behavioral smoking cessation with transdermal nicotine substitution. *Addict Behav*. 1989;14:229-238.
26. Buchkremer G, Benta H, Minneker E, Opitz K. Langfristige Effekte Einer Kombination von Transdermaler Nikotinzufuhr mit Verhaltenstherapie zur Raucherentwöhnung [Long-term effects of smoking cessation therapy combining behavior therapy and transdermal nicotine substitution]. *Nervenarzt*. 1988;59:488-490.
27. Daughton DM, Heatley SA, Prendergast JJ, et al. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy: a randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 1991;151:749-752.
28. Elan Pharmaceutical Research Corp. *NDA 19-983 for Approval of PROSTEP: Study 44-03*. Gainesville, Ga: Elan Pharmaceutical Research Corp; 1992.
29. Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 1990;65:1529-1537.
30. Elan Pharmaceutical Research Corp. *NDA 19-983 for Approval of PROSTEP: Study 90-03*. Gainesville, Ga: Elan Pharmaceutical Research Corp; 1992.
31. Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest*. 1994;105:524-533.
32. Hurt RD, Dale LC, Fredrickson PA, et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one-year outcome and percentage of nicotine replacement. *JAMA*. 1994;271:595-600.
33. Elan Pharmaceutical Research Corp. *NDA 19-983 for Approval of PROSTEP: Study 90-01*. Gainesville, Ga: Elan Pharmaceutical Research Corp; 1992.
34. Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomized trial in a general practice. *BMJ*. 1993;306:1304-1308.
35. Mulligan SC, Masterson JG, Devane JG, Kelly JG. Clinical and pharmacokinetic properties of a transdermal nicotine patch. *Clin Pharmacol Ther*. 1990;47:331-337.
36. Elan Pharmaceutical Research Corp. *NDA 19-983 for Approval of PROSTEP: Study 88-01*. Gainesville, Ga: Elan Pharmaceutical Research Corp; 1992.
37. Russell MAH, Stapleton JA, Feyerabend C, et al. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ*. 1993;306:1308-1312.
38. Sachs DPL, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med*. 1993;153:1881-1890.
39. Kabi Pharmacia. *FDA Application 020130 for Approval of Nicotrol: Study 1*. Piscataway, NJ: Kabi Pharmacia; 1992.
40. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med*. 1991;325:311-315.
41. Kabi Pharmacia. *FDA Application 020130 for Approval of Nicotrol: Study 1*. Piscataway, NJ: Kabi Pharmacia; 1992.
42. Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation: six-month results from two multicenter controlled clinical trials. *JAMA*. 1991;266:3133-3138.
43. Marion Merrell Dow. *FDA Application 020165 for Approval of Nicoderm: Study 010: 21 mg/day Dose and 0 mg/day Dose Conditions Only*. Kansas City, Mo: Marion Merrell Dow; 1991.
44. Marion Merrell Dow. *FDA Application 020165 for Approval of Nicoderm: Study 011: 21 mg/day Dose and 0 mg/day Dose Conditions Only*. Kansas City, Mo: Marion Merrell Dow; 1991.
45. Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation: a randomized trial with telephone counseling. *Arch Intern Med*. 1993;153:1917-1923.
46. Faulds J, Stapleton J, Feyerabend C, Vesey C, Jarvis M, Russell MA. Effect of transdermal nicotine patches on cigarette smoking: a double-blind crossover study. *Psychopharmacology (Berl)*. 1992;106:421-427.
47. Hartman N, Leong GB, Glynn SM, Wilkins JN, Jarvik ME. Transdermal nicotine and smoking behavior in psychiatric patients. *Am J Psychiatry*. 1991;148:374-375.
48. Krumpe P, Malani N, Adler J, et al. Efficacy of transdermal nicotine administration as an adjunct for smoking cessation in heavily nicotine addicted smokers. *Ann Rev Respir Dis*. 1989;139:A337. Abstract.
49. Meier-Lammerman E, Meyer M, Boleski PL. Combination of transdermal nicotine substitution and behavioural group therapy in smoking cessation. *Eur Respir J*. 1990;3(suppl 10):168S.
50. Rennard S, Daughton D, Fortmann S, et al. Transdermal nicotine enhances smoking cessation in coronary artery disease patients. *Chest*. 1991;100(suppl):5S.
51. Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. *Clin Pharmacol Ther*. 1990;47:323-330.
52. Report of the Surgeon General. *The Health Consequences of Smoking: Nicotine Addiction*. Washington, DC: US Dept of Health and Human Services; 1988. Publication CDC 88-8406.
53. Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed. New York, NY: John Wiley & Sons Inc; 1981.
54. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719-748.
55. SAS Institute Inc. *SAS/STAT Users Guide, Release 6.03 Edition*. Cary, NC: SAS Institute Inc; 1988.
56. Breslow NE, Day NE. *Statistical Methods in Cancer Research*. Lyon, France: International Agency for Research on Cancer; 1980:1.
57. Orleans CT. Treating nicotine dependence in medical settings: a stepped-care model. In: Orleans CT, Slade J, eds. *Nicotine Addiction: Principles and Management*. New York, NY: Oxford University Press; 1993:145-161.
58. Glynn TJ, Manley MW. *How to Help Your Patients Stop Smoking: A National Cancer Institute Manual for Physicians*. Washington, DC: US Dept of Health and Human Services, Public Health Service, National Institutes of Health; 1990. Publication NIH 90-3064.
59. Leventhal H, Baker TB, Brandon TH, Fleming R. Intervening and preventing cigarette smoking. In: Ney T, Gale A, eds. *Smoking and Human Behavior*. New York, NY: John Wiley & Sons Inc; 1989:313-336.
60. Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment*. New York, NY: Springer-Verlag; 1991.
61. Kottke TE, Battista RN, DeFriese GH, et al. Attributes of successful smoking cessation interventions in medical practice: a meta-analysis of 39 controlled trials. *JAMA*. 1988;259:2883-2889.
62. Hurt RD, Dale LC, Offord KP, et al. Serum nicotine and cotinine levels during nicotine-patch therapy. *Clin Pharmacol Ther*. 1993;54:98-106.

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Randomized Comparative Trial of Nicotine Polacrilex, a Transdermal Patch, Nasal Spray, and an Inhaler

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Background: There are several nicotine replacement products on the market, and physicians are likely to be asked with increasing frequency about which of these products their patients should use.

Objective: To provide a basis for rational advice by comparing nicotine polacrilex (gum), a transdermal patch, nasal spray, and an inhaler.

Design: Randomized trial with assessments at the quit date and 1, 4, and 12 weeks later.

Setting: Hospital smokers' clinic.

Patients: Male and female community volunteers (N = 504) smoking 10 or more cigarettes per day and seeking help to stop smoking.

Interventions: Patients were given brief advice, and purchased their nicotine replacement treatment at approximately half the regular retail price.

Main Outcome Measures: Nicotine replacement treatment use, ratings of withdrawal symptoms, ratings of product characteristics and helpfulness, and biochemically validated continuous lapse-free abstinence.

Results: The products did not differ in their effects on withdrawal discomfort, urges to smoke, or rates of abstinence. The continuous validated 12-week abstinence rates were 20%, 21%, 24%, and 24% in the gum, patch, spray, and inhaler groups, respectively. Compliance with recommended nicotine replacement treatment use was high for the patch, low for gum, and very low for the spray and the inhaler. The spray was underused because of adverse effects more often than the other products. In the subjects using the spray, the level of use among abstainers at week 1 predicted outcome at week 12. The inhaler was rated as more embarrassing to use than the other products, but provided at least as much nicotine as the gum.

Conclusion: When asked about nicotine replacement treatment products available, physicians should note that, despite low compliance with the recommended dose of the spray and inhaler and differences in product ratings, overall, there are no notable differences between the products in their effects on withdrawal discomfort, perceived helpfulness, or general efficacy.

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THERE ARE 4 nicotine replacement treatments (NRTs) available (nicotine polacrilex [gum], nicotine transdermal patch, nicotine nasal spray, and nicotine inhaler). They have all been shown to increase smokers' chances of stopping smoking for at least a year.[1] In 2 within-subject short-term (2-3 days) studies,[2,3] the gum and the patch had similar effects on withdrawal; in another within-subject study,[4] the patch and the spray were shown to produce similar nicotine and cotinine plasma levels during 5 days of use. Otherwise, no direct comparisons have been made between the different products for their ease of use, suitability for different patient groups, nicotine delivery or efficacy in relief of withdrawal symptoms, reduction in urges to smoke, or ability to maintain abstinence. Such direct comparisons are required between the 4 products to make rational decisions concerning their use. As the public becomes aware of various NRT options, health professionals are likely to be asked with increasing frequency about which of these products their patients should use.

Faster delivery products, such as nicotine nasal spray, may be more effective in relieving urges to smoke.[4] However, they have been reported to cause greater local irritation, which may translate into lower compliance and efficacy. The inhaler, which mimics some of the cigarette manipulation and puffing behaviors, may help to relieve discomfort

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SUBJECTS AND METHODS

SAMPLE

This randomized, controlled study was performed at 2 sites in London, England (Royal London Hospital and St George's Hospital). The project was approved by the appropriate ethics committees. Recruitment was conducted through advertisements and referrals. A total of 506 smokers met the study criteria and underwent randomization. Two became pregnant during the study, and their participation was discontinued, leaving 504 subjects.

The subjects were eligible for inclusion if they were at least 18 years old, had smoked an average of 10 or more cigarettes per day, were motivated to stop smoking, were generally in good health, were not receiving treatment for a psychiatric disorder, had not tried to stop smoking using an NRT within the past 3 months, and for whom none of the 4 NRT products was contraindicated. **Table 1** gives the sample characteristics. There were no significant differences between the groups ($P>.05$ for all comparisons).

PROCEDURE

Smokers volunteering for the study were screened by telephone interview. Those that fulfilled the entry criteria were invited to attend a hospital smokers' clinic. They were also sent a patient information sheet and a questionnaire to complete and bring with them at their first attendance. The questionnaire included questions concerning smoking history, previous NRT use, and demographic details. The subjects were instructed to smoke normally up to the first session and that the session would mark the beginning of the cessation attempt (ie, they should be prepared not to smoke thereafter).

At their first individual attendance at the clinic (week 0), smokers were reassessed for eligibility and invited to provide written consent for participation in the study. Subjects viewed an 8-minute videotape describing the 4 NRT products being tested, and provided ratings of their opinion of the products. They were then randomized, by a computer-generated schedule in sealed envelopes, to receive 1 of 4 NRT products as follows: (1) nicotine polacrilex (gum), 2 or 4 mg (n = 127) (subjects using ≥12 pieces of 2-mg gum per day were offered 4-mg gum); (2) a nicotine transdermal patch, 15 mg, for 16 hours (n = 124); (3) a nicotine nasal spray (n = 126); and a nicotine inhaler (n = 127).

The subjects agreed to participate in the study knowing that they might be allocated to use any one of these products. They were also aware that they would have to purchase the products at approximately half the regular retail price (£7; ie, $12 for 105 pieces of gum, 7 patches, 1 bottle of nasal spray solution giving 200 0.5-mg doses, or 42 inhaler cartridges). The reason for this was to mimic as far as possible the conditions in countries such as England, where NRT is not reimbursable.

The subjects then viewed a 7-minute videotape describing in greater detail how to use the product to which they had been assigned. The videotapes standardized the presentation of information about the NRT products as far as possible. The subjects rated their mood and physical symptoms to provide a baseline for later measurements of withdrawal symptoms.

Subjects tried 1 U of their NRT product at the first session under supervision and then were dispensed their supply of NRT to last them for 1 week. Subjects were given brief encouragement to remain abstinent and were

Table 1. Sample Characteristics of 504 Subjects

Characteristics*	Nicotine Replacement Treatment			
	Nicotine Polacrilex (Gum) (n = 127)	Transdermal Patch (n = 124)	Nasal Spray (n = 126)	Inhaler (n = 127)
Men, %	35	33	42	32
Age, mean (SD), y	40 (10.0)	40 (10.8)	41 (10.3)	39 (10.2)
No. of cigarettes smoked per day, mean (SD)	24 (8.0)	25 (10.0)	25 (9.0)	24 (9.1)
FTND score, mean (SD)	5.9 (2.5)	5.6 (2.3)	5.9 (2.4)	5.9 (2.1)
CO, mean (SD), ppm	29 (11.3)	29 (10.8)	29 (12.3)	30 (12.5)
No. of prior quit attempts, mean (SD)	2.8 (2.9)	2.5 (2.4)	2.7 (3.2)	2.9 (3.0)
White collar, %	50	41	50	50

*FTND indicates Fagerstrom Test of Nicotine Dependence; CO, end-expired carbon monoxide.

related to behavioral components of smoking.[5] Another hypothesis assumes that the gum, spray, and inhaler, which all provide sensory stimulation, should have bigger impact than the patch on initial craving.[6] The patch, because it is only put on once a day, is much easier to use than the other products and may, therefore, be associated with better compliance and outcome. None of these issues has been addressed empirically within a single randomized trial.

To our knowledge, we performed the first study to directly compare the 4 products on a range of variables. Results from a comparison of the 4 products in their use, acceptability, cotinine levels, rated helpfulness, withdrawal symptom relief, and abstinence rates up to 3 months are reported. Findings regarding the products' dependence potential, subject preferences, and product effects in different patient subgroups will be reported separately.

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instructed to use the NRT product to which they had been assigned according to the manufacturer's instructions for up to 12 weeks. For the gum, this involved at least 10 to 15 pieces per day, approximately hourly; for the patch, this involved 1 patch per day applied to the skin on waking; for the nasal spray, this involved at least 30 single shots per day, approximately hourly; and for the inhaler, this involved using the inhaler hourly for some 20 minutes and using at least 6 cartridges per day, with each cartridge being used 3 to 4 times. Subjects were also given a sheet containing written guidance on use of their product.

Subsequent individual visits to the clinic were scheduled as follows: session 2, 1 week after the quit date; session 3, 4 weeks after the quit date; and session 4, 12 weeks after the quit date (only those abstinent at session 3 were invited).

Subjects received £10 for expenses per visit, excluding session 1. Those who were abstinent and using NRT at week 12 were invited back 3 weeks later to assess dependence on their product.

The following measures were taken:

1. In sessions 2 through 4, data regarding NRT use since the last session, reasons for nonuse (subjects using less than the recommended dose were asked to choose 1 of the following: forgot, it is not helping, adverse effects, did not need it, to save money, or another reason), and ratings concerning ease of use (ranging from 1 [very difficult] to 9 [very easy]) and embarrassment using NRT (1 indicates not at all; 2, somewhat; and 3, very much so) were obtained.

2. In sessions 1 through 4, ratings of depression, irritability, restlessness, hunger, and poor concentration (using the Mood and Physical Symptoms Scale)[7] were obtained.

3. In sessions 2 through 4, ratings of strength of urges to smoke, time spent with urges to smoke, and difficulty not smoking[7] were obtained.

4. In sessions 2 through 4, data regarding complete, lapse-free abstinence from cigarettes, verified by expired-air carbon monoxide concentrations (cutoff point <10 ppm), were obtained. If biochemical verification was not possible because of nonattendance at a session, subjects were counted as smokers.

5. In session 2, the saliva cotinine concentration was obtained.

STATISTICAL ANALYSES

Between-product comparisons on categorical variables used χ^2 analyses with pairwise comparisons made using Bonferroni adjustment for multiple comparisons. Comparisons involving continuous variables used analysis of variance with the Scheffé test for post hoc pairwise comparisons. The withdrawal score at week 1 was calculated by subtracting the week 1 ratings of irritability, depression, restlessness, poor concentration, and hunger from the ratings at week 0. The total withdrawal score was calculated by adding the previously described ratings. The compliance and abstinence rates were calculated on an intention-to-treat basis, while other analyses were based on subjects who provided the required measures, as stated in the "Results" section. The sample size of 504 subjects provided 80% statistical power to detect a difference between any 2 groups in total withdrawal scores of 1.4 scale points (scores can range from −20 to 20) (2-tailed tests, $P<.001$). It provided 80% power to detect differences between any 2 groups of 15% in abstinence rates (2-tailed tests, $P<.001$). Logistic regression was used to assess whether cotinine measures in smokers abstaining at 1 week predicted success at 12 weeks.

Table 2. Compliance With the Minimum Recommended Use of NRT During the First Week and Mean NRT Use*

	NRT				
Variable	Nicotine Polacrilex (Gum) (1)	Transdermal Patch (2)	Nasal Spray (3)	Inhaler (4)	Difference (*P*)
Compliance, %					
All subjects	38	82	15	11	2>1>3 and 4 (<.01)
Abstinent subjects	48	96	24	17	2>1>3 and 4 (<.01)
NRT use per day in week 1 abstainers, mean (SD)	9.5 (3.0) Pieces	1.0 (0.2) Patches	24.5 (11.8) Single shots	4.3 (1.9) Cartridges	. . .

*Nonattendees were assumed to be noncomplying. NRT indicates nicotine replacement treatment; ellipses, data not applicable.

RESULTS

Table 2 shows that compliance was high for the patch and low for the other products: only 17% to 48% of even those abstaining in the first week used the recommended amount. It also shows the mean NRT use among those abstinent at week 1. Subjects using the spray and the inhaler complied with recommended use less often than subjects using the gum, and all 3 groups had lower compliance than subjects using the patch. In the gum group, 6 subjects used 4-mg gum.

Table 3 shows that self-reported reasons for nonuse were different for the different products. The most common reason for not using the patch was forgetting, while for the other products it was believing that subjects did not need it. Adverse effects were cited more often as a reason for nonuse with the spray than with the other products. The "other" category included items such as embarrassing to use, being ill, and avoiding dependence.

Table 4 shows that, during the first week, the patch was rated as easier to use than all the other products, which did not differ significantly from each other. The inhaler

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was rated as more embarrassing to use than the other products, followed by the spray. The products did not differ in perceived helpfulness and in stress relief.

Table 5 shows that subjects allocated to use the spray and abstaining at week 1 had lower saliva cotinine concentrations after 1 week of abstinence than those using the gum. Among subjects who complied with the minimum recommended use, those using the inhaler had higher cotinine concentrations than those using the patch.

Table 6 shows that the products did not differ significantly for effects on withdrawal symptoms, difficulty not smoking, urges to smoke at week 1, or weight gain at week 12. There were no differences between subjects abstinent for 12 weeks at any point. Table 6 only shows the total withdrawal scores, but there were no significant differences in any of the constituent ratings.

Table 3. Subjects Attending the Smokers' Clinic at Week 1 Who Underused NRT Giving Reasons for Not Using the Recommended Amount*

	NRT			
Reason	Nicotine Polacrilex (Gum) (n = 67)	Transdermal Patch (n = 23)	Nasal Spray (n = 72)	Inhaler (n = 80)
Forgot	10	65	21	14
Do not need it	43	0	39	41
Adverse effects	16	4	25	8
Impractical	3	0	3	18
Other†	27	30	13	20

*Values are given as percentage of subjects. $\chi^2 = 68.9$ for table, df = 12, P<.001. NRT indicates nicotine replacement treatment.
†Other indicates embarrassing to use, being ill, avoiding dependence, etc.

Table 7 shows that the products did not differ for abstinence rates. We compared the relapse rates in nonsmoking subjects who used with those in nonsmoking subjects who failed to use at least the minimum recommended NRT dose during the first week of abstinence. The differences were not significant in the gum ($P = .57$), patch ($P = .72$), and inhaler ($P = .90$) groups. However, subjects using at least the minimum recommended dose of the nasal spray at week 1 did significantly better at week 12 (69% vs 39% still abstinent, $\chi^2 = 4.5$, $P = .02$). There was also a significant positive association between amount of nasal spray used in week 1 and abstinence at week 12 in the nasal spray group (logistic regression, Wald score = 5.2, $P = .02$, 2-tailed test).

COMMENT

In naturalistic conditions, the 4 nicotine replacement products did not differ in their effects on withdrawal discomfort, and there was no difference in 3-month sustained abstinence rates. However, there were significant differences in compliance with recommended use and in some of the product ratings. In the nasal spray group only, level of initial use was positively related to subsequent abstinence.

It may be argued that with only 504 subjects participating in the study, the failure to find a difference between the products for abstinence rates may have been due to low statistical power. However, the abstinence rates in the 4 groups were similar, and there was little suggestion of a clinically significant difference. Lack of power to detect a difference is unlikely to explain the failure to find a difference in relief of withdrawal discomfort, where the outcome variable was a quantitative index. Thus, based on these results, we could not recommend one product vs the others for overall efficacy. On the other hand,

Table 4. Ratings for NRT in Subjects Attending the Smokers' Clinic at Week 1*

	NRT				
Variable	Nicotine Polacrilex (Gum) (1) (n = 104)	Transdermal Patch (2) (n = 108)	Nasal Spray (3) (n = 105)	Inhaler (4) (n = 97)	Difference (*P*)
Rating of ease of use (1-10), mean (SD)	6.2 (2.6)	8.6 (1.1)	5.6 (2.7)	5.7 (2.7)	2>1, 3 and 4 (<.01)
Subjects reporting at least some embarrassment, %	10	3	37	58	4>3>2 and 1 (<.05)
Helpfulness (1-5), mean (SD)	4.4 (0.7)	4.4 (0.8)	4.4 (0.8)	4.5 (0.7)	None (>.10)
Stress relief (1-5), mean (SD)	3.1 (0.9)	3.2 (1.0)	3.5 (1.0)	3.3 (1.0)	None (<.05)†

*NRT indicates nicotine replacement treatment.
†No post hoc comparisons were significant.

Table 5. Saliva Cotinine Concentrations in Subjects Abstinent From Smoking at Week 1

	Nicotine Replacement Treatment*				
Subjects	Nicotine Polacrilex (Gum) (1)	Transdermal Patch (2)	Nasal Spray (3)	Inhaler (4)	Difference
All those abstaining	949 (943) (n = 64)	818 (312) (n = 68)	562 (432) (n = 68)	863 (778) (n = 54)	1>3
Abstaining subjects using at least the minimum recommended dose	1238 (1216) (n = 31)	829 (307) (n = 63)	909 (511) (n = 16)	1624 (1164) (n = 9)	4>2

*Values are given as mean (SD) cotinine concentrations, measured in nanomoles per liter.

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Table 6. Ratings of Urges to Smoke and Withdrawal Symptoms in Subjects Abstinent at Week 1 and Weight Gain and NRT Use in Subjects Abstinent for 12 Weeks*

Variable	NRT			
	Nicotine Polacrilex (Gum) (n = 64)	Transdermal Patch (n = 68)	Nasal Spray (n = 68)	Inhaler (n = 54)
Difficulty not smoking†	2.0 (1.4)	2.1 (1.3)	2.2 (1.2)	1.9 (1.4)
Time spent with urges†	2.0 (1.1)	2.0 (1.0)	1.9 (1.0)	1.7 (0.8)
Strength of urges†	2.6 (1.3)	2.4 (1.2)	2.6 (1.1)	2.3 (1.3)
Total withdrawal score‡	1.6 (3.9)	1.7 (4.2)	2.3 (4.2)	1.9 (4.1)
NRT use at week 12, % (N)§	76.0 (19)	53.8 (14)	90.0 (27)	74.2 (23)
Weight gain at week 12, kg	3.6 (3.0)	3.6 (3.5)	2.5 (1.8)	2.3 (2.8)

*Values are given as mean (SD), unless otherwise indicated. There were no significant differences between the groups, except for NRT use at week 12.
†The scale was from 0 to 15.
‡The scale was from –20 to 20, and is the sum of the differences of 5 ratings from baseline (each rating being a 5-point scale).
§Overall $\chi^2 = 9.6$, P = .02. The nicotine polacrilex (gum), nasal spray, and inhaler groups were significantly (P<.05) different from the patch group by post hoc comparison, after Bonferroni adjustment. N signifies number of subjects.

Table 7. Abstinence From Smoking in Each NRT Group (n = 504)*

Abstinence	NRT			
	Nicotine Polacrilex (Gum) (n = 127)	Transdermal Patch (n = 124)	Nasal Spray (n = 126)	Inhaler (n = 127)
Up to 1 wk	64 (50.4)	68 (54.8)	68 (54.0)	54 (42.5)
Up to 4 wk	39 (30.7)	45 (36.3)	48 (38.1)	44 (34.6)
Up to 12 wk	25 (19.7)	26 (21.0)	30 (23.8)	31 (24.4)

*Values are given as number (percentage) of total in each group. There were no significant differences between the groups (P = .19, .65, and .77 for weeks 1, 4, and 12, respectively). NRT indicates nicotine replacement treatment.

this still leaves the possibility that the products are differentially effective in different types of smokers. It is also possible that products that might be considered on a priori grounds to be more effective had lower compliance, which undermined their potential efficacy. Thus, the nasal spray, which has the fastest nicotine delivery but is initially particularly unpleasant to use, yielded lower cotinine concentrations than the other products, and level of use at week 1 was positively associated with outcome at week 12.

The fact that the inhaler was no more effective than the other products and that the actions of puffing as a person would on a cigarette and the irritation in the throat do not seem to enhance efficacy can be interpreted as an indication that efficacy is determined primarily by the extent of nicotine rather than behavioral substitution. However, participants typically used less than the recommended amount, which could have diluted its potential behavioral impact. The study included only 1 type of nicotine patch. There are several other types of patches on the market with 24-hour delivery,[8] and some caution is needed in generalizing the study results to the other patch types.

The study differed from most previous NRT trials in that subjects paid for their NRT. This was to mimic as far as possible the real-life situation in which use of different NRT products is to a different degree codetermined by their cost. In particular, products other than the patch readily allow "economizing," and clinical experience and research data suggest that this is 1 of the reasons for their underuse. In a study involving NRT accompanied by brief advice, Hughes et al[9] found that when the gum was provided free, its rate of use and its efficacy were higher than when it had to be purchased. Despite having to pay for the products, the self-reported use of the inhaler and the nasal spray was only slightly lower than that reported in studies[10,11] providing NRT free, while the use of the gum and the patch was at least as high as in previous trials.[2] The comparatively good product use could be related to carefully briefing subjects on NRT use and to recommending hourly vs ad lib use.[12]

Although the products were used as much as in other trials, the gum and the spray were used less than recommended (ie, subjects used an average of 25 rather than a minimum of 30 single shots of nicotine nasal spray per day and 9 rather than 10-15 pieces of gum per day), and the inhaler was used much less than the recommended dose (4 per day rather than at least 6 per day). Equivalent use of the inhaler and the gum can be expected to provide similar saliva cotinine levels, because absorption in both cases is primarily buccal. In this study, subjects in the gum group using 90% of the minimum recommended dose had cotinine levels similar to those in the inhaler group, who only used 67% of the recommended dose, while in those using the recommended dose, cotinine levels in subjects using the inhaler were 25% higher than in subjects using the gum. Taking the gum as a benchmark, the recommendation for inhaler use may be too high. Another point that arose with the inhaler was that we instructed subjects to use it hourly for about 20 minutes but that each cartridge could be used 3 to 4 times. The instructions on the (now commercially available) packet state that each cartridge should be used once intensively for 20 minutes. This is based on laboratory results with forceful inhalations every few seconds. In real life, subjects are unlikely to puff on the inhaler with the required intensity for long enough to use its nicotine contents at 1 use. As would be expected, the patch was generally not considered embarrassing to use, while the spray and especially the inhaler were considered embarrass-

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ing by many subjects. Since the study, the inhaler has been launched in several countries; it can be expected that as its use becomes more widespread, embarrassment will decrease.

The study was not set up to evaluate NRT efficacy compared with a placebo, as there is extensive literature[1] showing the treatment to be efficacious. The follow-up period did not extend beyond 3 months, as there was little reason to expect any new differences between products to emerge after the cessation of their use, and the study had sufficient statistical power for short-term comparisons. About two thirds of the sample were women, which is typical for smoking cessation clinics.[13] The absolute cessation rates achieved in this naturalistic setting with minimal behavioral support seem encouraging, and are in accord with other studies.[1]

In conclusion, it appears that, in a naturalistic setting, the type of NRT has little bearing on overall NRT efficacy despite the differences in the sensory and behavioral aspects of NRTs and in the speed of nicotine absorption. The nasal spray, which has the fastest nicotine delivery, may be more helpful to those who manage to use it properly, but it causes more adverse effects than the other products and tends to be underused. The inhaler was more embarrassing to use than the other products, although this may subside when its use becomes more widespread. The products may have different appeal and efficacy in different subgroups of smokers, but the results indicate that overall, the 4 therapies have similar perceived helpfulness and similar effects on craving, withdrawal symptoms, and abstinence rates.

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REFERENCES

1. Silagy C, Mant D, Fowler G, Lancaster T. *Nicotine Replacement Therapy for Smoking Cessation* [serial on CD-ROM]. Oxford, England: Update Software; 1999.
2. Fagerstrom KO, Schneider N, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology.* 1993;111:271-277.
3. Leischow S, Valente S, Hill A, et al. Effects of nicotine dose and administration method on withdrawal symptoms and side effects during short-term smoking abstinence. *Exp Clin Psychopharmacol.* 1997;5:54-64.
4. Benowitz N, Zevin S, Jacob P. Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *Br J Clin Pharmacol.* 1997;43:259-267.
5. Hajek P, Jarvis M, Belcher M, Sutherland G, Feyerabend C. Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. *Psychopharmacology.* 1989;97:99-102.
6. Rose J, Levin E. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *Br J Addict.* 1991;86:605-609.
7. West R, Russell M. Pre-abstinence smoke intake and smoking motivation as predictors of severity of cigarette withdrawal symptoms. *Psychopharmacology.* 1985; 87:334-336.
8. Gorsline J. Nicotine pharmacokinetics of four nicotine transdermal systems. *Health Values.* 1993;17:20-24.
9. Hughes J, Wadland W, Fenwick J, Lewis J, Bickel W. Effect of cost on the self-administration and efficacy of nicotine gum: a preliminary study. *Prev Med.* 1991; 20:489-496.
10. Sutherland G, Stapleton J, Russell M, et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet.* 1992;340:324-329.
11. Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of nicotine inhaler in smoking cessation. *JAMA.* 1993;269:1268-1271.
12. Killen J, Fortmann S, Newman B, Varady A. Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. *J Consult Clin Psychol.* 1990;58:85-92.
13. Hajek P. Helping smokers to overcome tobacco withdrawal: background and practice of withdrawal-oriented therapy. In: Richmond R, ed. *Interventions for Smokers: An International Perspective.* Baltimore, Md: Williams & Wilkins; 1994:29-46.

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Smoking Without Nicotine Delivery Decreases Withdrawal in 12-hour Abstinent Smokers

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BUTSCHKY, M. F., D. BAILEY, J. E. HENNINGFIELD AND W. B. PICKWORTH. *Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers.* PHARMACOL BIOCHEM BEHAV **50**(1) 91-96, 1995.—The contribution of sensory factors to smoking satisfaction and nicotine withdrawal symptoms was assessed by evaluating responses to three types of cigarettes: a regular cigarette, a de-nicotinized cigarette (de-nic), and a lettuce leaf cigarette. Doses were varied by requiring subjects to smoke cigarettes using a five-port cigarette manifold. The ratio of the regular or de-nic cigarettes to the lettuce cigarettes was varied across the following values: zero, one, two, and four of five. Seven male smokers were tobacco-deprived for 12 h before testing. On one test day they smoked the de-nic cigarettes, and on another day they smoked the regular cigarettes. Ratings of satisfaction and cigarette liking were directly related to the number of regular or de-nic cigarettes, but were generally higher after the regular cigarette. The regular and de-nic cigarettes were equivalent in reducing acute withdrawal symptoms. Expired CO was similar on both experimental days. The regular cigarette dose-dependently increased plasma nicotine, but the de-nic cigarette did not increase plasma nicotine. These results indicate that sensory characteristics of cigarettes contribute to the abuse liability of smoke-delivered nicotine. The results suggest that smoking cigarettes that do not provide nicotine may temporarily suppress cigarette withdrawal symptoms.

De-nicotinized cigarette Tobacco withdrawal Sensory factors Smoking behavior

AS DESCRIBED in the Surgeon General's Report on the Health Consequences of smoking (25), cigarette smoking is a process involving both behavioral and pharmacologic factors. For example, reinforcement of cigarette smoking and the discriminative stimulus effects of nicotine depend on nicotinic receptor activation (24) and sensory factors (19). Similarly, the strength of withdrawal symptoms varies as a function of both pharmacologic and environmental factors (6,15). Systematic study of "non-pharmacologic" factors has been confounded by the lack of palatable control cigarettes—for example, lettuce-leaf cigarettes (9).

A new cigarette, Next (Philip Morris, Richmond, VA) was test marketed as a "de-nicotinized" cigarette from which most of the nicotine had been removed from the tobacco. Its nicotine yield rating in machine tests is similar to the widely available "ultralight" cigarettes. The tobacco of ultralight cigarettes, which may contain more than 8 mg nicotine, can actually deliver significant amounts of nicotine to cigarette smokers. Presumably, the Next cigarette would be incapable of delivering significant levels of nicotine to smokers because it is made of de-nicotinized tobacco. The tar yield (10.8 mg) is in the range of medium-yield cigarettes. This de-nic cigarette may provide the taste and odor sensations and cues of a subject's preferred brand of cigarette better than the nontobacco control cigarettes often used in research studies.

Presumably, smoking a de-nicotinized cigarette would evoke all the sensory and environmental cues of smoking, without substantial nicotine delivery. For example, Robinson et al. (18) reported that a de-nicotinized cigarette caused minimal increases in plasma nicotine and heart rate compared with a low-nicotine control cigarette. Robinson et al. did not systematically measure subjective effects. One purpose of the present study was to evaluate the subjective effects from smoking the de-nic cigarette by comparing subjects' responses on a tobacco withdrawal scale (16) and on several "liking" scales after smoking de-nic and regular cigarettes.

Benowitz et al. (1) showed that low-FTC yield nicotine cigarettes (< 0.4 mg/cigarette) produce blood cotine levels equivalent to those produced by high-nicotine yield cigarettes. Herning et al. (13) reported that blood nicotine levels are controlled by how a cigarette is smoked, and that smokers adjust their smoking behavior to optimize nicotine delivery. There-

[1] Requests for reprints should be addressed to Wallace B. Pickworth, NIDA/ARC, P.O. Box 5180, Baltimore, MD 21224.

fore, a second purpose of this study was to determine whether experimentally directed smoking of this de-nic cigarette would deliver pharmacologically active doses of nicotine to human cigarette smokers.

METHOD

Subjects

Seven male residential subjects participated in the study. All were recruited from the research ward of the Addiction Research Center to participate before or after their scheduled primary study. Subjects were consistent smokers of at least one pack (mean ± SD = 2 6.4 ± 8.5 cigarettes) per day, and their mean Fagerstrom (5) score was 8.43 ± 1.99, indicating a high level of dependence. Nicotine delivery ratings of subjects' usual brand of cigarettes averaged 1.15 ± .19 mg. Subjects' mean age was 35.7 ± 4.3 years. They weighed an average of 79.5 ± 10.0 kg. Before beginning the study, subjects gave informed consent in accordance with guidelines of the Department of Health and Human Services and the local institutional review board. The day before the experimental sessions started, the subjects were familiarized with the testing room, equipment, and smoking procedures.

Cigarette Administration

Cigarettes were smoked five at a time through a five-port manifold similar to one described by Chait and Griffiths (3). Subjects puffed through a mouthpiece centrally located on the side opposite to the ports, thus receiving smoke from all five cigarettes (Fig. 1).

Three brands of nonmenthol cigarettes were used: "regular" (Marlboro King Size Soft Pack [Philip Morris]; nicotine delivery = 1.1 mg/cigarette, tar = 15.9 mg/cigarette); the test "de-nic" cigarette (Next; nicotine = .09 mg/cigarette, tar = 10.8 mg/cigarette) and a "lettuce cigarette" (Bravo, a nontobacco cigarette, Safer Smokes, Inc., Ft. Lee, NJ). The cigarette manifold always contained five cigarettes. On each study day, subjects smoked varying numbers of tobacco cigarettes (regular or de-nic) in the following treatment order: zero tobacco cigarettes (five lettuce cigarettes); one tobacco cigarette and four lettuce cigarettes; two tobacco and three lettuce cigarettes; four tobacco and one lettuce cigarette. Thus, subjects smoked the equivalent of: zero, one, two, or four of five tobacco cigarette during each smoking treatment. The order of tobacco cigarette type varied randomly across subjects.

Procedure

Subjects were required to abstain from tobacco, caffeine, and other drugs for 12 h before the 3.5-h testing sessions. The two testing sessions were completed on two different days. An intravenous catheter was inserted into an arm vein at 0800 h of the study day for blood collection. Testing began at 0900 h and consisted of the four smoking treatments occurring about 45 min apart. Physiologic and subjective measurements were taken throughout the session.

For each smoking treatment, all five cigarettes were lit by the experimenter. The subjects were instructed to puff every 30 s for a total of eight puffs according to the following procedure: puff for 1 s, inhale and hold smoke for 5 s, then exhale. Although during smoking treatments the subjects puffed according to instructions, actual puff duration was recorded by a computer via a "pressure tube" that was connected to simulate activation of the computer mouse, which turned the computer timer on and off. Duration of each puff was then saved to a file.

Systolic and diastolic blood pressure, pulse, oral and skin temperature, and pupil diameter were recorded every 8 min for 45 min after the smoking treatments. Exhaled carbon monoxide (CO) was measured at the beginning and the end of each study day on an Ecolyzer carbon monoxide monitor (National Draeger, Pittsburgh, PA). Venous plasma samples for nicotine and cotinine analysis were obtained immediately before and 10 min after each of the four smoking treatments.

Subjects completed a scale measuring tobacco withdrawal symptoms (16) before and after the testing session and on an orientation day, when subjects were smoking ad lib. Other subjective questionnaires were administered by means of a computer 5 min after smoking treatments. Computerized visual analog scales of cigarette ratings were used; subjects used the computer mouse to place a mark on a 95-mm horizontal line to index their endorsement of the following phrases: "drug strength," "good effects of drug," "bad effects of drug," "like effects of drug," "cigarette strength," "hotness of cigarette," "harshness of cigarette," "draw level of cigarette," "taste of cigarette," "overall satisfaction," "good effects of cigarette," and "bad effects of cigarette." Anchors for visual analog lines were specific to each question; for example, "like effects of drug" was scored between "not at all" and "very much." A short form of the Addiction Research Center Inventory (ARCI) (10), which included the MBG, PCAG, and LSD subscales (17), and the Single Dose Questionnaire (8) were administered after each smoking treatment.

Statistical Analyses

Data from this within-subject, repeated-measure study were analyzed by univariate analyses of variance (ANOVA) with the two main factors of cigarette type (two levels: regular and de-nic) and dose (four levels: zero, one, two, and four of five tobacco cigarettes) using SPSS software. When the ANOVA indicated significant effects of cigarette type, dose, or interaction and adjustments of the degrees of freedom were made for the repeated measure design. Posthoc comparisons were made using a Studentized Tukey's test of critical differences and Student *t*-tests (23).

RESULTS

Both tobacco cigarette types caused similar and significant carbon monoxide boosts (Fig. 2A) over the study day [$F(1, 6) = 23.05$, $p < 0.01$], indicating that subjects smoked with equal rapacity on both days. This result was supported by the puff duration, which averaged 1.3 s over each dose (number of cigarettes) condition and for each cigarette type. For plasma nicotine boosts (from immediately before to 10 min after treatment), the ANOVA showed a cigarette-type effect [$F(1, 6) = 20.66$, $p < 0.01$], a dose effect [$F(3, 18) = 63.76$, $p < 0.001$], and an interaction [$F(3, 18) = 56.96$, $p < 0.001$], indicating that the regular cigarette caused increases in plasma nicotine that were orderly, dose-dependent, and significant. Average increases in venous plasma nicotine levels were: − 1.4ng/ml after the zero treatment, 2.4 ng/ml after the one of five treatment, 6.4 ng/ml after the two of five treatment, and 10.1 ng/ml after the four of five treatment (Fig. 2B). The de-nic cigarette produced no significant increases in venous plasma nicotine. The maximal increase in venous plasma nicotine after de-nic cigarette was 0.8 ng/ml in the four of five

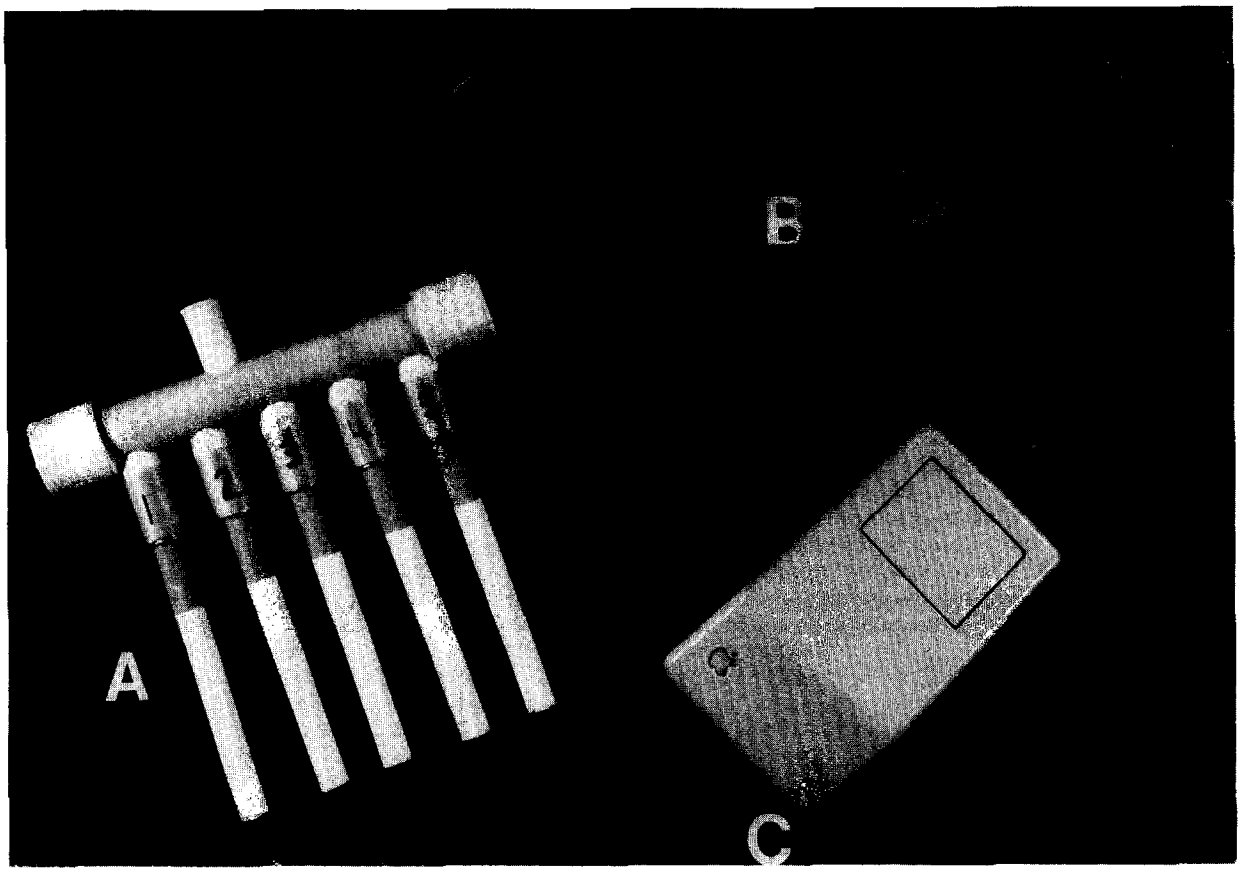


FIG. 1. Five-port cigarette manifold (A) connected to a computer mouse (C) by a plastic tubing (B). Modified after Chait and Griffiths (3).

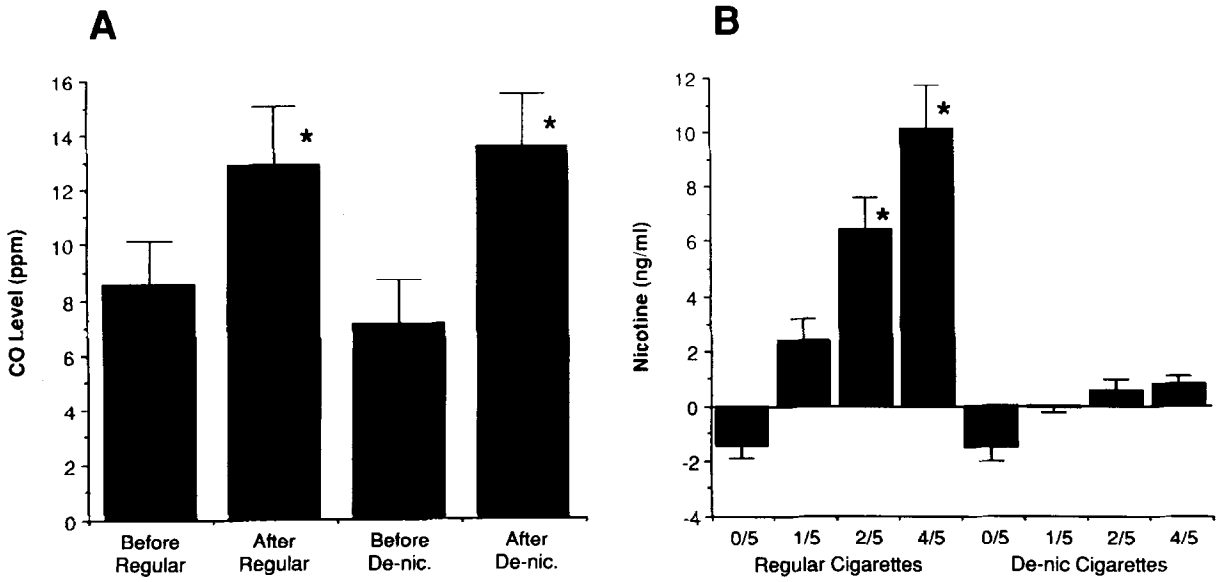


FIG. 2. (A) Mean exhaled carbon monoxide (CO) levels before and after regular and de-nic cigarettes. Measures were collected before and after the four smoking treatments on each experimental day. *Significant differences ($p < 0.01$, Tukey critical difference) from presmoking levels. (B) Venous plasma nicotine increases after each smoking treatment. *Plasma nicotine is significantly different ($p < 0.01$) from zero of five cigarettes (all lettuce cigarette) condition.

de-nic treatment condition. Neither tobacco cigarette significantly increased plasma cotinine levels; in fact, there was a significant decrease in cotinine levels after the zero treatments; the decreases averaged 6.6 and 10.1 ng/ml on regular and de-nic cigarette days, respectively.

Heart rate was significantly higher after the regular cigarette than after de-nic [$F(1, 6) = 22.59, p < 0.01$]. Posthoc paired t-test showed significant increases from 8 min before to 5 min after the two highest doses of regular cigarette (two of five cigarettes: [6 df] t = 7.1; $p = 0.004$, four of five cigarettes: [6 df] t = 3.09, $p = 0.02$). Heart rate was not significantly affected by the de-nic cigarettes. Neither the regular nor de-nic cigarette significantly changed systolic or diastolic blood pressure.

As shown in Fig. 3A, both the regular and de-nic cigarettes significantly reduced scores on the tobacco withdrawal scale (16) to a similar extent [$F(1, 6) = 9.34, p < 0.05$]. After regular cigarette treatments, average total scores decreased from 10.0 to 5.3, and after de-nic, from 10.7 to 6.6. Before either treatment condition, the withdrawal scores were significantly elevated compared with the scores on an orientation day (average score of 2.3) on which the subjects were not deprived (vs. regular, t[6 df] = 3.63, $p < 0.01$; vs. de-nic, t[6 df] = 4.86, $p < 0.01$). Scores for the "craving for nicotine" item of the tobacco withdrawal scale (16) (Fig. 3B) were also significantly reduced after the regular cigarette (from 3.7 to 1.7) and de-nic (from 4.0 to 2.6). The craving item accounted for approximately 36% of subjects' total scores on the tobacco withdrawal scale.

Five subjects completed the Single Dose Questionnaire (8) (Fig. 4A). Subjects rated their "liking of the drug" from "1—not at all" to "5—an awful lot," significantly higher with increasing doses of regular cigarette or de-nic [$F(3, 12) = 6.72, p < 0.01$].

Results for the visual analog questions (Figs. 4B–D) generally indicated that both the regular and de-nic cigarettes were more acceptable than the lettuce cigarette; the regular cigarette was rated consistently higher than the de-nic cigarette. For example, subjects dose-dependently rated both regular and de-nic higher than the all lettuce cigarette (zero of five) condition for "How much do you like the effects of the drug?" [$F(3, 18) = 17.52, p < 0.001$]. Subjects' endorsement of "Rate the good effects of the drug" significantly increased with higher doses of either cigarette [$F(3, 18) = 23.14, p < 0.001$], as did responses to "Rate the overall satisfaction of these cigarettes" [$F(3, 18) = 23.32, p < 0.001$]. There were no effects of cigarette type or dose on answers to "Rate how hot these cigarettes are," "Rate the harshness of these cigarettes," "Rate the draw level of these cigarettes," or "Rate the strength of these cigarettes." On the satisfaction question (Fig. 4D) only, there was a significant effect of cigarette type [$F(1, 6) = 8.03, p < 0.05$], indicating that the regular cigarette was, overall, more satisfying than de-nic. There were no significant effects on subject ratings of subscales of the ARCI.

DISCUSSION

The main finding of this study was that a de-nicotinized cigarette that did not increase plasma nicotine levels and had no cardiovascular effects produced subjective effects of liking and satisfaction. The de-nic cigarette significantly reduced acute nicotine withdrawal symptoms in 12-h tobacco-deprived smokers. These results support and extend the observation that contextual and nonpharmacologic factors that are known to influence acute nicotine effects and nicotine craving are also important in the relief of cigarette withdrawal symptoms (6,15).

The smoking procedure in this study caused significant increases in exhaled CO after smoking either regular or de-nic, indicating that smoke inhalation was similar in each of the experimental sessions and to ad lib smoking (25). The regular cigarette delivered nicotine in amounts similar to those reported by Benowitz et al. (2), (boost of 10 ng/ml 10 min after our high dose) and produced an increase in heart rate. Our

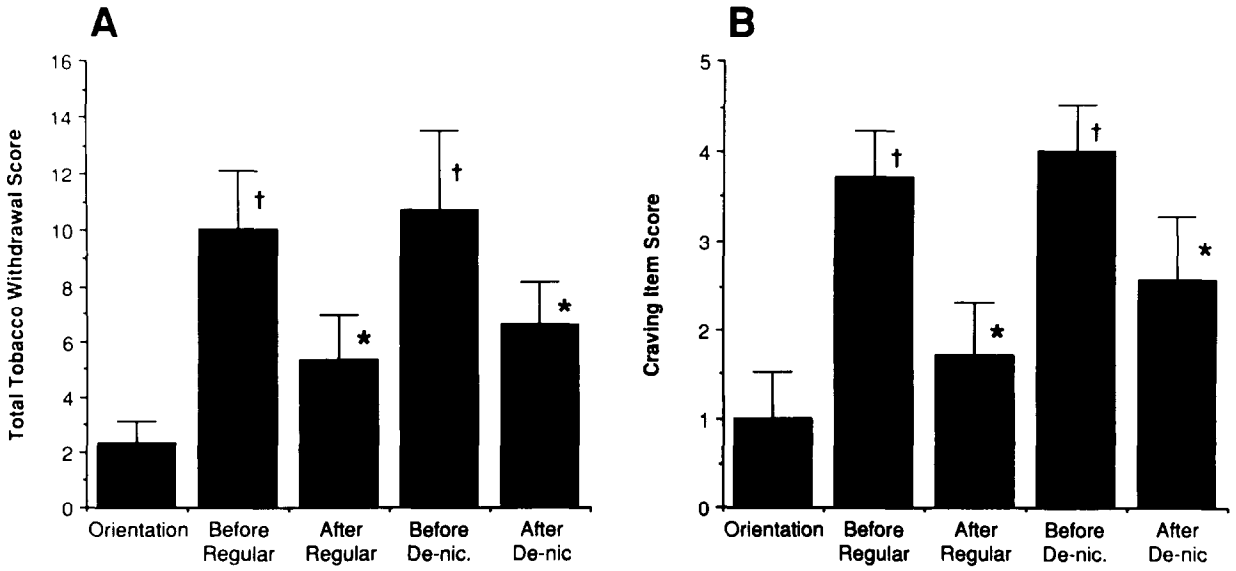


FIG. 3. Mean total tobacco withdrawal scale (A) and craving question (B) scores (16) during ad lib smoking (at orientation), and before and after regular and de-nic cigarettes. Tombstone indicates significant difference between orientation and presession scores. *Significant difference between pre- and postsession scores ($p < 0.05$, paired t-test).

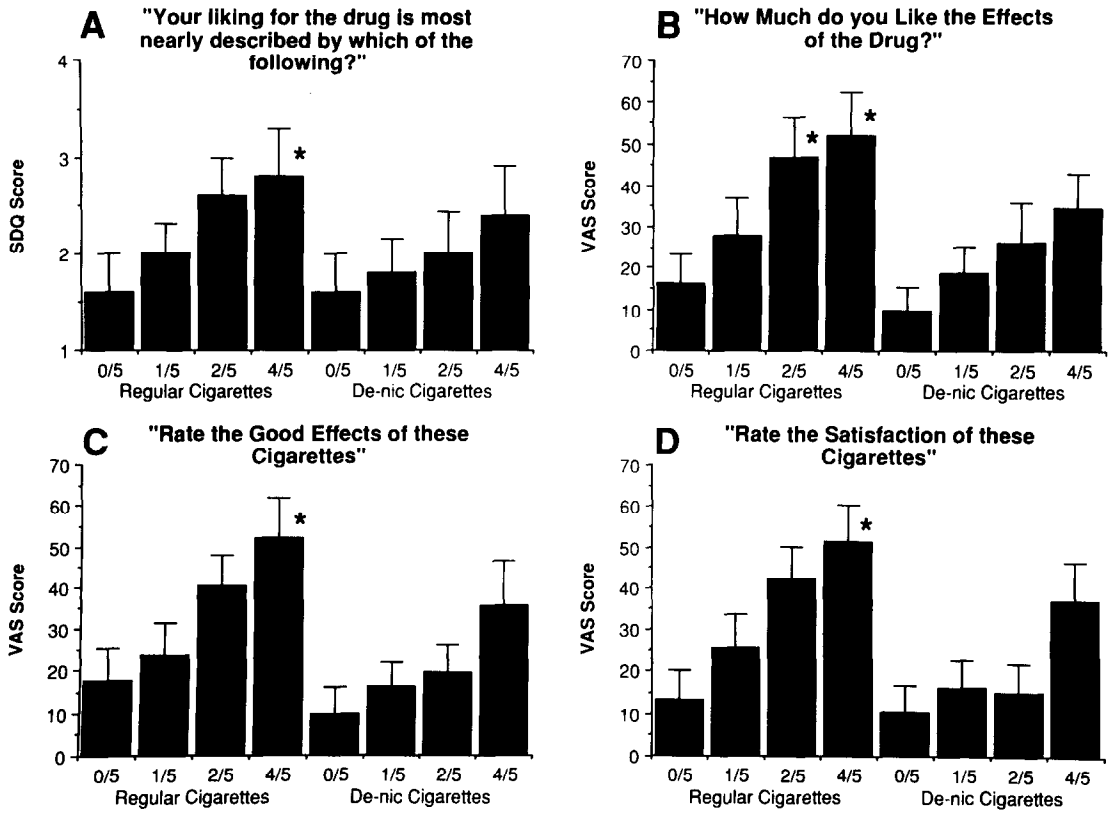


FIG. 4. Mean scores on the drug liking question of the Single Dose Questionnaire (8) (A), and on visual analog scales (B-D). *Mean score is significantly different from zero of five cigarettes, all lettuce cigarette, condition ($p < 0.05$, Tukey critical difference).

results show that the de-nic cigarette did not affect cardiovascular measures. The lack of any physiologic effects after de-nic cigarettes is in concert with the lack of change in nicotine levels. On the other hand, Robinson et al. (18) reported that a de-nicotinized cigarette similar to the one used in the present study caused small but significant increases in plasma nicotine and heart rate, although no EEG changes were reported. It is possible that the paced puffing procedure and the intermixture of the nontobacco smoke from the lettuce cigarettes in the present experiment reduced the amount of nicotine exposure compared with the ad lib smoking of single cigarettes in the study by Robinson et al.

Although the de-nic cigarette did not elevate blood nicotine levels, it decreased total withdrawal scores and scores on the nicotine craving question of a widely used tobacco withdrawal scale (16). The effects of the de-nic cigarette were similar in magnitude to those produced by the regular cigarette. Because nicotine withdrawal was measured before any smoking and at the end of the session, the contribution of the lettuce cigarette to nicotine withdrawal could not be estimated. Nevertheless, these results suggest that contextual, somatosensory, and behavioral cues evoked by the experimental smoke delivery were sufficient to cause short-term reductions in nicotine withdrawal.

Both de-nic and regular cigarettes caused orderly and dose-related increases in scales measuring satisfaction, liking, and positive effects. The Single Dose Questionnaire (8) has been used extensively to assess subjective feeling from and liking for a single dose of a particular drug. It has been used to measure effects of opiates (17) and of IV as well as smoked nicotine (12). In the present study, the regular cigarette increased the "liking" score on this questionnaire dose-dependently, as expected; the de-nic cigarette also significantly increased liking scores in a dose-related manner. On several visual analog scales measuring satisfaction with the cigarette treatments (e.g., "Rate the satisfaction of these cigarettes," "Rate the good effects of the drug," etc.), subjects' scores increased with increasing doses of de-nic and regular cigarettes. Taken together, these findings indicate that subjects can obtain cigarette satisfaction and temporary relief from tobacco withdrawal without the delivery of nicotine. The results are consistent with the conclusion that the high-abuse liability of cigarettes is partly determined by their sensory characteristics (25). These observations are not unique to cigarettes. The role of the drug delivery system itself as a factor in abuse liability and withdrawal symptoms has been documented for cocaine, heroin, and other drugs of abuse (4).

Taste and odor have long been understood to be important determinants of smoking behavior (22). Cigarette smoke delivers thousands of compounds, including nicotine, that evoke strong conditioned associations important for the maintenance of smoking. Thus, both sensory aspects of smoking (e.g., taste, heat, odor, irritation), the conditioned stimuli, and nicotine delivery, the unconditioned stimulus, determine overall smoking behavior (14,22). The importance of sensory factors in tobacco dependence was also confirmed in a study

by Rose and Hickman (21), in which subjects reported that inhaling aerosol puffs of a 15% citric acid solution produced sensations of strength and harshness similar to those produced by smoking cigarettes, and that some pleasure was associated with these sensations. Furthermore, recent results from Hasenfratz et al. (11) suggest that the tar content of cigarettes is more important than nicotine content in the regulation of smoking behavior. In their study, subjects exhibited compensatory smoking behavior when smoking a low-nicotine, low-tar yield cigarette (0.22 mg/cigarette nicotine, 1.83 mg/cigarette tar) but not when smoking the de-nic cigarette, which has low nicotine and medium tar. In the study by Hasenfratz et al. (11), subjects smoked the experimental cigarettes on the day preceding the experiment. Ratings for the liking and satisfaction for the de-nic cigarettes were much lower than those for the nicotine containing cigarette, suggesting that the beneficial effects of de-nic cigarettes on withdrawal we observed may be subject to rapid extinction.

The limited success of nicotine replacement strategies for smoking cessation also indicates that factors other than nicotine delivery modulate smoking behavior. In fact, neither nicotine gum (15), transdermal patch (20), nor intranasal nicotine administration (7) completely abolished cigarette craving. These findings support the importance of sensory factors in the maintaining of smoking behavior and tobacco withdrawal. They also suggest that future smoking cessation aids that provide sensory stimuli that safely mimic the effects of tobacco smoke may be useful in the relief of acute withdrawal symptoms, and possibly in sustaining tobacco abstinence. Such aids might used alone or in combination with a nicotine replacement medication to achieve tobacco abstinence.

REFERENCES

1. Benowitz, N. L.; Hall, S. M.; Herning, R. I.; Jacob, P. III; Jones, R. T.; Osman A. L. Smokers of low-yield cigarettes do not consume less nicotine. N. Engl. J. Med. 309:139–142; 1983.
2. Benowitz, N. L.; Porchet, H.; Sheiner, L.; Jacob, P. III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. Clin. Pharmacol. Ther. 44:23–28; 1988.
3. Chait, L. D.; Griffiths, R. R. Differential control of puff duration and interpuff interval in cigarette smokers. Pharmacol. Biochem. Behav. 17:155–158; 1982.
4. Childress, A. R.; McLellan, A. T.; Ehrman, R.; O'Brien, C. P. Classically conditioned responses in opioid and cocaine dependence: A role in relapse? In: B. A. Ray, ed. Learning factors in substance abuse. NIDA Research Monograph 84. Washington D.C.: U.S. Government Printing Office; 1988:25–43.
5. Fagerstrom, K. O. Measuring degree of physical dependency to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3:235–241; 1978.
6. Finnegan, J. K.; Larson, P. S.; Haag, H. B. The role of nicotine in the cigarette habit. Science 102:94–96; 1945.
7. Fertig, J. B.; Pomerleau, O. F.; Sanders, B. Nicotine-produced antinociception in minimally deprived smokers and ex-smokers. Addict. Behav. 11:239–248; 1986.
8. Fraser, H. F.; Van Horn, G. D.; Martin, W. R.; Wolbach, A. B.; Isbell, H. Methods of evaluating addition liability. (A) Attitude of opiate addicts towards opiate-like drugs, (B) a short term direct addiction test. J. Pharmacol. Exp. Ther. 133:371–387; 1961.
9. Goldfarb, T. L.; Jarvik, M. E.; Glick, S. D. Cigarette nicotine content as a determinant of human smoking behavior. Psychopharmacologia 17:89–93; 1970.
10. Haertzen, C. A. An overview of addiction research center inventory scales (ARCI): An appendix and manual of scales. U.S. Dept. of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse. DHEW Publication No. (ADM) 74-92, 1974.
11. Hasenfratz, M.; Baldinger, B.; Battig, K. Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology 112:253–258; 1993.
12. Henningfield, J. E.; Miyasato, K.; Jasinski, D. R. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J. Pharmacol. Exp. Ther. 234:1–12; 1985.
13. Herning, R. I.; Jones, R. T.; Benowitz, N. L.; Mines, A. H. How a cigarette is smoked determines blood nicotine levels. Clin. Pharmacol. Ther. 33:84–90; 1983.
14. Herskovic, J. E.; Rose, J. E.; Jarvik, M. E. Cigarette desirability and nicotine preference in smokers. Pharmacol. Biochem. Behav. 24:171–175; 1986.
15. Hughes, J. R.; Hatsukami, D. K.; Pickens, R. W.; Krahn, D.; Malins, S.; Luknic, A. Effect of nicotine on the tobacco withdrawal symptom. Psychopharmacology 83:82–87; 1984.
16. Hughes, J. R.; Hatsukami, D. Signs and symptoms of tobacco withdrawal. Arch. Gen. Psychiatry 43:289–294; 1986.
17. Jasinski, D. R. Assessment of the abuse potentiality of morphine-like drugs (methods used in man). In: Martin, W. R., ed. Handbook of experimental pharmacology, Vol. 45. Berlin: Springer-Verlag; 1977:197–258.
18. Robinson, J. H.; Pritchard, W. S.; Davis, R. A. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. Psychopharmacology 108:466–472; 1992.
19. Rose, J. E.; Zinser, M. C.; Tashkin, D. P.; Newcomb, R.; Ertle, A. Subjective response to cigarette smoking following airway anesthetization. Addict. Behav. 9:211–215; 1984.
20. Rose, J. E.; Levin, E. D.; Behm, F. M.; Adivi, C.; Schur, C. Transdermal nicotine facilitates smoking cessation. Clin. Pharmacol. Ther. 47:323–330; 1990.
21. Rose, J. E.; Hickman, C. S. Citric acid aerosol as a potential smoking cessation aid. Chest 92:1005–1008; 1987.
22. Rose, J. E.; Levin, E. D. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br. J. Addict. 86:605–609; 1991.
23. Sokal, R. R.; Rohlf, F. J. Biometry: The principles and practice of statistics in biological research. San Francisco: W.H. Freeman; 1969:237–238.
24. Stolerman, I. P.; Kumar, R.; Pratt, J. A.; Reavill, C. Discriminative stimulus effects of nicotine: Correlation with binding studies. In: W. R. Martin; G. R. Van Loon; E. T. Iwamoto; L. Davis, eds. Tobacco smoking and nicotine: A neurobiological approach. New York: Plenum Press; 1987:113–124.
25. U.S. Department of Health and Human Services. The health consequences of smoking: Nicotine addiction. A report of the surgeon general. Washington, D.C.: U.S. Government Printing Office; 1988.

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Dissociating the Nicotine and Airway Sensory Effects of Smoking

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WESTMAN, E. C., F. M. BEHM AND J. E. ROSE. *Dissociating the nicotine and airway sensory effects of smoking.* PHARMACOL BIOCHEM BEHAV **53**(2) 309–315, 1996.—This study examined the subjective and cardiovascular effects of two of the components of cigarette smoking when given separately: nicotine and airway sensations. Using a within-subjects design, six healthy volunteer smokers, age 18–45 years, who smoked at least 20 cigarettes per day were given six conditions in a randomized, counterbalanced order. The effects of IV nicotine, IV saline, and denicotinized cigarettes were compared to a standard 1-mg cigarette. The standard cigarette produced more of a calming effect and more irritability reduction than either the nicotine or airway sensations alone. The denicotinized cigarette was similar to the standard cigarette condition, except the cigarette condition was associated with higher feelings of "exhilaration." Many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette. These data support the hypothesis that replacement of the sensory cues of smoking with "airway sensory replacement" may be useful for smoking cessation.

Nicotine Smoking Intravenous Infusion

SMOKING is currently understood as a drug addiction to nicotine (18). However, nicotine replacement therapy alone for smoking cessation is only partially successful. For example, the average success rate at 6 months combining 17 nicotine patch studies is only about 22% (6). Nicotine replacement therapy may be only partially successful for smoking cessation because it does not replicate the rapid, high doses of nicotine delivered by cigarette smoking. Alternatively, nicotine replacement may be only partially successful for smoking cessation because nicotine only partially explains the smoking addiction.

The low success rates with nicotine replacement alone may be due to the lack of adequate attention to the sensory and motor components of smoking. These sensory and motor components are then linked to the primary reinforcing drug: nicotine. From the smoker's perspective, these sensory and motor cues may be equally as reinforcing as nicotine. In previous studies from our laboratory using airway anesthesia to block airway sensations, smoking was less enjoyable, and by inference less reinforcing, without the usual associated airway sensations of smoking (11,12). The observation that many of the major reinforcing sensory cues are in the smoker's airway led to the "airway sensory hypothesis" of smoking (13).

If nicotine alone could explain the smoking addiction, then smoking cessation research should continue to focus on ways to replace nicotine. On the other hand, if the airway sensory hypothesis also explains part of the smoking addiction, then research efforts should also be placed upon reproducing the airway sensations of smoking.

The purpose of this study was to examine the subjective effects of two of the components of smoking when given separately: nicotine and airway sensations. In this study, overnight-deprived smokers were studied under conditions of: 1) IV nicotine without the airway sensory components of smoking; 2) the airway sensory components of smoking without the nicotine; 3) the combined nicotine and airway sensory components of smoking, and 4) a standard nicotine-containing cigarette. We hypothesized that the administration of nicotine and airway sensations alone would reproduce many of the effects of a standard cigarette.

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METHOD

Subjects

Six healthy volunteer smokers, age 18–45 years, who smoked at least 20 cigarettes per day, were recruited by newspaper advertisement. Subjects were screened by history, physical, serum chemistries, complete blood count, and resting electrocardiogram prior to study enrollment. Light smokers were excluded if the baseline (afternoon) exhaled carbon monoxide level was less than 15 ppm. The six subjects had a mean age of 34.3 years (range 19–43 years); all were male; five were Caucasian, one was African-American. Subjects smoked 28.5 cigarettes per day on average (range 20–40), and had been smoking for an average of 20.3 years (range 3–35). The mean baseline carbon monoxide level was 27.7 ppm (range 17–40); the mean Fagerstrom score (FTND) was 6.5 (range 5–9) (7). Two subjects were college graduates; two had completed some college, one some high school, and one eighth grade or less. Subjects were paid $10/h for compensation. Informed consent approved by the local Institutional Review Board was read and signed prior to participation.

Design

Using a within-subjects design, each subject was given six conditions in a randomized, counterbalanced order using a Latin square (Table 1). Nicotine IV was given during conditions A, B, D, and E; saline IV was given during conditions C and F. The dose of 1 mg nicotine was chosen to approximate the nicotine delivery from a medium strength cigarette, and was given either as: 1) 1-mg nicotine base solution continuously infused over 10 min (conditions A, D) or 2) 0.1-mg nicotine base solution pulse injected every minute for 10 min (conditions B, E). There was no smoking during conditions A and B, smoking of a denicotinized cigarette during conditions C, D, and E, and smoking of a standard 1-mg nicotine (by FTC analysis) cigarette during condition F. The denicotinized cigarettes were similar to the medium strength cigarettes in tar, draw, and other nonnicotine sensory features (1).

Conditions A and B were designed to assess the effect of nicotine alone when given without the airway sensations. Condition C assessed the effect of airway sensations of a denicotinized cigarette alone. Conditions D and E assessed the combination of the IV nicotine and denicotinized smoke. Condition F served as the nicotine cigarette reference.

The study staff administering the conditions and questionnaires were unaware of the study hypotheses, and the study physician administering the infusions had little interaction with the subjects.

Procedures

Subjects reported to the Nicotine Research Laboratory at 0730 h after overnight smoking abstinence (verified by self-report of no smoking since 2400 h of the study day and exhaled carbon monoxide < 20 ppm). After completing a baseline craving and side effect questionnaire, the subjects were seated in a chair in the semirecumbent position. Two 22-ga IV catheters (one in each antecubital vein) were inserted 30 min prior to the infusions. During all conditions, cardiac rhythm was monitored continuously, and blood pressure and pulse were measured each minute via an automated oscillometric blood pressure recorder (Dinamap model 1846sx, Critikon, Tampa, FL).

The conditions were administered every 30 min over a 3.5-h period. The IV solutions were delivered via infusion pump (conditions A, C, D, F) or syringe (conditions B, E), and in the syringe conditions were started approximately 5–10 s prior to each puff to approximate the usual 7-s time interval between puffing and arrival of nicotine at the brain (normal range of arm to brain circulation time = 9–16 s; estimated lung to brain circulation time = 7 s) (5). The cigarettes were smoked through a cigarette holder positioned at the subject's mouth. One puff was inhaled every minute for 10 min, and five puffs were taken from each of two cigarettes to maintain consistency of puff delivery of nicotine.

Measures

Venous nicotine levels. Blood samples were taken immediately before and after each condition. Samples were centrifuged, frozen, and sent for nicotine determination by gas chromatography (Clinical Pharmacology Unit of the Medical Service, San Francisco Hospital Medical Center).

Exhaled carbon monoxide. Carbon monoxide levels (Vitalograph, Lanexa, KS) were measured before and after each condition after 10 s of breath holding.

Vital signs. Blood pressure and pulse were measured upon arrival to the laboratory, 10 min prior to each condition, then every minute during the conditions.

Satisfaction and liking. Questionnaire items assessing satisfaction and liking were completed at the end of each condition. The items asked "Was it satisfying?," "How much did you like the puffs that you just took?" The items were rated on a scale from 1 ("not at all") to 7 ("extremely").

TABLE 1

STUDY CONDITIONS AND NICOTINE AND EXHALED CARBON MONOXIDE BOOST

Condition	Intravenous Solution	Airway Sensations	Venous Nicotine Boost* [ng/ml (sd)]	Exhaled CO Boost† [ppm (sd)]
A	Nicotine infusion	No smoking	4.2 (2.9)	0.7 (4.2)
B	Nicotine pulses	No smoking	8.9 (3.0)	−0.8 (1.5)
C	Saline infusion	Denic cigarette	0.2 (5.2)	12.7 (7.0)
D	Nicotine infusion	Denic cigarette	7.1 (4.0)	7.8 (0.8)
E	Nicotine pulses	Denic cigarette	7.6 (2.9)	9.8 (0.8)
F	Saline infusion	Cigarette	16.7 (3.5)	7.2 (1.2)

*Venous nicotine boost comparisons: AB vs. C, $p = 0.001$; AB vs. F, $p = 0.0001$; C vs. F, $p = 0.0001$; DE vs. F, $p = 0.0001$; DE vs. C, $p = 0.0003$.

†Exhaled CO boost comparisons: AB vs. C, DE, or F, $p < 0.0001$; C vs. DE, $p = 0.03$; C vs. F, $p = 0.01$.

Craving reduction. One item asked "Did it immediately reduce your craving?," rated from 1 ("not at all") to 7 ("extremely"). A modified Shiffman-Jarvik smoking withdrawal questionnaire was administered after each condition to measure postcondition craving (15). From this questionnaire, a craving subscale was used containing six items (craved a cigarette, would have liked a cigarette, thought of cigarettes, missed a cigarette, had urges to smoke and, scored oppositely, would have refused a cigarette). The items were also rated on a scale from 1 ("not at all") to 7 ("extremely").

Airway sensory effects. A questionnaire regarding the strength of sensations in the mouth and tracheobronchial tree was completed at the end of each condition: "Rate how strong the puffs were in the following places: tongue, nose, back of mouth & throat, windpipe, chest." Another item asked "Did you enjoy the sensations of the smoke in your throat and chest?" These items were rated from 1 ("not at all") to 7 ("extremely").

Other effects. A questionnaire was administered after each condition asking if the subjects experienced calming effects ("calm you down," "a feeling of relaxation," "a feeling of comfort," "less irritable," "a sense of well-being"), arousing effects ("more awake," "help you concentrate," "exhilaration," "pleasurable excitement"), or adverse effects ("dizziness," "lightheadedness," "nausea," "nervousness"). "The items were scored from 1 ("not at all") to 7 ("extremely"). After each condition, an open-ended side effect questionnaire was given, and subjects were asked if they thought they had received nicotine.

Analysis Plan

Each of the outcome measurements was compared first in an overall repeated-measures analysis of variance (ANOVA) model (Superanova, Abacus Concepts Inc., Berkeley, CA) Because there was no significant difference in nicotine delivery between the IV infusion and the IV bolus injections, the IV nicotine conditions (A, B) were combined, and the IV + denicotinized cigarette conditions (D, E) were combined. If the overall model was significant, the following planned comparisons were made:

1. Nicotine alone vs. nicotine and airway sensory cues (AB vs. DE).
2. Nicotine effect with airway sensory cues held constant (C vs. DE).
3. Nicotine alone vs. standard nicotine cigarette (AB vs. F).
4. Airway sensory cues vs. standard nicotine cigarette (C vs. F).
5. Airway sensory cues + nicotine vs. standard nicotine cigarette (DE vs. F).

All comparisons were two-tailed, using a $p = 0.05$ as the level of statistical significance.

RESULTS

Venous Nicotine Levels

The combined mean nicotine levels of conditions A + B (6.6 ng/ml) and conditions D + E (7.3 ng/ml) were significantly higher than the saline condition C (0.2 ng/ml), and were significantly lower than the standard nicotine cigarette condition F (16.7 ng/ml) (Table 1). The mean nicotine levels of the IV infusion conditions (A and D) were not significantly different from the nicotine pulse conditions (B and E).

Exhaled Carbon Monoxide

The highest mean carbon monoxide level was observed in the denicotinized cigarette condition (C), and was significantly higher than the other smoking conditions (D, E, and F) (Table 1). The mean carbon monoxide levels from the combined nicotine/sensory conditions (D, E) were not significantly different from the cigarette condition (F). All of the smoking conditions (C, D, E, F) had significantly higher carbon monoxide boosts than the nonsmoking conditions A and B ($p < 0.0002$).

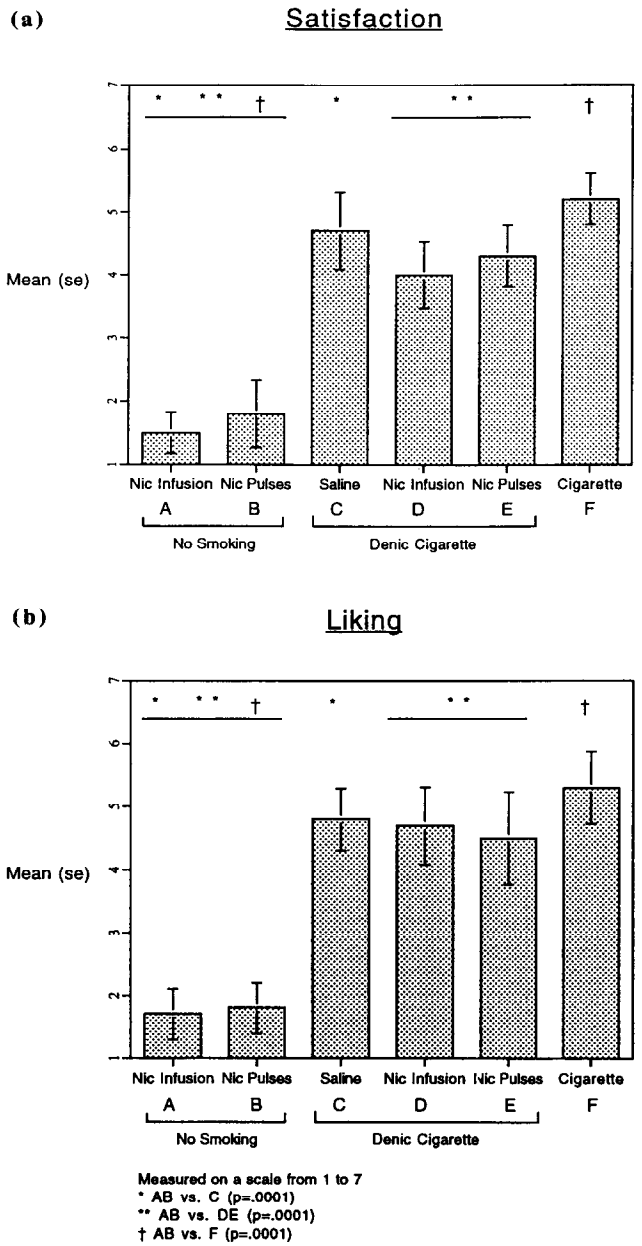


FIG. 1. (a) Mean ± SEM subjective satisfaction for the six study conditions ($n = 6$). (b) Mean ± SEM subjective liking for the six study conditions ($n = 6$).

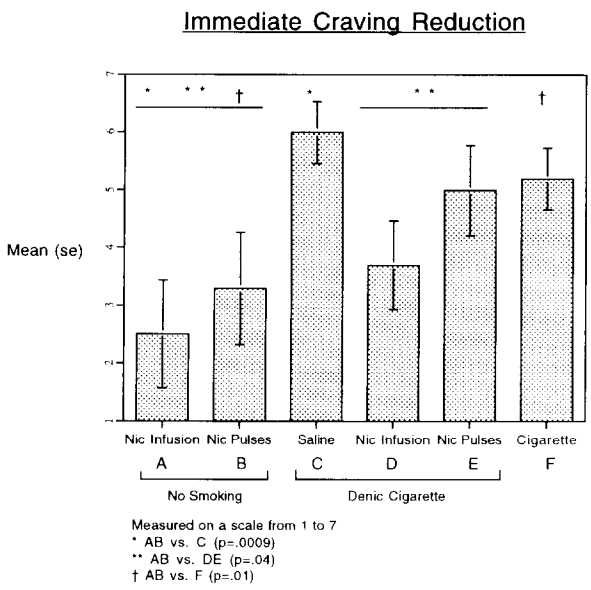


FIG. 2. Mean ± SEM subjective immediate craving reduction for the six study conditons (n = 6).

Vital Signs

There were no statistically significant overall model differences among the conditions for mean maximal rise in pulse, systolic blood pressure, or diastolic blood pressure. The maximal rise in pulse (bpm) for condition A was 12.2, condition B was 11.2, condition C was 11.3, condition D was 13.0, condition E was 12.8, and condition F was 15.5. The maximal rise in systolic blood pressure (mmHg) for condition A was 6.5, condition B was 15.2, condition C was 7.8, condition D was 11.2, condition E was 10.0, and condition F was 9.5. The maximal rise in diastolic blood pressure (mmHg) for condition A was 7.3, condition B was 9.5, condition C was 7.8, condition D was 12.3, condition E was 6.7, and condition F was 7.8.

Satisfaction and Liking

Satisfaction and liking were both significantly higher for the four smoking conditions (C, D, E, and F) than for the two IV nicotine conditions (Fig. 1a,b). There were no significant differences among the four smoking conditions for satisfaction or liking.

Craving Reduction

On the single item of immediate craving reduction, there were no significant differences among any of the smoking conditions (C, D, E, and F), but craving reduction was higher for all of the smoking conditions than the IV nicotine conditions alone (A, B) (Fig. 2). There were no differences among the conditions on the postcigarette craving subscale, with scores ranging from 3.7 to 3.9.

Airway Sensory Effects

There were no significant differences for strength in the tongue, nose, back of mouth & throat, windpipe, and chest among any of the smoking conditions (C, D, E, and F), but these sensations were significantly higher for all of the smoking conditions than the IV nicotine alone conditions (A, B). The chest sensations are shown in Fig. 3a. The enjoyment of chest sensations was similar for any type of smoking, and significantly higher for the smoking conditions than the IV nicotine conditions (Fig. 3b). Good taste was similar for the smoking conditions, and significantly higher for the smoking conditions than the nonsmoking conditions. Good taste for condition A was 1.8, condition B was 1.3, condition C was 4.3, condition D was 3.3, condition E was 3.6, and condition F was 4.3.

Other Effects

The cigarette condition (F) was consistently higher than the IV conditions (A, B) for four of the five calming items ["calm

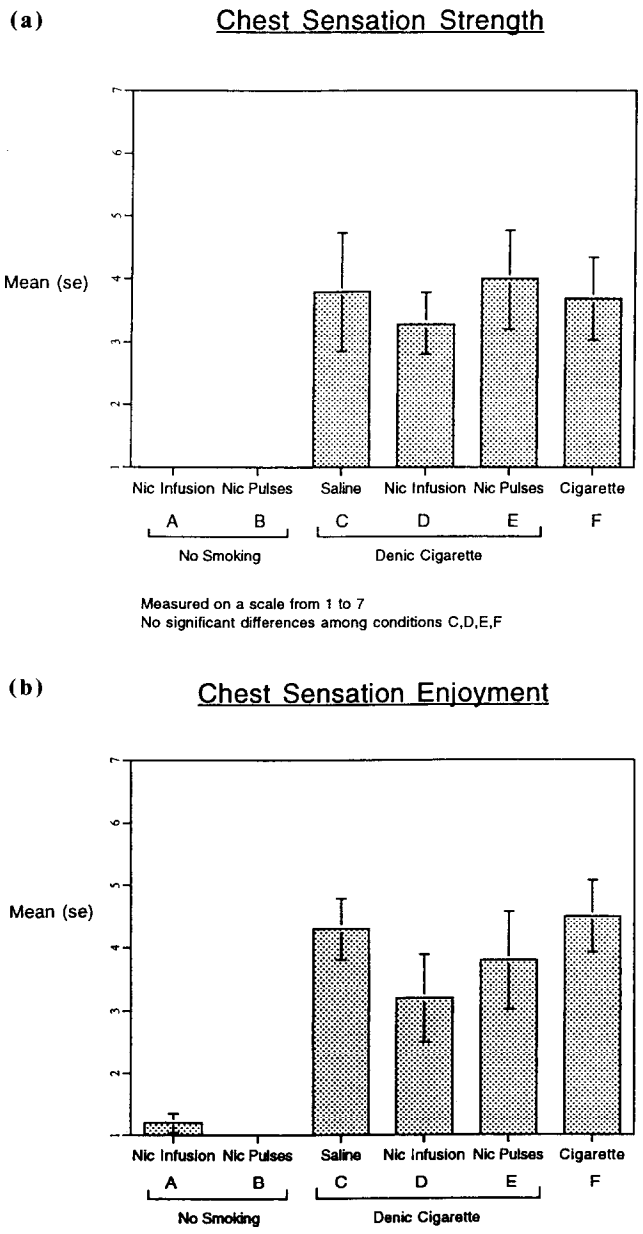


FIG. 3. (a) Mean ± SEM subjective chest sensation strength for the six study conditions (n = 6). (b) Mean ± SEM subjective chest sensation enjoyment for the six study conditions (n = 6).

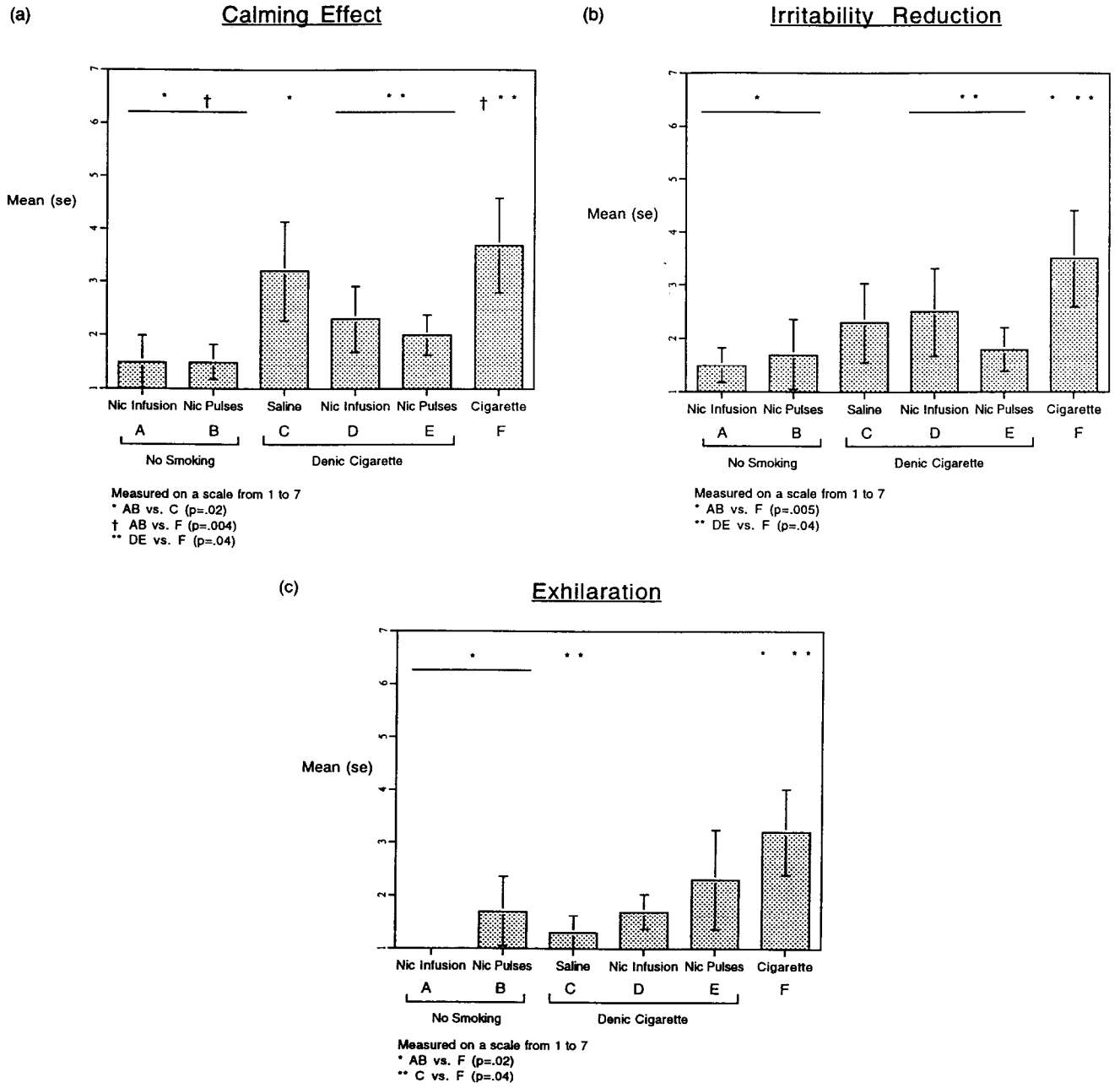


FIG. 4. (a) Mean ± SEM subjective calming effect for the six study conditions (n = 6). (b) Mean ± SEM irritability reduction for the six study conditions (n = 6). (c) Mean ± SEM subjective exhilaration for the six study conditions (n = 6).

you down" (p = 0.004), "a feeling of relaxation" (p = 0.02), "a feeling of comfort" (p = 0.01), "less irritable" (p = 0.005)], three of four arousing items ["more awake" (p = 0.03), "help you concentrate" (p = 0.03), "exhilaration" (p = 0.02)], and one of four adverse items ["dizziness" (p = 0.006)].

The cigarette condition (F) was similar to the nicotine/sensory conditions (D, E) except it had higher scores for the items "calm you down," and "less irritable" (Fig. 4a,b). Additionally, the cigarette condition (F) was similar to the denicotinized cigarette condition (C), except the cigarette condition had higher feelings of "exhilaration" (Fig. 4c).

All conditions were well tolerated. Mild burning at the catheter site occurred in several subjects, but there was no significant difference among the conditions. Of the other adverse effects, there were no differences for lightheadedness, nausea, or nervousness. For dizziness, the cigarette (F) and denicotinized cigarette (C) conditions were significantly higher than the IV nicotine conditions (p = 0.006, p = 0.04, respectively). Dizziness for condition A was 1.2, condition B was

1.8, condition C was 3.2, condition D was 2.2, condition E was 2.7, and condition F was 3.8.

Subjects were generally well blinded to the drug administration. In ascertaining the presence or absence of nicotine, the percent correct for each subject (out of six conditions) was 16.7%, 33.3%, 50%, 50%, 50%, and 83.3%. Subjects correctly identified nicotine being present or absent 50% of the time (6/12) for conditions A and B, 33.3% of the time (2/6) for condition C, 41.7% of the time (7/12) for conditions D and E, and 66.7% of the time (4/6) for condition F.

DISCUSSION

In this study, we attempted first to recreate the experience of cigarette smoking, and then to focus on the sensory and nicotine components independently. Although we were unable to replicate the nicotine levels of smoking, we were able to reproduce many of the subjective experiences of cigarette smoking. Because satisfaction and immediate craving reduction were reproduced by a denicotinized cigarette, we conclude that the airway sensations of smoking may be just as important as nicotine for short-term smoking satisfaction and craving reduction.

Many of the effects of a standard 1-mg cigarette were reproduced by the denicotinized cigarette in this study. The denicotinized cigarette produced airway sensations, craving reduction, arousal, and relaxation similar to the standard 1-mg cigarette. However, the standard 1-mg nicotine cigarette produced more calming effect and irritability reduction than the combined sensory/nicotine conditions, and more "exhilaration" than the denicotinized cigarette. Because some of the airway sensations of a cigarette arise from nicotine, a denicotinized cigarette should not be expected to entirely reproduce the airway sensations of a nicotine cigarette. Differences between the two cigarettes in this study may result from the greater nicotine and tar delivery from the standard cigarette, or may be due to the unique qualities of the airway sensations of nicotine-containing smoke.

By design, the subjects were able to adjust their intake of cigarette smoke in this study by controlling the depth and duration of inhalation. As a result, subjects achieved higher boosts in carbon monoxide while smoking a denicotinized cigarette than while smoking a standard 1-mg nicotine cigarette. This increase in inhalation may have been the subjects' attempts to increase nicotine intake from the denicotinized cigarette. An alternative hypothesis may be that the subjects were compensating for the loss in nicotine stimulation by increasing the amount of airway sensations received. This ability to control smoke intake may have allowed the subjects to receive more craving reduction and higher satisfaction in the smoking conditions than the nonsmoking conditions.

Intravenous nicotine had a small effect on craving reduction, satisfaction, and liking. Although the subjective effects of IV nicotine were subtle, IV nicotine decreased the amount of smoked inhaled: the mean carbon monoxide level after condition C was 12.7 compared to 8.8 for conditions D and E combined ($p = 0.03$).

Intravenous nicotine can be a useful tool for studying the pharmacological reinforcement of smoking in the absence of the usual behavioral components of cigarette smoking (3,4,8,9,14). In this study we used a nicotine dose and rate of delivery similar to the dose and rate expected from smoking a cigarette, but did not entirely achieve nicotine levels comparable to smoking. Although in previous studies higher doses of IV nicotine were sometimes used, these studies did not use standard measures to assess craving, satisfaction, and other subjective effects.

We used IV nicotine to study the effects of nicotine alone without the sensory components of smoking. Although nicotine could be replaced with nicotine sprays or inhalers, the associated sensory effects of these delivery systems would then need to be taken into account in the effect of nicotine: the nasal spray produces an aversive nasal mucosa irritation; the nicotine inhaler can elicit the cough reflex (16,17). To optimize cerebral blood nicotine levels, further studies should use higher peripheral venous IV doses or even pulmonary artery infusion of nicotine.

The extrapolation of our study findings to smoking is limited because we only addressed the short-term administration of nicotine and airway sensations. Long-term administration may diminish the conditioned cues over time such that the same effect may not be observed. In addition, by not incorporating the holding and manipulating of the cigarette usually associated with smoking, we may have reduced the magnitude of satisfaction and craving reduction, thereby decreasing the power for finding significant results.

Our laboratory has focused on the importance of airway sensations to the smoking behavior in developing new methods for smoking cessation. The airway sensory hypothesis of smoking has led to the promising initial studies of an ascorbic acid inhaler, and a citric acid inhaler (2,10). In another study, a citric acid inhaler combined with the nicotine patch improved short-term smoking cessation rates over the nicotine patch alone (19). If devices like these, which only partially substitute for the sensory effects of smoking, have robust effects on craving, then sensory replacements that are more similar to smoking may have even greater effectiveness.

In this study, we examined the subjective effects of the nicotine and airway sensory components of smoking in combination and separately. We found that many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette. Therefore, we hypothesize that replacement of the conditioned sensory cues of smoking with "airway sensory replacement" may improve the effectiveness of nicotine replacement for smoking cessation.

ACKNOWLEDGEMENTS

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REFERENCES

1. Baldinger, B.; Hasenfratz, M.; Battig, K. Switching to ultra-low nicotine cigarettes: Effects of different tar yields and blocking of olfactory cues. Pharmacol. Biochem. Behav. 50:233–239; 1995.
2. Behm, F. M.; Schur, C.; Levin, E. D.; Tashkin, D. P.; Rose, J. E. Clinical evaluation of a citric acid inhaler for smoking cessation. Drug Alcohol Depend. 31:131–138; 1993.
3. Benowitz, N. L.; Jacob, P., III. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. J. Pharmacol. Exp. Ther. 254:1000–1005; 1990.
4. Benowitz, N. L.; Jacob, P. J., III; Olsson, P.; Johansson, C. Intravenous nicotine retards transdermal absorption of nicotine: Evidence of blood flow-limited percutaneous absorption. Clin. Pharmacol. Ther. 52:223–230; 1992.

5. Braunwald, E. Heart disease: A textbook of cardiovascular medicine. 2nd ed. Philadelphia: W. B. Saunders; 1984:500.
6. Fiore, M. C.; Smith, S. S.; Jorenby, D. E.; Baker, T. B. The effectiveness of the nicotine patch for smoking cessation. JAMA 271:1940–1947; 1994.
7. Heatherton, T. F.; Kozlowski, L. T.; Frecker, R. C.; Fagerstrom, K. L. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. Br. J. Addict. 86:1119–1127; 1991.
8. Henningfield, J.; Goldberg, S. Control of behavior by intravenous nicotine injections in human subjects. Pharmacol. Biochem. Behav. 19:1021–1026; 1983.
9. Henningfield, J. E.; Goldberg, S. R. Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol. Biochem. Behav. 19:989–992; 1983.
10. Levin, E. D.; Behm, F. M.; Carnahan, E.; LeClair, R.; Shipley, R.; Rose, J. E. Clinical trials using ascorbic acid aerosol to aid smoking cessation. Drug Alcohol Depend. 33:211–223; 1993.
11. Rose, J. E.; Tashkin, D. P.; Ertle, A.; Zinser, M. C.; Lafer, R. Sensory blockade of smoking satisfaction. Pharmacol. Biochem. Behav. 23:289–293; 1985.
12. Rose, J. E.; Zinser, M. C.; Tashkin, D. P.; Newcomb, R.; Ertle, A. Subjective response to cigarette smoking following airway anesthetization. Addict. Behav. 9:211–215; 1984.
13. Rose, J. E. The role of upper airway stimulation in smoking. In: Pomerleau, O. F.; Pomerleau, C. S., eds. Nicotine replacement: A critical evaluation. New York: Alan R. Liss, Inc.; 1988:95–106.
14. Rosenberg, J.; Benowitz, N. L.; Jacob, P. J., III. Disposition kinetics and effects of intravenous nicotine. Clin. Pharmacol. Ther. 28:517–522; 1980.
15. Shiffman, S.; Jarvik, M. E. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology (Berlin) 50:35–39; 1976.
16. Sutherland, G.; Stapleton, J. A.; Russell, M. A. H.; et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 340:324–329; 1992.
17. Tonnesen, P.; Norregaard, J.; Mikkelsen, K.; Jorgensen, S.; Nilsson, F. A double-blind trial of a nicotine inhaler for smoking cessation. JAMA 269:1268–1271; 1993.
18. USDHHS. The health consequences of smoking: Nicotine addiction. A report of the Surgeon General, 1988. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. Center for Disease Control. DHHS Publ. No. (CDC) 88-8406; 1988.
19. Westman, E. C.; Behm, F. M.; Rose, J. E. Airway sensory replacement combined with nicotine replacement for smoking cessation: A randomized, placebo controlled trial using a citric acid inhaler. Chest 107:1358–1364; 1995.

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Nicotine-Containing Versus De-Nicotinized Cigarettes: Effects on Craving and Withdrawal

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GROSS, J., J. LEE AND M. L. STITZER. *Nicotine-containing versus de-nicotinized cigarettes: Effects on craving and withdrawal.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 159–165, 1997.—Nicotine exposure levels and subjective effects from smoking a de-nicotinized cigarette (Next) were examined under controlled conditions. Ten tobacco smokers smoked 20 puffs from their own brand (1.1 mg nicotine delivery, commercial cigarettes), a 0.7 mg nicotine "light" cigarette, or the Next de-nicotinized cigarette (< 0.1 mg nicotine) during independent experimental test sessions. The Next cigarette did not deliver any appreciable nicotine, did not elevate heart rate during smoking, and was rated as less satisfying than the smokers' own brand. Subjective ratings of cigarette craving and tobacco withdrawal symptoms increased during a 90 min post-smoking abstinence period. However, there were no measurable differences on these subjective ratings across the three cigarette test brands. It is concluded that nicotine can be removed from cigarettes without affecting the onset time course or intensity of cigarette cravings and other tobacco withdrawal symptoms in an acute abstinence model. Further studies to determine the subjective and physiological effects of nicotine-free cigarettes would contribute to a greater understanding of tobacco withdrawal and the processes involved in smoking maintenance. © 1997 Elsevier Science Inc.

De-nicotinized cigarettes Withdrawal effects Craving Light cigarettes Next cigarette Subjective effects

IT is generally accepted that nicotine is the primary active ingredient that supports addictive patterns of tobacco cigarette smoking (16). While the direct effects of nicotine have been fairly well documented when nicotine is delivered in uncontaminated forms, for example, by IV infusion (8), nicotine gum (10), and nicotine nasal spray (11), the complex pharmacological and sensory factors associated with tobacco cigarette smoking need to be better understood in order to develop more effective smoking cessation strategies. Studies which have examined nicotine outside the smoking context do not allow for the interpretation of the very important non-nicotine aspects of cigarette smoking such as sensory and gustatory effects as well as the complex contextual and behavioral factors which are thought to maintain much of the smoking habit (13,7). However, research has shown that smokers will report enjoyment from and can achieve withdrawal relief from smoking de-nicotinized cigarettes (4). Without a tool such as the de-nicotinized cigarette, it has been difficult to understand the role that nicotine *per se* plays in the acute effects of tobacco smoking and abstinence.

De-nicotinized cigarettes, once marketed in the US as Next (machine yield < 0.1 mg nicotine), have been used to examine the role of non-nicotine factors in producing the subjective and biobehavioral effects of smoking (2) and in suppressing withdrawal symptoms (4). Baldinger et al. (2), for example, took a variety of measures during 24 h periods when subjects smoked cigarettes delivering 0.95 mg on average versus 0.08 mg nicotine. They detected differences in pulse rates but found no differences in cigarette consumption or craving ratings. Butschky et al. (4) manipulated nicotine dose during laboratory test sessions both by varying the number of cigarettes smoked (0–5) and the nicotine delivery characteristics of test cigarettes (1.1 versus 0.09 mg) using Next as the nicotine-free cigarette. Subjective ratings of liking and satisfaction differed for the nicotine-containing and denicotinized cigarettes. However, these produced strikingly similar reductions in craving and withdrawal measures immediately post-smoking.

The purpose of this study was to replicate findings from Baldinger et al. (2) and Butschky et al. (4) concerning rated

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sensory and reinforcing characteristics of de-nicotinized versus nicotine containing cigarettes. In addition, the study was intended to extend the observations of Butschky et al. (4) by determining whether more intense withdrawal ratings (i.e. craving and distress symptoms) would be detected during a more extended post-smoking observation period after subjects smoked a de-nicotinized cigarette compared to nicotine-containing cigarettes. The experimental model utilized detailed measures of subjective effects both during and after cigarette smoking in order to examine the onset time course of cigarette cravings following the smoking of cigarettes with differing nicotine delivery characteristics including denicotinized cigarettes.

METHOD

Subjects

Smokers were recruited using community-based advertising for a 3 day laboratory study of cigarette smoking. Participants included 7 males and 3 females with a mean age of 38.2 years who were not interested in quitting smoking. These subjects smoked between 23–45 nonmenthol cigarettes per day (mean = 28.25) with an average nicotine yield of 1.07 (range = 0.9–1.1). Subjects had been smoking regularly from 15–30 years (mean = 22.1). The mean Fagerstrom (5) score of 8.3 (s.d. = 1.7) was evidence of the high degree of dependence for all subjects. Prior to participation in the study, volunteers signed an informed consent that had been approved by this institution's human subject review board. On average, subjects earned $85 for their participation.

Materials

Three different brands of cigarettes were used during the experimental sessions. The test cigarette, against which the other two brands served as comparisons, was the brand "Next" manufactured by Philip Morris, Inc. (Richmond, VA, USA). Next is a de-nicotinized cigarette with a machine nicotine yield of < 0.1 mg and a tar yield of 10.8 mg (4). The first comparison cigarette was the subjects' own preferred brand (Own). All subjects smoked cigarettes with rated nicotine yields between 0.9 and 1.1 mg. The average nicotine yield of the Own condition was 1.07 and average tar yield was 15.8. The second comparison cigarette selected was Winston Lights king size (Light; FTC rated machine yield of 0.7 mg nicotine and 10 mg tar). The tar yield of Light is similar to the Next while still providing a substantial contrast with Next on nicotine delivery.

Procedures

Each subject participated in three laboratory smoking sessions. Each session included a morning standardized exposure period (0930–1200) followed by an afternoon experimental testing period (1201–1400). Procedure for both morning and afternoon sessions were identical except for the cigarettes that were smoked. During all morning standardized exposure periods, subjects smoked their own preferred brand cigarettes while during the afternoon experimental period, subjects smoked the experimental cigarettes provided by research staff. A randomized counter-balanced design determined which of the three experimental smoking conditions, Own, Next, or Light brand, was assigned each afternoon.

The format of the daily sessions was as follows. The first step was to obtain baseline data utilizing a core battery of measures that included expired air carbon monoxide (CO), heart rate, craving ratings, and a withdrawal symptom questionnaire (measures are described more fully below). The subject then smoked the designated cigarettes under monitored conditions. Specifically, subjects smoked 20 puffs of the assigned cigarette through a plastic mouthpiece attached to monitoring equipment that recorded puff durations and interpuff intervals. In order to account for any differences in burn characteristics across cigarettes, subjects smoked a fixed number of puffs (four) from each of 5 cigarettes during test periods rather than smoking the entire cigarette. During the afternoon testing period, cigarette brand names were not visible and subjects were uninformed concerning the identity of the current test cigarette. Puff spacing and intensity was not controlled.

During each smoking bout, craving and satisfaction ratings were completed after each puff. At the end of the smoking bout, the core battery and questions about cigarette characteristics were administered. Following this, there was a 90 min deprivation period during which the subject sat quietly in the lab and completed a craving report every 15 min. At the end of the 90 min deprivation period, subjects completed the core battery once again.

Blood was drawn twice each day for the purpose of determining plasma nicotine. The first blood draw was at the end of the morning standardized exposure period (i.e., just prior to experimental smoking). This represents the pre-experimental smoking nicotine exposure level (hereafter referred to as "before smoking"). The second draw was immediately following puff 20 of the afternoon experimental smoking period.

Measures

Physiologic measures. Expired breath carbon monoxide was obtained by asking subjects to first exhale, and then inhale and hold their breath for 15 s. Subjects then exhaled into a mouthpiece attached to a Vitalograph EC50 CO monitor which provided immediate CO analysis in parts per million (ppm; Vitalograph Incorporated, Lenexa, KS). Heart rate was taken manually by the research assistant at the radial pulse for 10 s and converted to beats per min. Blood was drawn in a standard fashion from a forearm vein and analyzed by an outside lab (Labstat, Ontario) for nicotine using gas chromatography.

Subjective report measures. A 3-item craving/satisfaction measure was used during smoking bouts. Questions were presented on the computer screen using a 100 mm VAS. Subjects rated the following after each cigarette puff: 1) "How much did you like or enjoy the puff you just took?"; 2) "How much do you want to smoke right now?"; and 3) "How satisfying was your last puff?" Ratings ranged from "not at all" to "very much." An 8-item cigarette characteristics measure was used to rate the sensory and reinforcing properties of the cigarettes. At the end of the smoking bout, subjects were asked to rate the cigarettes as follows: "How strong was the cigarette?; "How hot was the cigarette?"; "How hard was it to draw smoke from the cigarette?"; "How harsh was the cigarette?"; "How much taste did you get from the cigarette?"; "How satisfying was the cigarette?"; "How much tobacco vs. 'just air' did you get from the cigarette?"; and "What is the likelihood that you would buy cigarettes like these?" Anchor points (eg: "no taste" = 0 to "a lot of taste" = 100) appropriately reflected extreme responses to each question.

During the 90 min deprivation periods (at 0, 15, 30, 45, 60, 75 and 90 min), subjects were asked to rate their craving or

urge for a cigarette using a 4-item measure. Items included: 1) "How pleasant would a puff be right now?"; 2) "How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking?"; 3) "How much do you need to smoke right now, for relief?"; and 4) "How much do you want to smoke right now?" Responses ranged from "not at all" to "very much."

The tobacco withdrawal scale, administered at the start and end of each 90 min smoking deprivation interval, was based on the measure developed by Hughes and Hatsukami (9) but was modified for use with a 100 mm VAS. Subjects rated their subjective distress based on the following items: 1) Urges to smoke; 2) Irritability/frustration/anger; 3) Anxious; 4) Difficulty concentrating; 5) Restlessness; 6) Hunger; 7) Impatient; 8) Craving cigarettes/nicotine; 9) Drowsiness; 10) Depression/Feeling blue; and 11) Desire for sweets. Anchor points at the ends of the VAS line were "none" and "severe."

Statistical Analyses

Because all subjects underwent all three experimental smoking conditions, this constituted a within-subject repeated measures study. Multivariate repeated measures ANOVA (experimental cigarette condition × measurement time point) was used to assess changes in dependent variables (CO, nicotine, heart rate, craving scores) measured before and after the 20 puff smoking bout. Effects of the 90 min smoking abstinence period were also assessed using repeated measures ANOVA for the 4-item craving scale administered at 15 min intervals throughout and for the withdrawal symptoms measure administered at the start and end of this interval. Analyses were conducted using SPSS for the Macintosh. Huynh-Feldt corrected p-values are presented to correct for any violations of the sphericity assumption. When post hoc analyses were relevant, Tukey's honestly significant difference test was conducted to ascertain differences between means.

RESULTS

Physiological Effects of Smoking

A multivariate repeated measures ANOVA was used to examine equivalency of pre-smoking measures across conditions and changes produced by smoking the three types of test cigarettes. Mean nicotine levels before smoking Own, Light, and Next brands were 11.3, 12.2 and 10.8 ng/ml respectively. Mean CO values were 29.9, 29.1, and 28.2 ppm while mean heart rates were 70, 75.4, and 73.8 bpm (Fig. 1). Heart rates for Own versus Light differed across conditions prior to smoking ($q = 6.14$, $p < 0.01$).

For nicotine, as shown in Fig. 1, there was a significant main effect of time ($F(2,18) = 6.87$, $p < 0.03$) with nicotine levels greater, on average, after smoking the experimental cigarette than before. There was also a significant main effect of cigarette brand ($F(1,9) = 9.12$, $p < 0.002$) with the Own brand having the highest nicotine level overall, and a significant interaction ($F(2,18) = 9.65$, $p < 0.001$). Post hoc analysis revealed that pre-to-post smoking increase in nicotine was significant only for Own brand (6.0 ng/ml; q = 7.89, $p < 0.01$) with no significant differences in pre-to-post smoking nicotine levels for either the Light (1.4 ng/ml) or Next (−0.5 ng/ml) brands. Post hoc analyses also revealed that absolute after smoking nicotine levels were significantly higher for Own brand versus Light ($q = 4.85$, $p < 0.05$) and Own versus Next ($q = 9.11$, $p < 0.01$).

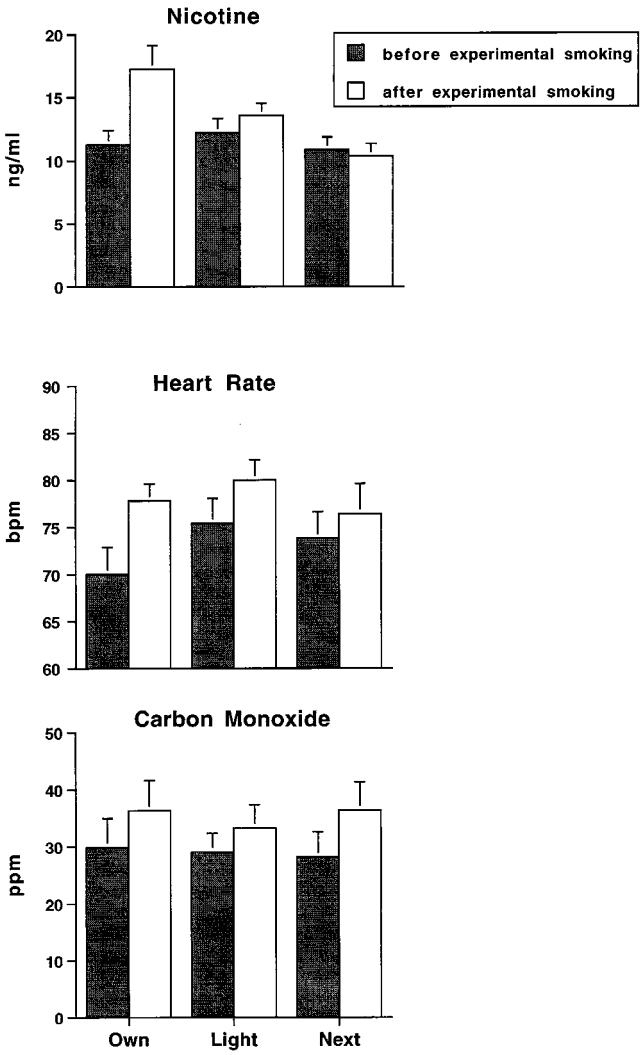


FIG. 1. Mean plasma nicotine, heart rate, and carbon monoxide levels before and after smoking the experimental cigarettes. Nicotine boost was significant for Own brand ($p < 0.01$) but not for Light or Next. For heart rate, Own ($p < 0.01$) and Light ($p < 0.05$) showed significant heart rate boosts. CO boost was significant for all three cigarette brands; Own and Light (p's < 0.001), Next ($p < 0.05$). Shaded bars reflect before smoking while open bars reflect after smoking periods. SEMs are shown.

Also shown in Fig. 1, there was a significant time effect ($F(2,18) = 12.1$, $p < 0.007$) and brand × time interaction ($F(2,18) = 4.45$, $p < 0.03$) for heart rate. Post hoc analyses found that the heart rate increase from before to after smoking was significant for the Own ($q = 8.87$, $p < 0.01$) and the Light ($q = 5.23$, $p < 0.05$) brand conditions but not for the Next brand. Heart rates rose 7.8 bpm for Own, 4.6 for Light, and 2.6 for Next. Also shown in Figure 1 is CO for each brand before and after smoking, which was not expected to be influenced by the varying nicotine content of the three brands. Consistent with the prediction, there was only a significant main effect of time ($F(2,18) = 29.7$, $p < 0.0001$). Post hoc analyses showed that CO levels after smoking were significantly higher than before smoking for each of the three brands

(Own $p < 0.01$, Light $p < 0.05$, Next $p < 0.01$). CO values rose, on average, 6.3 ppm following smoking of 20 puffs.

Craving and Satisfaction Ratings During Smoking

The three-item craving/satisfaction measure was administered after each of the 20 puffs during the experimental smoking session to assess craving and satisfaction during smoking as a function of nicotine content of the cigarette. Using a repeated measures ANOVA for cigarette brand (3 brands) × time (20 puffs), there was a significant main effect of cigarette brand for each of the two items: "How much did you like or enjoy the puff you just took?" (enjoyable); ($F(2,18) = 5.05$, $p < 0.02$) and "How satisfying was your last puff?" (satisfying); ($F(2,18) = 4.19$, $p < 0.04$). Subjects rated the Own brand as significantly more "enjoyable" than the Next or Light brands (mean rating over 20 puffs was 65.5 for Own, 38.1 for Light and 33.9 for Next). Similarly for the "satisfying" question, mean ratings were 59.8 for Own, 35.9 for Light, and 33.9 for Next. For neither of these questions was there a significant effect of time or a significant brand × time interaction. For the question "How much do you want to smoke right now?", there was no brand main effect or brand × time interaction; "want to smoke" ratings were 72.1, 59.9, and 62.6 for Own, Light and Next brands, respectively. There was, however, a significant main effect for time, reflecting a decrease in ratings for successive puffs across all brands ($F(19,171) = 5.22$, $p < 0.001$). Ratings decreased from a mean of 70.9 following puff number 1 to 56.1 following puff number 20.

Cigarette Characteristic Ratings

To assess the sensory effects of cigarettes at the end of the experimental smoking bout, ratings on eight items were analyzed independently using a one-way (test cigarette condition) repeated measures ANOVA. Table 1 shows the means for each of the cigarette brands and the F and p values. Overall, these scores suggest that the subjects could differentiate among the three test cigarettes based on their sensory characteristics. Particularly on the two items with statistically significant condition effects (strong, $p < 0.009$, and more smoke than air, $p < 0.01$), there was a graded response with highest ratings given to Own brand, lowest to Next brand, and intermediate ratings observed for Light. A similar although statistically nonsignificant pattern was seen for the item harsh. On items that were more reflective of cigarette "liking" (satisfy, taste, buy), subjects tended to give high ratings to the Own brand with lower and approximately equivalent ratings observed for Light and Next brands; these effects achieved borderline statistical significance.

Craving and Withdrawal Effects During the Deprivation Period

The 4-item craving measure was administered immediately after smoking and every 15 min throughout the 90 min deprivation period to compare the urge to smoke following exposure to each brand. In addition, this measure allowed us to assess the comparative suppression of craving by each brand. The items reflecting "urge or desire to smoke for pleasure" and "need to smoke for relief" are shown as representative items in Fig. 2, as all four questions showed similar patterns of responding. A cigarette brand (3 brands) × time point (pre, 0, 15, 30, 45, 60, 75, 90 min) repeated measures ANOVA was used. The time point designated "pre" is the 90 min post-smoking data point from the morning standardized exposure session and is used as a pre-experimental smoking comparison point to illustrate suppression of craving. For each of the four deprivation period craving questions, ratings increased significantly over time and there was a significant time main effect (all p's < 0.0001). There was no significant main effect nor a significant brand × time point interaction for any of the questions, as illustrated in Fig. 2. The "relief" question (lower panel, Fig. 2) was the only craving item on which scores after smoking the Next brand appeared consistently higher, albeit not significantly so, than scores for the other two brands. Comparison of data point "pre" versus the "0 min post-smoking" scores demonstrates that the three test cigarettes produced equivalent craving suppression.

The withdrawal scale was administered at the beginning and at the end of the 90 min deprivation period to determine the acute withdrawal effects for each of the cigarette brands. A cigarette brand (3 brands) × time (before, after) repeated measures ANOVA was used to analyze each item and the total score. There were no significant brand effects, nor any brand × time interactions. As seen in Table 2, there were significant increases over time during the deprivation period for 8 of the 11 individual items: urge to smoke ($p < 0.002$), irritable/frustrated/angry ($p < 0.022$), anxious ($p < 0.004$), difficulty concentrating ($p < 0.011$), restlessness ($p < 0.021$), hunger ($p < 0.002$), impatient ($p < 0.035$), and craving cigarettes/nicotine ($p < 0.003$). The total withdrawal score also showed a significant main effect for time ($p < 0.007$). The only items which did not change over time were drowsiness, depression/feeling blue, and desire for sweets; these three items were uniformly low at all assessment intervals.

TABLE 1

MEAN VALUES BY BRAND FOR THE EIGHT CIGARETTE CHARACTERISTIC VARIABLES

	Own Mean	Light Mean	Next Mean	F	p Value
Strong	57.3[a]	40.9	25.8[b]	6.15	0.009
Smoke than air	63.5[a]	40.2	26.3[b]	6.89	0.01
Harsh	52.7	44.1	28.5	2.59	ns
Satisfy	56.1	35.4	31.6	3.66	0.05
Buy	53.6	33.3	22.9	3.33	0.07
Taste	63.6	42.7	38.8	3.17	0.07
Hot	22.9	29.3	13.5	2.90	0.08
Draw	36.1	53.0	59.8	1.78	ns

[a,b]Means with different superscripts indicate significantly different values based on post hoc tests.

DISCUSSION

This laboratory study examined the subjective effects of nicotine-containing versus denicotinized cigarettes before, during, and after smoking a cigarette. Objective measures of nicotine exposure and heart rate changes (Fig. 1) confirmed that no appreciable nicotine was delivered by the denicotinized Next cigarettes, while expired breath CO measures supported the conclusion that similar amounts of smoke were inhaled from the three test cigarettes. Light cigarettes, rated as delivering 0.7 mg nicotine, were selected as a comparison for the Next brand on tar delivery (10.0 mg v. 10.8 mg) while theoretically producing a substantially greater nicotine boost. However, the magnitude of nicotine boost actually observed

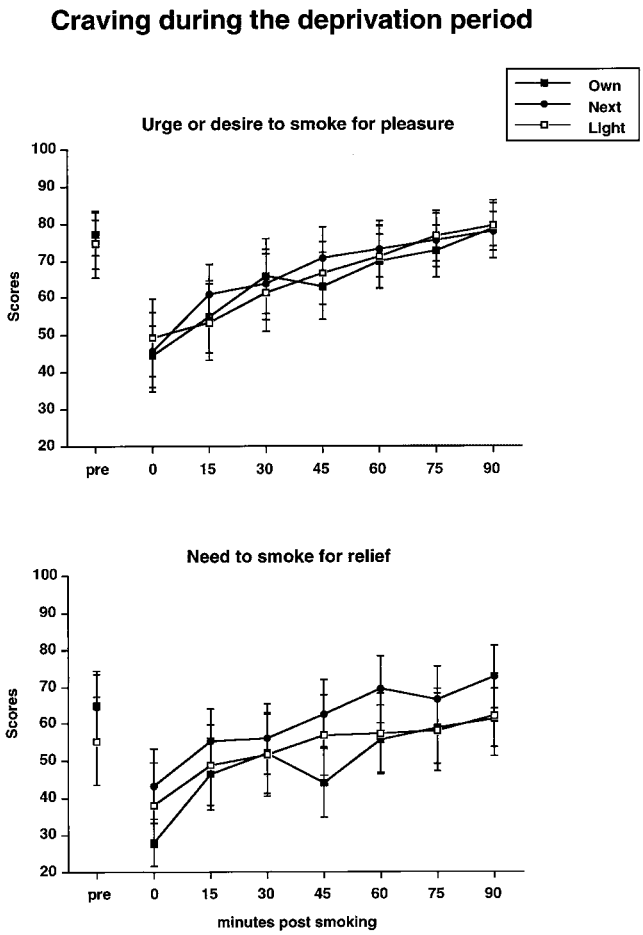


FIG. 2. Mean craving scores during the 90 min deprivation period is shown for two of the four craving questions. Time main effects are significant while there are no brand or interaction effects. The "pre" data point reflects the craving scores at the 90 min post-smoking time point from the morning standardized exposure period.

after smoking the light cigarettes (1.4 ng/ml), was less than expected and less than previously reported in studies which employed similar smoking protocols using cigarettes delivering 0.6–0.8 mg nicotine (12,18). In these previous studies, nicotine increases ranging from 14 to 26.4 ng/ml were observed. One possible explanation for the low nicotine boost with the light cigarette could be that in the present study, only 4 puffs were drawn from each cigarette, while in comparable studies, such as Zachny & Stitzer (18) and Robinson et al. (12) the entire cigarette was smoked. The implication is that our subjects would not have been exposed to the higher concentrations of nicotine which develop in the proximal portion of the cigarette as it is smoked. This argument could also be applied to the lack of nicotine increase detected after smoking Next cigarettes (Fig. 1). However, previous studies have independently verified the lack of nicotine delivery from the Next cigarettes (4).

Cigarette sensory characteristic ratings from the present study (particularly strength ratings) suggested that subjects could discriminate differences among the test cigarettes. This is consistent with recent data reported by Baldinger et al. (2). Subjects rated both Next and Light comparison cigarettes as less satisfying than their own brand (Table 1). These findings replicate those of Butschky et al. (4), who also found lower ratings of the Next cigarette compared to a regular brand on measures of liking, good effects, and satisfaction. Based on the unexpectedly low nicotine boost produced by smoking of "light" cigarettes in the present study, it would be predicted that these and Next would be rated similarly on measures that reflect smoking satisfaction and liking, a prediction that was generally upheld in the data (Table 1). However, neither this nor the previously published studies allow for any conclusions regarding the bases for these discriminations (i.e. nicotine delivery, tar delivery, filtration characteristics, etc.). In fact, previous observations suggest that subjects tend to rate unfamiliar cigarettes as less satisfying even if these deliver amounts of nicotine and tar comparable to their own brand (18). Thus, these acute ratings may not be very useful for determining long-term acceptance of cigarettes with altered delivery characteristics.

The present study extended previous findings regarding postsmoking withdrawal suppression by determining whether the nicotine delivery characteristics of cigarettes influence the onset time course of cigarette craving during a brief period of smoking abstinence (Fig. 2). Consistent with previous data from this laboratory (14), we observed a post-smoking suppression of craving ratings followed by an orderly rise in cigarette craving scores during the 90 mins following smoking of test cigarettes. In addition, several typical tobacco withdrawal symptom scores were elevated following as little as 90 mins of smoke deprivation; these included ratings of irritable, anxious, difficulty concentrating, restlessness, hunger and impatience. However, neither the magnitude nor the time course of these ratings was influenced by the nicotine delivery or other characteristics of cigarettes smoked during the session. The observation that nicotine-free cigarettes can suppress craving ratings in a manner similar to nicotine-containing cigarettes is consistent with data reported by Hasenfrantz et al. (7) and by Butschky et al. (4).

The ability of nicotine-free cigarettes to suppress withdrawal and craving ratings can most likely be attributed to conditioned sensory characteristics of smoking. Rose and colleagues (13,3) have strongly argued for the importance of these sensory effects in smoking and have demonstrated experimentally that lownicotine aerosols and citric inhalers produce airway stimulation which can influence satisfaction and craving ratings. It has also been suggested that the particulate constituents ("tars") delivered by cigarettes may have pharmacological reinforcing properties beyond the sensory effects they produce when inhaled (7). On the other hand, there is also evidence that pure nicotine delivered by methods other than tobacco cigarettes can suppress withdrawal and craving ratings. For example, Perkins and colleagues (11) showed that desire to smoke was suppressed with repeated administrations of nicotine nasal spray. Similar findings have been reported by Hajek and colleagues with the use of a smoke-free cigarette nicotine vaporizer (6). There is also some support for reduction in craving with the use of nicotine gum and nicotine patch although this effect is not very robust (1,15).

One of the most interesting questions that can be addressed with the nicotine-free cigarettes concerns the longer-term effects of removing nicotine both on cigarette satisfaction ratings and on the emergence of tobacco withdrawal symptoms. Baldinger and co-workers (2) have recently shown that no excess withdrawal symptoms or cravings could be detected when denicotinized cigarettes were smoked for a full 24 h. Similarly,

TABLE 2

MEAN VALUES FOR WITHDRAWAL SYMPTOM SCALE ITEMS DURING THE DEPRIVATION PERIOD

		Cigarette Brand			
	Time	Own (Mean)	Light (Mean)	Next (Mean)	Time Main Effect *p*-value
Urge to smoke	0 min post-smoking	41.6	48.6	47.6	
	90 min post-smoking	71.4	74.9	73.6	0.002
Irritable/Frustrated/Angry	0 min post-smoking	12.7	18.4	9.5	
	90 min post-smoking	27.4	27.2	18.0	0.002
Anxious	0 min post-smoking	13.6	17.3	11.1	
	90 min post-smoking	25.5	28.5	24.4	0.004
Difficulty concentrating	0 min post-smoking	9.1	15.3	12.7	
	90 min post-smoking	13.9	23.0	19.9	0.010
Restlessness	0 min post-smoking	15.3	12.2	13.7	
	90 min post-smoking	23.3	25.7	25.1	0.020
Hunger	0 min post-smoking	27.6	31.1	25.8	
	90 min post-smoking	34.4	43.6	43.2	0.002
Impatient	0 min post-smoking	13.9	15.8	14.4	
	90 min post-smoking	17.5	25.9	23.2	0.040
Craving cigarettes/nicotine	0 min post-smoking	27.0	36.7	38.1	
	90 min post-smoking	62.1	60.4	59.5	0.003
Drowsiness	0 min post-smoking	16.1	11.9	23.6	ns
	90 min post-smoking	20.9	18.5	21.6	
Depression/Feeling blue	0 min post-smoking	7.4	5.6	7.4	ns
	90 min post-smoking	7.0	10.3	9.7	
Desire for sweets	0 min post-smoking	12.5	6.3	18.9	ns
	90 min post-smoking	17.2	13.8	15.8	
Composite score	0 min post-smoking	16.8	18.0	18.9	
	90 min post-smoking	26.2	29.1	27.9	0.007

West et al. (17) found that smoking an ultra-low yielding cigarette (0.1 mg nicotine) for 10 days also did not lead to excess withdrawal symptom reporting or significantly increased craving for a higher nicotine cigarette. It is possible that switching to very low or nicotine-free cigarettes prior to a cessation attempt could be a potentially useful prerequisite to the quit attempt if post-cessation withdrawal symptoms were less severe as a result of removing the influence of nicotine. The fact that post-smoking withdrawal and craving ratings were elevated to the same extent after nicotine-containing versus denicotinized cigarettes in the present study argues against the clinical efficacy of such a maneuver. However, the single 20 puff smoking test employed here would not provide sufficient exposure to stabilize a nicotine-free state in the smoker. Thus, withdrawal effects after longer-term exposure to nicotine-free cigarettes should be evaluated.

Although nicotine has been clearly identified as the primary active alkaloid in tobacco smoke that sustains addiction (16), its specific role in the complex pharmacology of tobacco cigarette smoking remains to be clearly delineated. This study has supported previous observations that removal of nicotine from a medium tar tobacco cigarette produces reduced ratings of satisfaction as compared to the subjects' usual brand, but has little impact on immediate post-smoking ratings of craving or other tobacco withdrawal symptoms. The availability of nicotine-free filtered cigarettes with characteristics otherwise similar to marketed brands would be a great benefit to researchers wishing to disentangle the role of the various cigarette smoke constituents. Such research tools would also allow a better understanding of the role of tar delivery, upper airway stimulation and other sensory effects of smoking that may support continued smoking behavior via conditioned reinforcing effects.

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REFERENCES

1. Abelin, T.; Buehler, A.; Muller, P.; Vesanen, K.; Imhof, P. R. Controlled trial of transdermal nicotine patch in tobacco withdrawal. Lancet 1:7–10; 1989.
2. Baldinger, B.; Hasenfratz, M.; Battig, K. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. Human Psychopharmacology 10:127–136; 1995.
3. Behm, F. M.; Schur, C.; Levin, E. D.; Tashkin, D. P.; Rose, J. E. Clinical evaluation of a citric acid inhaler for smoking cessation. Drug Alcohol Depend. 31:131–138; 1993.
4. Butschky, M. F.; Bailey, D.; Henningfield, J. E.; Pickworth, W. B. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. Pharmacol. Biochem. Behav. 50:91–96; 1995.
5. Fagerstrom, K. O. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3:235–241; 1978.
6. Hajek, P.; Jarvis, M. J.; Belcher, M.; Sutherland, G.; Feyerabend, C. Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. Psychopharmacology 97:99–102; 1989.
7. Hasenfratz, M.; Baldinger, B.; Battig, K. Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology 112:253–258; 1993.
8. Henningfield, J. E.; Miyasato, K.; Jasinski, D. R. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J. Pharmacol. Exp. Ther. 234:1–12; 1985.
9. Hughes, J. R.; Hatsukami, D. Signs and symptoms of tobacco withdrawal. Arch. Gen. Psychiatry 43:289–294; 1986.
10. Nemeth-Coslett, R.; Henningfield, J. E.; O'Keeffe, M. K.; Griffiths, R. R. Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92:424–430; 1987.
11. Perkins, K. A.; Sexton, J. E.; Reynolds, W. A.; Grobe, J. E.; Fonte, C.; Stiller, R. L. Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking versus nasal spray. Pharmacol. Biochem. Behav. 47:295–299; 1994.
12. Robinson, J. H.; Pritchard, W. S.; Davis, R. A. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. Psychopharmacology 108: 466–472; 1992.
13. Rose, J. E.; Behm, F. M.; Levin, E. D. Role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacol. Biochem. Behav. 44:891–900; 1993.
14. Schuh, K. J.; Stitzer, M. L. Desire to smoke during spaced smoking intervals. Psychopharmacology 120:289–295; 1995.
15. Tonnesen, P.; Norregaard, J.; Simonsen, K.; Sawe, U. A double-blind trial of a 16 h transdermal nicotine patch in smoking cessation. N. Engl. J. Med. 325:311–315; 1991.
16. U.S. Department of Health and Humans Services The health consequences of smoking: Nicotine addiction. Government Printing Office, Washington, D.C.: 1988.
17. West, R. J.; Russell, M. A. H.; Jarvis, M. J.; Feyerabend, C. Does switching to an ultra-low nicotine cigarette induce nicotine withdrawal effects? Psychopharmacology 84:120–123; 1984.
18. Zacny, J. P.; Stitzer, M. L. Cigarette brand-switching: Effects on smoke exposure and smoking behavior. J. Pharmacol. Exp. Ther. 246:619–627; 1988.

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Pharmacodynamic effects of new de-nicotinized cigarettes

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The effects of cigarette smoking result from the delivery of nicotine, other components of smoke, and sensory stimulation. In the present study, pharmacological effects of new tobacco-derived de-nicotinized cigarettes (controls) were compared with standard cigarettes. The de-nicotinized cigarettes had the appearance, draw and taste of standard cigarettes but contained and delivered virtually no nicotine (<0.06 mg), but delivered tar and carbon monoxide (CO). They were compared with cigarettes that delivered nicotine, CO and tar. Subjects ($n = 20$: 10 men, 10 women) participated in four experimental sessions in which they smoked either a standard cigarette or a de-nicotinized cigarette after either 3 or 12 h of tobacco deprivation. Heart rate, blood pressure, and EEG were recorded before, and for 1 h after, *ad lib* smoking. Plasma nicotine concentrations verified that de-nicotinized cigarettes did not deliver nicotine. The de-nicotinized cigarettes did not increase heart rate or activate the EEG. The subjects preferred the cigarettes that delivered nicotine compared to the de-nicotinized cigarettes. However, both types of cigarettes reduced subjective measures of tobacco craving and withdrawal. These data extend previous research that suggested the process of smoking and components of tobacco smoke other than nicotine mediate some effects of cigarette smoking. The de-nicotinized cigarettes may prove useful in evaluating effects of smoking independent of the delivery of nicotine.

Introduction

As described in the US Surgeon General's Report (US-DHHS, 1988), cigarette smoking is a process that involves both pharmacological and behavioral factors. The reinforcing and discriminative stimulus effects of cigarette smoking depend on the occupation of nicotine receptors (Stolerman, Kumar, Pratt, & Reavill, 1987) and sensory factors such as taste, heat, odor, and pharyngeal stimulation (Pritchard, Robinson, Guy, Davis, & Stiles, 1996). Systematic study of non-nicotine factors has been confounded by the lack of a suitable control cigarette. For the control smoking condition in previous smoking studies, investigators have used lettuce cigarettes (Butschky, Bailey, Henningfield, & Pickworth, 1995; Goldfarb, Jarvik, & Glick, 1970), herbal cigarettes (Wesnes & Warburton, 1983; West & Hack, 1991), or puffing on an unlighted cigarette (Morris & Gale, 1994). An ideal control cigarette would have the taste, look, feel, draw and smell of a commercial cigarette, but would not deliver pharmacologically active doses of nicotine.

Philip Morris Inc. (Richmond, VA) tested the market acceptability of a de-nicotinized cigarette (Next®) in 1990. Although the cigarette was not well accepted in the retail market, it proved useful in clinical studies to estimate the effects of smoking with minimal nicotine delivery. For example, the Philip Morris de-nicotinized cigarette did not increase heart rate and plasma levels of nicotine (Robinson, Pritchard, & Davis, 1992). Butschky *et al.* (1995) found that these cigarettes decreased subjective measures of tobacco withdrawal. Hasenfratz, Baldinger, & Bättig (1993) used the de-nicotinized cigarettes to study the relative importance of tar and nicotine delivery to the smoking process. Thus, these cigarettes could be used to study the role of

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nicotinic and non-nicotinic determinants of the effects of cigarette smoke intake. However, the Philip Morris de-nicotinized cigarette is no longer commercially available.

In response to the need among tobacco researchers for a de-nicotinized cigarette, the National Institute on Drug Abuse contracted with a private firm (Ultratech Corporation, Lafayette Hill, PA) to develop and manufacture de-nicotinized cigarettes. The de-nicotinized cigarettes were to have similar characteristics as commercial cigarettes, but to contain and deliver virtually no nicotine. Four types of cigarettes were developed and tested: reduced- and full-tar standard cigarettes and identically appearing reduced- and full-tar de-nicotinized cigarettes that delivered CO and tar, but not nicotine. The purposes of the present study were to assess the pharmacodynamic properties of these cigarettes, to evaluate their potential as control cigarettes for tobacco research and to distinguish the effects of nicotine from other components of tobacco smoke in an experimental setting.

Methods

Subjects

Twenty research volunteers (10 males, 10 females) who were regular smokers participated in the study. Subjects were randomly assigned to two groups of 10 subjects each (five males, five females). Subjects were excluded from the study if they reported any chronic physical or mental health conditions requiring medication, current drug or alcohol addiction (except tobacco or caffeine dependence), use of tobacco products other than cigarettes, and current treatment for smoking cessation. Mean age of the subjects was 34.1 years (range = 22–41). The subjects reported smoking an average of 31 cigarettes per day (range = 20–40) and reported having smoked for an average of 18.3 years (range = 5–27). Their current brand of cigarettes was labeled as delivering an average of 1.2 mg of nicotine (range = 0.9–1.4). Sixteen of the subjects smoked mentholated cigarettes. Their mean score on a revision of the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was 8.0 (range = 6–10); scores above 6 on this test indicate a high degree of dependence. Prior to participation in the study, the subjects signed a consent form that had been approved by the local institutional review board and met US Department of Health and Human Services guidelines for the protection of human research participants. Subjects were paid approximately $300 for their participation.

Experimental cigarettes

Four types of cigarettes were developed and tested: reduced- and full-tar standard cigarettes and identically appearing reduced- and full-tar de-nicotinized cigarettes that delivered CO and tar, but not nicotine (Table 1). The cigarettes were filtered, king size (85 mm overall; 25 mm cork tip overwrap). The cigarettes were produced from a mixture of shredded tobacco: 25% burley blend, 55% flue cured, 15% stems, 5% sheet tobacco) prepared at 32 cuts per inch. The cigarettes weighed an average of 1.0 g and had a moisture content of 13–15%. A cellulose acetate filter was placed on all cigarettes. The cigarettes had similar draw levels equal to a pressure drop of 8 cm of water. Nicotine was removed from the tobacco of the de-nicotinized cigarettes with a mild alkaline (ammonium solution) wash. The tobacco was steamed, air-dried and the final pH was adjusted with a citric acid solution. Full-tar cigarettes were designed to deliver >15 mg tar estimated by methods of the Federal Trade Commission (FTC; Federal Register, 1967; Pillsbury, 1996); reduced-tar cigarettes were designed to deliver about 11 mg of tar. Aeration holes (single column) were placed around the cork tip overwrap of the reduced-tar cigarettes; no holes were used in the cork tip overwrap of the full-tar cigarettes. The nicotine content of the dried tobacco from de-nicotinized cigarettes (reduced- and full-tar), determined by gas chromatography methods, indicated that the de-nicotinized cigarettes contained no measurable quantity of nicotine (personal communication, Peter Crooks, University of Kentucky). The de-nicotinization process also reduced tobacco-specific nitrosamines including: nitrosonornicotine (NNN), nitrosoanatabine (NAT), nitrosoanabasine (NAB) and 4- (methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK; personal communication, William Rosen, Ultratech Incorporated).

Table 1. Characteristics of experimental cigarettes

		FTC Nicotine (mg/cig)	FTC Tar (mg/cig)	Nicotine content (mg/cig)
Full Tar	Standard	1.10	15.9	7.17
	De-nicotinized	0.07	17.3	0
Reduced Tar	Standard	0.60	10.0	5.58
	De-nicotinized	0.07	12.1	0

FTC nicotine and tar estimates were obtained by the Cambridge filter method by a commercial laboratory (Labstat Inc, Kirchner Ontario, Canada). Analysis of the nicotine content of dried tobacco made by Peter Crooks, University of Kentucky, College of Pharmacy (Lexington, KY).

Dependent measures

Biochemical markers. Biochemical markers of smoke and nicotine exposure were exhaled carbon monoxide (CO) and plasma nicotine and cotinine. Exhaled CO was measured with a breath carbon monoxide detector (Vitalograph, Lexena, KS) before, and 15 and 60 min after smoking. Plasma nicotine and cotinine were measured using a high-performance liquid-chromatography method (Hariharan, VanNoord, & Greden, 1988). The lower limit of detection was 1 ng/ml. Blood samples (10 ml) were collected before smoking and 2, 5, 10, 15, 30 and 60 min after smoking. Blood samples were kept on ice until they were centrifuged and the plasma withdrawn. Plasma was stored frozen (–20°C) until the time of analysis.

Smoking behavior. The time taken to smoke *ad libitum* the experimental cigarettes and the number of puffs was recorded.

Physiological markers. Blood pressure and heart rate were measured with an automated instrument (IVAC, San Diego, CA) at the same times that blood samples were drawn. Scalp EEG recordings (2 min resting, eyes closed) from Fz, Cz and Pz were recorded before and 5 min after smoking with an automated computer-based acquisition and analysis system (BioLogic, Chicago, IL). Analog EEG signals were digitized (256 Hz) and a fast Fourier transform algorithm converted data to the power and frequency domain. The power and peak mean frequency were derived for the typical clinical frequency bands (delta, theta, alpha, beta1, beta2) as described elsewhere (Pickworth, Herning, & Henningfield, 1988, 1989).

Subjective measures. Standardized tests for the quantification of tobacco withdrawal symptoms including: the Minnesota Withdrawal Scale (MWS) (Hughes & Hatsukami, 1986); Questionnaire on Smoking Urges (QSU), short version (Tiffany & Drobes, 1991), and a drug-liking question (Fraser, Van Horn, Martin, Wolbach, & Isbell, 1961) were presented on a computer before smoking, 2, 30 and 60 min after smoking. Cigarette characteristics (strength, taste, satisfaction, harshness, ease of draw, good effects, and bad effects) were measured 20 min after smoking with computerized visual analog scales. The subjects used the computer mouse to place a line on a 100-mm horizontal line to index their endorsement of the adjectives describing the cigarette. Anchors for the lines were appropriate for the adjectives; for example 'ease of draw' was scored between 'very easy' and 'very hard'.

Procedure

This double-blind study was performed on an outpatient basis at NIDA, Division of Intramural Research (DIR). Subjects were randomly assigned to two experimental groups (five men, five women) of 10 subjects each. Subjects in Group 1 smoked full-tar standard and de-nicotinized cigarettes; those in Group 2 smoked reduced-tar standard and de-nicotinized cigarettes.

All subjects reported to the laboratory for an orientation session (where the procedure was described and practiced) and for four experimental sessions. On two experimental days, subjects refrained from smoking for 3 h prior to the beginning of the experiment; on the two other experimental days, subjects were overnight (>12 h) abstinent from cigarettes and were required to have CO <13 ppm. The order of the abstinence days and the cigarette conditions was randomized. Each subject smoked the de-nicotinized and standard cigarettes after 3 h and overnight abstinence.

On the study day, an in-dwelling catheter was placed in a forearm vein. Baseline physiologic, subjective, and biochemical measures were collected. Then, subjects smoked an experimental cigarette *ad libitum* to a line drawn on the tobacco rod 50 mm from the tip. The number of puffs and the time taken to smoke the cigarette were recorded. For 60 min after smoking, experimental measures were repeated as indicated above.

Data analysis

Data was analyzed using standard analysis of variance (ANOVA) techniques for repeated measures design (Winer, Brown, & Michels, 1991). An initial ANOVA on each dependent variable was performed using five main factors: group (reduced- or full-tar), gender (two levels), cigarette type (standard or de-nicotinized), time of abstinence (>3 and >12 h), time after smoking (one, two, three or seven levels depending upon the variable). These analyses indicated that there were no significant effects of gender, group, or time of abstinence. The data were collapsed across gender and separate ANOVAs for the full- and reduced-tar cigarettes were completed using cigarette type (standard or de-nicotinized), abstinence and time after smoking as the main factors.

Results

Biochemical markers of smoking

As shown in Figure 1 (upper panel), both the reduced- and full-tar standard (nicotine delivering) cigarettes increased venous plasma nicotine concentrations. After the full-tar standard cigarette, plasma levels of nicotine increased from 3.1 to 13.7 ng/ml. After the reduced-tar standard cigarette, plasma levels of nicotine increased from 3.3 to 15.5 ng/ml. The highest plasma levels occurred at 2 min after smoking. In contrast, de-nicotinized cigarettes did not increase plasma levels of nicotine. The ANOVA for the full-tar cigarette indicated that there was a significant effect of cigarette [$F(1,9) = 32.5$; $p < 0.001$]; time [$F(54,6) = 22.3$; $p < 0.001$]; and a significant cigarette by time interac-

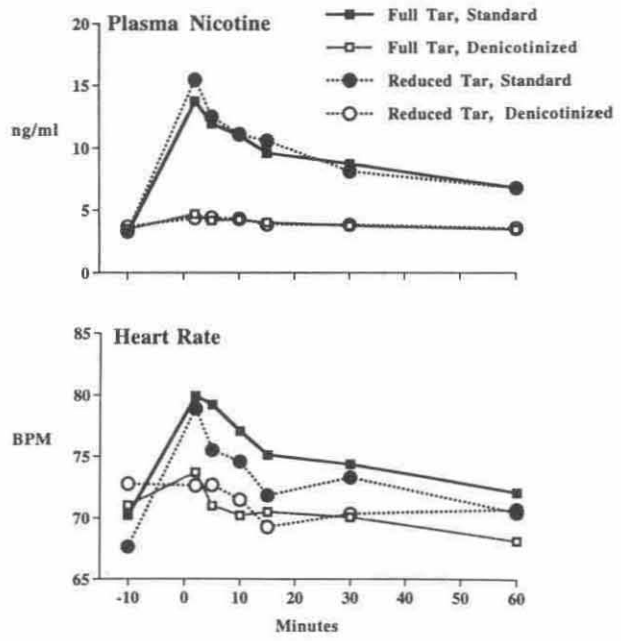


Figure 1. Upper panel: Mean ($n = 10$) venous plasma nicotine concentration before and up to 60 min after smoking experimental cigarettes. Time = 0 minutes when subjects finished smoking the experimental cigarette. Lower panel: Mean ($n = 10$) heart rate (beats per minute, BPM) before and up to 60 min after smoking experimental cigarettes.

tion [$F(6,54) = 19.4$; $p < 0.001$], Similarly, the ANOVA for the reduced-tar cigarette indicated that there was a significant effect of cigarette [$F(1,9) = 17.0$; $p < 0.003$]; time ($F(6,54) = 24.4$; $p < 0.001$]; and a significant cigarette by time interaction [$F(6,54) = 21.1$; $p < 0.001$].

Plasma venous cotinine levels before smoking the experimental cigarettes averaged 257.5 ng/ml in subjects that were at least 3-h tobacco-deprived and 229.2 ng/ml in subjects that were at least 12-h tobacco deprived. Plasma cotinine levels did not significantly change as a function of cigarette type, abstinence, or time after smoking.

Baseline exhaled CO averaged 13 ppm in subjects that were >3 h tobacco-abstinent and 8.3 ppm in subjects that were >12 h tobacco abstinent. After smoking, exhaled CO increased to 19.5 ppm at 15 min and 17.9 ppm at 60 min in subjects that were >3 h tobacco-abstinent. In subjects that were 12-h tobacco abstinent, CO averaged 15.3 and 13.9 ppm at 15 and 60 min after smoking. The ANOVA for the full-tar cigarette indicated a significant effect of abstinence [$F(1,9) = 8.6$, $p < 0.02$) and time [$F(2,18) = 48.8$, $p < 0.001$]. Similarly, the ANOVA for the reduced-tar cigarette indicated that there was a significant effect of abstinence [$F(1,9) = 9.1$, $p < 0.001$] and time [$F(2,18) = 50.2$, $p < 0.001$]. There were no significant differences between the standard and de-nicotinized cigarettes on the exhaled CO levels.

Smoking behavior

The time to smoke the full-tar cigarettes averaged 238 and 249 s for the standard and de-nicotinized, respectively. The time to smoke the reduced-tar cigarettes averaged 272 and 274 s for the standard and de-nicotinized, respectively. The ANOVAs for both the reduced- and full-tar cigarettes indicated there was no significant effect of cigarette or abstinent condition and no significant interaction.

The number of puffs per cigarette averaged 12.3 and 12.8 for the standard and de-nicotinized full-tar cigarettes and 15.3 and 16.7 for the standard and de-nicotinized reduced-tar cigarettes, respectively. The ANOVA for the regular indicated no significant effect of cigarette (standard vs. de-nicotinized) but a significant effect of abstinence [$F(1,9) = 6.4$, $p < 0.05$]. In the 3-h abstinence condition, 12.1 puffs were taken: in the 12-h abstinence condition, 13.2 puffs were taken. The ANOVAs for the reduced-tar cigarettes indicated no significant effect of cigarette or abstinence on number of puffs per cigarette.

Physiological measures

As illustrated in Figure 1 (lower panel), both standard (nicotine delivering) cigarettes increased heart rate by 10 beats per minute. The biggest increase occurred 2 min after smoking. Neither de-nicotinized cigarette type significantly changed heart rate. The ANOVA of the full-tar cigarette indicated a significant effect of cigarette [$F(1,9) = 22.8$, $p < 0.001$]; time [$F(6,54) = 14.5$, $p < 0.001$]; cigarette by abstinence interaction [$F(1,9) = 10.6$, $p < 0.01$]; and cigarette by time interaction [$F(6,54) = 6.4$, $p < 0.001$]. The ANOVA of the reduced-tar cigarette indicated a significant effect of time [$F(6,54) = 7.0$, $p < 0.001$]; and a significant cigarette by time interaction [$F(6,54) = 6.3$, $p < 0.001$].

Immediately after smoking the standard cigarettes (>3 h abstinence) there was an increase in systolic blood pressure of 9 mm Hg. The change in systolic blood pressure after de-nicotinized cigarettes was smaller and the ANOVAs indicated that there was no significant effect of either cigarette type on systolic blood pressure. Diastolic pressure increased immediately after smoking.

The ANOVA for the full-tar cigarette indicated a significant difference between standard and de-nicotinized cigarettes on this measure, [$F(1,9) = 8.04$, $p < 0.02$] and a significant effect on time [$F(6,54) = 2.5$, $p < 0.05$]. Full-tar cigarettes that delivered nicotine increased diastolic blood pressure more than the de-nicotinized cigarettes. There was no significant effect of the reduced-tar cigarettes on diastolic pressure.

The effects of the experimental cigarettes on two measures of EEG activity, theta power and alpha frequency, were assessed. Theta power decreased after smoking full-tar standard cigarettes to an average of 88% of the baseline value; conversely, after smoking

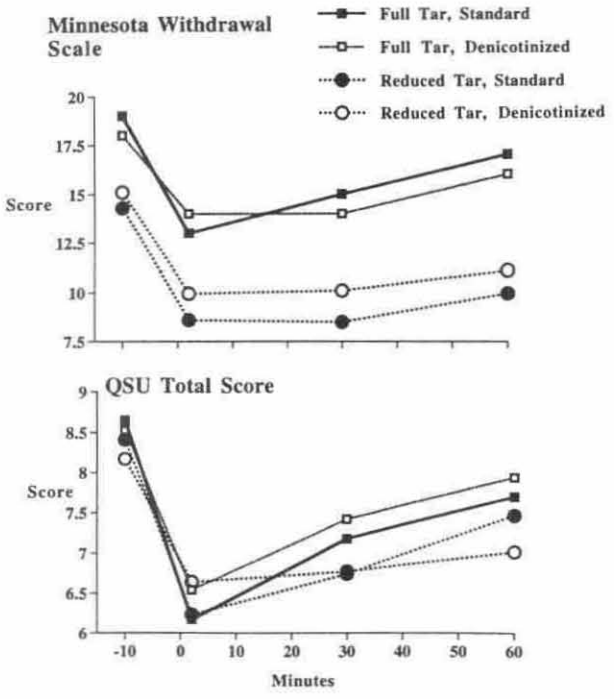


Figure 2. Upper panel: Mean ($n = 10$) score on the Minnesota Withdrawal Scale before and up to 60 min after smoking experimental cigarettes. Lower panel: Mean ($n = 10$) score on Questionnaire on Smoking Urges before and up to 60 min after smoking experimental cigarettes.

full-tar de-nicotinized cigarettes, theta power increased to 127% of baseline values. The ANOVA for the full-tar cigarettes indicated a significant effect of cigarette [$F(1,9) = 12.62$, $p < 0.006$] and a trend toward a significant effect of abstinence [$F(1,9) = 4.3$, $p < 0.07$]. The reduced-tar cigarettes did not significantly affect measures of theta power. The EEG alpha frequency was not significantly affected by any of the experimental cigarettes.

Subjective measures

The Minnesota Withdrawal Scale (MWS) was used to measure the effects of the experimental cigarettes on tobacco abstinence symptoms. As shown in Figure 2 (upper panel), all of the experimental cigarettes (standard and de-nicotinized) immediately reduced scores on the MWS. Baseline scores that averaged 18.8 for the full-tar cigarettes and 17.3 for the reduced-tar cigarettes were reduced to 13.3 and 10.5 respectively immediately after smoking. Even 60 min later, the scores of tobacco withdrawal remained reduced below baseline levels. The ANOVA of the full-tar cigarette indicated there was a significant effect of time [$F(3,27) = 3.1$, $p < 0.05$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions. Similarly, the ANOVA for the reduced-tar cigarettes indicated a significant effect of time [$F(3,27) = 4.8$, $p < 0.01$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions.

A short form of the Questionnaire on Smoking Urges (QSU) was used to assess cigarette craving. The total QSU score is illustrated in Figure 2 (lower panel). All of the experimental cigarettes reduced cigarette craving immediately after smoking and scores were reduced for as long as 60 min after smoking. The ANOVA for the full-tar cigarette indicated there was a significant effect of time [$F(3,27) = 6.6$, $p < 0.01$], but no significant effect of cigarette (standard vs. de-nicotinized) and no significant interactions. Similarly, the ANOVA for the reduced-tar cigarettes indicated a significant effect of time [$F(3,27) = 5.0$, $p < 0.01$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions. The ANOVAs on both Factor 1 and Factor 2 of the QSU also indicated a significant effect on time but no significant effects of cigarettes (or interactions).

Responses on the visual analog scales measured cigarette characteristics and smoking satisfaction (Table 2). The ANOVAs indicated that for both reduced- and full-tar cigarettes there was no significant difference between standard and de-nicotinized cigarettes on 'draw', 'good effects', or 'strength'. There were no significant main effects of abstinence and no abstinence by cigarette interactions. On some measures there were significant differences between the standard and de-nicotinized cigarettes. For example, the full-tar cigarettes showed significant differences between the de-nicotinized and standard cigarettes on measures of: 'bad effects' [$F(1,9) = 5.03$, $p < 0.05$]; 'satisfaction' [$F(1,9) = 6.44$, $p < 0.05$]; and 'taste' [$F(1,9) = 5.88$, $p < 0.05$]. Standard and de-nicotinized full-tar cigarettes also differed on the responses on the drug-liking question of the Single Dose Questionnaire [$F(1,9) = 4.81$, $p < 0.05$]. The reduced-tar cigarettes showed significant differences between the de-nicotinized and standard cigarettes on measures of: 'bad effects' [$F(1,9) = 11.7$, $p < 0.01$], 'harsh' [$F(1,9) = 20.1$, $p < 0.01$], and 'taste' [$F(1,9) = 6.62$, $p < 0.05$]. Standard and de-nicotinized reduced-tar cigarettes also differed on the responses on the drug-liking question of the Single Dose Questionnaire [$F(1,9) = 22.1$, $p < 0.01$].

Discussion

Although the importance of a control condition in clinical research is well recognized, smoking research has been hampered by the unavailability of a de-nicotinized control cigarette. The rapid delivery of nicotine is an integral part of cigarette smoking (Henningfield, Stapleton, Benowitz, Grayson, & London, 1993). Furthermore, in smoking, more than after other forms of drug ingestion, sensory stimuli evoke responses that are highly conditioned and reliably associated with the onset of drug action (Rose, Behm, & Levin, 1993). Thus, a tobacco-based, nicotine-free, control cigarette could be used to distinguish the effects of smoke-delivered nicotine from the effects of other components of tobacco smoke and the process of smoking *per se*.

Table 2. Evaluations of experimental cigarette characteristics

VAS Measure	Full tar standard	Full tar de-nicotinized	Reduced tar standard	Reduced tar de-nicotinized
Strength	37 ± 10.8	30 ± 3.8	37 ± 5.7	32 ± 11.8
Harsh	61 ± 12.5	42 ± 8.6	35 ± 9.5	68 ± 9.7
Taste	17 ± 5.8	14 ± 1.8	38 ± 6.4	13 ± 5.9
Satisfaction	12 ± 3.8	17 ± 2.9	35 ± 6.2	17 ± 9.6
Good effects	25 ± 4.9	23 ± 2.9	44 ± 10.6	23 ± 10.0
Bad effects	47 ± 10.3	36 ± 8.1	41 ± 9.1	66 ± 7.7
Draw level	46 ± 10.3	32 ± 4.9	39 ± 9.4	39 ± 10.3

Visual Analog Data for seven measures of cigarette characteristics. Numbers are mean (SEM on 100 mm scale ($n = 10$); data are collapsed across the two abstinence conditions (> 3 and > 12 h).

The present study was an evaluation of a new de-nicotinized cigarette. The results of the study indicated that the de-nicotinized cigarette met many of the criteria for a suitable control and may be useful in smoking research.

The de-nicotinized cigarettes used in the study contained negligible levels of nicotine. In contrast, the tobacco in so-called 'light' and 'ultra light' commercial cigarettes contained substantial amounts of nicotine that are typically similar to those found in standard nicotine-delivering cigarettes. For example, the nicotine content (per cigarette) of six brands of 'light' cigarettes averaged 11.75 mg; three brands of 'ultra light' cigarettes was 10.94 mg; and of six brands of 'full flavor' cigarettes was 12.19 mg (Massachusetts Department of Public Health, 1998). The FTC smoking machine estimates of nicotine and tar delivery differ among cigarette types because the smoke from 'light' and 'ultra light' cigarettes is diluted through filter ventilation—the more the ventilation, the lower the yield of nicotine and tar (Kozlowski, Mehta, Sweeney, Schwartz, Vogler, Jarvis, & West, 1998). In practice, the delivery of nicotine to the smoker is determined by how the cigarette is smoked (Kozlowski *et al.*, 1998; Herning, Jones, Benowitz, & Mines, 1983). Nicotine absorption as measured by plasma levels of cotinine in smokers of low FTC nicotine yield cigarettes (< 0.4 mg) were similar to the levels of cotinine in high-nicotine yield cigarettes (Benowitz, Hall, Herning, Jacob, Jones, & Osman, 1983). In spite of the low FTC estimates of nicotine and tar delivery in 'ultra light' cigarettes, they are unacceptable as a control condition for tobacco research because substantial amounts of nicotine can be obtained. The de-nicotinized cigarettes used in this study contained virtually no nicotine; thus, regardless of how they were smoked, no nicotine was available for delivery.

Venous plasma nicotine concentrations verified that neither the reduced- nor the full-tar de-nicotinized cigarette delivered measurable levels of nicotine to the volunteers. However, reduced- and full-tar standard cigarettes increased plasma nicotine by 10.6 and 12.2 ng/ml, respectively. These increases were similar to those reported after smoking a commercial cigarette (Pickworth, Fant, Nelson & Henningfield, 1998).

The de-nicotinized cigarettes failed to cause the physiological effects ordinarily seen after smoking cigarettes that deliver nicotine. For example, heart rate increased after the standard cigarettes were smoked, but not after de-nicotinized cigarettes. Others have reported that smoking nicotine-free cigarettes did not increase heart rate (Butschky *et al.*, 1995; Rose & Behm, 1991). Furthermore, EEG activation, indicated by a decrease in theta power (Ulett & Itil, 1969), occurred after smoking the standard cigarettes but not after the de-nicotinized cigarettes. In fact, after smoking de-nicotinized cigarettes, theta power increased, a sign of tobacco abstinence (Herning, Jones, & Bachman, 1983; Pickworth *et al.*, 1989; Ulett & Itil, 1969). The increase in theta power was especially evident after subjects smoked the full tar de-nicotinized cigarettes. This EEG change may result from the exposure of cues associated with smoking without the delivery of nicotine. Tiffany & Hakenewerth (1991) reported that cigarette craving increased when smokers listened to audio tapes of situations where smoking occurred.

Measures of smoking behavior did not appear to be related to the nicotine content of the cigarette. The time to smoke and the number of puffs to smoke the cigarette did not differ between the de-nicotinized and standard cigarettes. The boost in exhaled CO was similar after standard and de-nicotinized cigarettes. In the present study, as in an earlier study in which cigarettes were smoked through a tar- and nicotine-trapping occlusive filter (Pickworth *et al.*, 1998), the fact that only one cigarette was smoked may have prevented demonstration of the compensatory changes in smoking that are typical when nicotine dosing levels are varied (Hurt & Robertson, 1998; Djordjevic, Fan, Ferguson, & Hoffmann, 1995). In the present research, the short period of tobacco abstinence, unfamiliar and unsatisfactory cigarette taste, and the subject recognition that they could smoke their own cigarette in 1 h may have diminished efforts to change smoking behavior to obtain more nicotine. Further studies will be needed to characterize the possible changes in smoking that could develop across sequential cigarettes smoked within a test session, as well as across days, weeks, or even months of smoking. It would also be interesting to determine the possible interaction of nicotine by different instructional sets, e.g., 'smoke as you desire' vs. 'gradually reduce your smoking'.

Experimental cigarettes were assessed after >3 and >12 h of tobacco abstinence. We expected that subjective liking of the cigarettes, ability to relieve tobacco withdrawal symptoms and cardiovascular effects would be greater after 12-h than after 3-h abstinence. For reasons that are not clear, this was not observed. Compliance to the 12-h abstinence was verified by lower levels of plasma nicotine, cotinine and exhaled CO. However, significant baseline differences in tobacco abstinence measures (QSU and MWS) in the 3- and 12-h conditions were not observed. Furthermore, the standard cigarettes did not have greater effects on subjective measures of tobacco abstinence, change in heart rate, measures of smoking behavior in the longer abstinence condition. Neither did the longer abstinence enhance the subjective responses to the de-nicotinized cigarettes. These findings have theoretical and practical implications. The effects of the standard cigarettes on physiological responses should be enhanced with longer abstinence as the smokers lose tolerance to nicotine (Fant, Schuh, & Stitzer, 1995; Schuh & Stitzer, 1995). If de-nicotinized cigarettes were used to facilitate smoking cessation through extinction, they would need sufficient acceptability to sustain continued administration.

De-nicotinized and standard cigarettes reduced acute measures of tobacco withdrawal. Scores on the MWS and QSU decreased immediately after smoking. Similar results were reported in other laboratory studies after another de-nicotinized cigarette, Next® (Butschky *et al.*, 1995; Gross, Lee, & Stitzer, 1997; Rose & Behm, 1991). In a field study that compared subjective and physiological effects of standard and de-nicotinized cigarettes, both cigarettes reduced subjective craving (Baldinger, Hasenfratz, & Bättig, 1995). On the other hand, it has been well established that substitution of nicotine-free cigarettes leads to withdrawal (Finnegan, Larson, & Haag, 1945) as well as dissatisfaction and inability to sustain the addiction (Hurt & Robertson, 1998). The persistence of nicotine-associated subjective effects and withdrawal symptom relief in acute settings is not surprising in light of the massive conditioning histories of subjects prior to the study. For example, in this study, assuming our subjects typically took 10 puffs per cigarette and that they smoked 31 cigarettes per day, then they had averaged smoking more than 200,000 cigarettes and taken more than 2 million nicotine-associated puffs prior to our study. Even assuming that subjects smoked fewer cigarettes in their first few years of smoking, the conditioning opportunities are massive.

Scores on scales of liking indicated that subjects enjoyed cigarettes that deliver nicotine more than cigarettes that did not. Other measures of product satisfaction were less for the de-nicotinized than the standard cigarettes. For example, after smoking the reduced tar cigarettes, ratings of taste, satisfaction, and good effects were higher than after the de-nicotinized cigarettes; conversely, ratings of bad effects were lower. In other studies comparing a commercially prepared de-nicotinized cigarette, Next® (Butschky *et al.*, 1995; Gross *et al.*, 1997), with cigarettes that deliver nicotine, subjects reported less liking for the de-nicotinized cigarette. Smokers apparently find the characteristic taste and smell of nicotine appealing and cigarettes without those qualities are rated as less satisfactory.

The present study was an initial evaluation of new de-nicotinized cigarettes. Some of the non-significant effects of gender, time of tobacco abstinence and cigarette type on the physiological and subjective measures of the study may be due to the small sample size of the comparison groups. Furthermore, since 80% of the subjects ordinarily smoked menthol cigarettes, their subjective ratings of the non-mentholated experimental cigarettes may have been influenced. It is also important to emphasize that the effects of smoking a single experimental cigarette in a laboratory session may not reflect the effect of these cigarettes smoked chronically in the natural environment. Nevertheless, the de-nicotinized cigarettes in the present study met several important criteria: tobacco product, no nicotine content or delivery, levels of tar comparable to commercial cigarettes, and draw similar to nicotine-containing cigarettes. These features led to similar smoking behavior in both control and standard cigarettes indicating that the de-nicotinized cigarettes may be a useful control cigarette in smoking studies.

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References

Baldinger B, Hasenfratz M, Bättig K. 1995. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. *Human Psychopharmacology* 10:127–136.

Benowitz NL, Hall SM, Herning RI, Jacob P III, Jones RT, Osman AL. 1983. Smokers of low-yield cigarettes do not consume less nicotine. *New England Journal of Medicine* 309:139–142.

Butschky MF, Bailey D, Henningfield JE, Pickworth WB. 1995. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology, Biochemistry and Behavior* 50:91–96.

Djordjevic MV, Fan J, Ferguson S, Hoffmann D. 1995. Self-regulation of smoking intensity. Smoke yields of the low-nicotine, low-'tar' cigarettes. *Carcinogenesis* 16: 2015–2021.

Fant RV, Schuh KJ, Stitzer ML. 1995. Response to smoking as a function of prior smoking amounts. *Psychopharmacology* 119:385–390.

Federal Register 1967. 32:11178.

Finnegan JK, Larson PS, Haag HB. 1945. The role of nicotine in the cigarette habit. *Science* 102: 94–96.

Fraser HF, Van Horn GD, Martin WR, Wolbach AB, Isbell H. 1961. Methods of evaluating addiction liability. (A) Attitude of opiate addicts towards opiate-like drugs, (B) a short term direct addiction test. *Journal of Pharmacology and Experimental Therapeutics* 133:371–387.

Goldfarb TL, Jarvik ME, Glick SD. 1970. Cigarette nicotine content as a determinant of human smoking behavior. *Psychopharmacologia* 17:89–93.

Gross J, Lee J, Stitzer ML. 1997. Nicotine-containing versus de-

nicotinized cigarettes: effects on craving and withdrawal. *Pharmacology, Biochemistry and Behavior* 57:159–165.

Hariharan M, VanNoord T, Greden JF. 1988. A high-performance liquid-chromatographic method for routine simultaneous determination of nicotine and cotinine in plasma. *Clinical Chemistry* 34:724–729.

Hasenfratz M, Baldinger B, Bättig K. 1993. Nicotine or tar titration in cigarette smoking behavior? *Psychopharmacology* 112:253–258.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. 1991. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction* 86:1119–1127.

Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. 1993. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug and Alcohol Dependence* 33:23–29.

Herning RI, Jones RT, Bachman J. 1983. EEG changes during tobacco withdrawal. *Psychophysiology* 20:507–512.

Herning RI, Jones RT, Benowitz NL, Mines AH. 1983. How a cigarette is smoked determines blood nicotine levels. *Clinical Pharmacology and Therapeutics* 33:84–90.

Hughes JR, Hatsukami D. 1986. Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry* 43:289–294.

Hurt RD, Robertson CR. 1998. Prying open the door to the tobacco industry's secrets about nicotine: the Minnesota Tobacco Trial. *Journal of the American Medical Association* 280:1173–1181.

Kozlowski LT, Mehta NY, Sweeney CT, Schwartz SS. Vogler GP, Jarvis MJ, West RJ. 1998. Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom and the United States. *Tobacco Control* 7:369–375.

Massachusetts Department of Public Health, 1998. *1997 Cigarette Nicotine Disclosure Report.* Boston, Massachusetts.

Morris PH, Gale A. 1994. Is sham smoking an adequate control condition for the motoric component of smoking? *Addictive Behaviors* 19:393–400.

Pickworth WB, Herning RI, Henningfield JE. 1988. Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. *Pharmacology, Biochemistry and Behavior* 30:149–153.

Pickworth WB, Herning RI, Henningfield JE. 1989. Spontaneous EEG changes during tobacco abstinence and nicotine substitution in human volunteers. *Journal of Pharmacology and Experimental Therapeutics* 251:976–982.

Pickworth WB, Fant RV, Nelson RA, Henningfield JE. 1998. Effects of cigarette smoking through a partially occluded filter. *Pharmacology, Biochemistry and Behavior* 60:817–821.

Pillsbury, HC, Jr. 1996. Review of the Federal Trade Commission method for determining cigarette tar and nicotine yield. In: *Smoking and Tobacco Control Monograph #7; The FTC cigarette test method for determining tar, nicotine and carbon monoxide yields of U.S. cigarettes.* National Cancer Institute, NIH Publication No.96–4028: 9–14.

Pritchard WS, Robinson JH, Guy TD, Davis RA, Stiles MF. 1996. Assessing the sensory role of nicotine in cigarette smoking. *Psychopharmacology* 127:55–62.

Robinson JH, Pritchard WS, Davis RA. 1992. Psychopharmacological effects of smoking a cigarette with typical 'tar' and carbon monoxide yields but minimal nicotine. *Psychopharmacology* 108:466–472.

Rose JE, Behm FM. 1991. There is more to smoking than the CNS effects of nicotine. In: Adlkofer F, Thurau K, eds. *Effects of Nicotine on Biological Systems II, Advances in Pharmacologic Sciences.* Basel: Birkhauser, pp. 239–246.

Rose JE, Behm FM, Levin ED. 1993. Role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacology, Biochemistry and Behavior* 44:891–900.

Schuh KJ, Stitzer ML. 1995. Desire to smoke during spaced smoking intervals. *Psychopharmacology* 120:289–295.

Stolerman IP, Kumar R, Pratt JA, Reavill C. 1987. Discriminative stimulus effects of nicotine: correlation with binding studies. In: Martin WR, Van Loon GR, Iwamoto ET, Davis L, eds. *Tobacco Smoking and Nicotine: A Neurobiologic Approach.* New York: Plenum Press, pp. 113–124.

Tiffany ST, Drobes DJ. 1991. The development and initial validation of a questionnaire on smoking urges. *British Journal of Addiction* 86:1467–1476.

Tiffany ST, Hakenewerth DM. 1991. The production of smoking urges through imagery manipulation: psychophysiological and verbal manifestations. *Addictive Behaviors* 16:389–400.

Ulett JA, Itil TM. 1969. Quantitative electroencephalogram in smoking and smoking deprivation. *Science* 164:969–970.

US Department of Health and Human Services. 1988. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* Washington, D.C.: US Government Printing Office.

Wesnes K, Warburton DM. 1983. Effects of smoking on rapid information processing performance. *Neuropsychobiology* 9:223–229.

West R, Hack S. 1991. Effect of cigarettes on memory search and subjective ratings. *Pharmacology, Biochemistry and Behavior* 38:281–286.

Winer BJ, Brown DR, Michels KM. 1991. *Statistical Principles in Experimental Design*, 3rd edn. New York: McGraw-Hill.

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PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

Dissociating nicotine and nonnicotine components of cigarette smoking

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Abstract

To dissociate the sensorimotor aspects of cigarette smoking from the pharmacologic effects of nicotine, smokers rated the subjective effects of nicotine-containing or denicotinized cigarettes, and intravenous (IV) nicotine or saline infusions. Three groups of participants (n = 20 per group) received either: (1) continuous nicotine, (2) pulsed nicotine, or (3) saline. Each group was exposed to an IV condition once while smoking a denicotinized cigarette and once while not smoking, in a 3 2 mixed design. A fourth group (n = 20) received saline while smoking their usual brand of cigarette. The dose and rate of nicotine administration were individualized based on previous measures of ad lib smoke intake. Denicotinized cigarette smoke significantly reduced craving and was rated significantly more satisfying and rewarding than the no-smoking conditions. IV nicotine reduced craving for cigarettes, and increased ratings of lightheadedness and dizziness. However, no significant satisfaction or reward was reported after IV nicotine. The combination of IV nicotine and denicotinized cigarette smoke produced effects similar to those of smoking the usual brand of cigarette. The results suggest that sensorimotor factors are critical in mediating the immediate subjective response to smoking, and that the immediate subjective effects of nicotine administered in doses obtained from cigarette smoking are subtle. Thus, addressing smokers' needs for both for the sensorimotor aspects of smoking as well as for the direct CNS effects of nicotine may be critical in enhancing smoking cessation treatment outcome. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Nicotine; Smoking; Euphoria; Addiction; Craving; Substance abuse

1. Introduction

Considerable evidence supports the view that cigarette smoking is maintained by an addiction to nicotine [28]. This view has led to the development of smoking cessation treatment methods that provide nicotine replacement. One of the goals of nicotine replacement therapy is to partially substitute for the rewarding effects of cigarette smoke, reducing the need for tobacco [11]. However, the effects of nicotine, when delivered without cigarette smoke, have generally been found to be much less rewarding than smoking [10,18,19]. Moreover, most people trying to quit smoking eventually relapse even when provided with nicotine in the form of gum, patches, nasal spray, or inhaler [7]. While these alternative forms of nicotine delivery can effectively relieve some smoking withdrawal symptoms [12], craving for cigarettes is only partially alleviated during the initial days of smoking abstinence [1,23].

Why do current methods of nicotine replacement fail to provide adequate substitution for the reinforcing effects of cigarette smoking? Two main explanations have been proposed to account for the relatively low effectiveness of nicotine replacement. The first is that nicotine replacement techniques do not provide an adequate dose or rate of nicotine administration. Not only do many smokers inhale more nicotine per day than is delivered from alternative nicotine delivery systems, but in addition, the inhalation route is more rapid than current nicotine-based treatments. It has been argued that this rapid delivery is critical to the reinforcing potency of cigarette smoking [26]. However, a second explanation is that nicotine replacement methods lack important sensory/behavioral components of cigarette smoking [20]. Indeed, smokers report missing the behavioral aspects as well as the sensory cues of smoking, such as the taste, aroma, and respiratory tract sensations accompanying each puff of smoke [22,23]. In several studies we have shown that these sensations are especially important in

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relieving craving for cigarettes, and they have also been shown to facilitate smoking abstinence [2,29].

To evaluate these contrasting explanations it is important to dissociate nicotine administration from the behavior of cigarette smoking, using a method of nicotine administration that preserves the rapid pharmacokinetic profile of pulmonary delivery. Recently, we reported that the arterial nicotine concentrations measured at 5-s intervals following intravenous (IV) nicotine administration were very similar to those of inhaled nicotine [21]. Thus, IV nicotine delivery offers a feasible approach to duplicating the pharmacologic effects of smoking with minimal sensory/behavioral cues. In a preliminary study [30], we reported that IV nicotine, when administered in conjunction with smoking a denicotinized cigarette, had minimal effects on subjective measures such as satisfaction and craving for cigarettes. In contrast, smoking a denicotinized cigarette had robust effects on these subjective measures, demonstrating the importance of nonnicotine cues in mediating responses to smoking. However, this study had limited statistical power, as it included only six subjects, and a saline control was lacking in the no-smoking conditions, which would have allowed an assessment of the effects of IV nicotine in the absence of smoking.

In the present study, a considerably larger subject sample size was used, and a saline control condition was included in both smoking and no-smoking conditions. Our main goal was to evaluate the hypothesis that presentation of pharmacologic component of smoking using IV nicotine would produce significant rewarding effects. Moreover, individualized tailoring of IV nicotine doses was incorporated into the design to better evaluate the importance of the nicotine component of smoking with realistic dosing parameters. A second goal of this study was to determine with greater precision whether IV bolus nicotine injections are more effective in providing subjective rewarding effects than continuous nicotine infusions. Furthermore, we sought to assess how nicotine dose and sensory/behavioral cues interact in affecting subjective smoking reward. To accomplish this, we measured the immediate subjective responses to the nicotine and nonnicotine components of smoking, individually and in combination. As in the previous study, we assessed the effects of the sensory/behavioral components of smoking using denicotinized tobacco cigarettes, which presented most of the nonnicotine constituents of cigarette smoke with minimal doses of nicotine.

2. Materials and methods

2.1. Design

Eighty subjects were randomly assigned to four groups (see Fig. 1) receiving either: (1) rapid IV injections (boli) of puff-sized doses of nicotine, (2) continuous IV infusions of nicotine, or (3) saline infusions. Subjects in these three groups received two identical IV presentations in the same session, separated by 90 min. During one presentation, subjects smoked a denicotinized cigarette, and during the other presentation no smoke was given (order counterbalanced across subjects); (4) a fourth group also received two saline infusions, during one of which they smoked their usual brand of nicotine-containing cigarette (order counterbalanced). Thus, the first three groups comprised a 3 (nicotine bolus injections vs. nicotine infusions vs. saline) 2 (denic cigarette vs. no-smoking) mixed within/between design, with the nicotine factor being a between-subjects factor and smoking being a within-subjects factor. Group 4 (usual brand vs. no smoking) provided a useful benchmark for the rewarding effects of inhaled nicotine delivered in conventional cigarette smoke.

GROUP	CIGARETTE	I.V. CONDITION
1	DENIC (or no smoking)	Continuous Nicotine
2	DENIC (or no smoking)	Pulsed Nicotine
3	DENIC (or no smoking)	Saline
4	USUAL BRAND (or no smoking)	Saline

Fig. 1. Description of conditions for the different experimental groups.

2.2. Subjects

Healthy volunteers were recruited from the community by newspaper advertisements. To facilitate subject recruitment, prospective volunteers were offered two incentives; monetary payment of $75 per session, and after completion of the present study, smoking cessation treatment including a free 6-week course of nicotine skin-patch treatment. Subjects were 18–55 years of age, and smoked at least 20 cigarettes/day of a brand delivering at least 0.7 mg nicotine (by FTC method). Subjects' expired CO concentrations (measured in the afternoon) were >20 ppm (confirming inhalation). Subjects were healthy, based on physical examination, ECG, serum chemistries, CBC, and urinalysis, and were excluded if they had been diagnosed with coronary artery disease, cardiac rhythm disorder, or any serious medical condition, current psychiatric disease (aside from nicotine dependence), hypertension (systolic > 140 mm Hg, diastolic > 90 mm Hg), or hypotension (systolic < 90 mm Hg), or if pregnant or nursing.

2.3. Methods of IV nicotine delivery

Nicotine solutions: pure nicotine base was obtained from Eastman Kodak (Rochester, NY) in accord with our FDA-approved investigational new drug application for IV and inhaled nicotine administration. The Duke University Pharmacy service prepared a solution of 0.01% nicotine (w/w) in saline. The solution, which was basic, was then pH adjusted to 7.0 using acetic acid, sterilized by filtration and autoclaving, and finally was tested for pyrogens.

At least 30 min prior to the first IV infusion, two 22-gauge IV catheters with injection ports were inserted: one catheter

was placed in the antecubital vein of the non-dominant arm for IV infusions (in pilot work we found that bolus injections into the cephalic vein produced pain at the catheter site, extending up the forearm); the second catheter was placed in the antecubital vein or cephalic vein of the dominant arm for blood sampling. The arm was wrapped in polyvinylidine chloride (Saran® wrap) to minimize the risk of contamination of samples from smoke particles in ambient air. Catheters were flushed or maintained with saline infusion per standard technique. IV solutions were administered with an IVAC pump or syringe in double-blind fashion.

Because the arm-to-brain transit time for IV nicotine injections in the bolus condition was expected to be approximately 13–14 s [26], as compared to the 7–8-s lung-to-brain transit time for inhaled nicotine, each bolus injection was administered approximately 3–4 s prior to initiating each puff. Taking a puff and inhaling required 3–4 s and thus the time between actual inhalation of denicotinized smoke and arrival of a nicotine bolus to the brain should have been similar to the usual 7–8 s delay experienced with normal smoking. A partition shielded the IV catheter from view so that subjects did not witness the timing of injections. In the continuous nicotine (or saline) conditions, infusions began with the first puff and ended 1 min after the last puff.

2.4. Methods of cigarette smoke delivery

2.4.1. Denicotinized cigarettes

We obtained denicotinized cigarettes, manufactured by Phillip Morris, which were used in the proposed work. These cigarettes contain tobacco from which the nicotine has been selectively extracted by supercritical carbon dioxide, and have a taste and tar delivery similar to nicotine-containing brands of cigarette. The tar delivery of these cigarettes, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg. Hasenfratz et al. [8] measured smoking behavior and nicotine intake after smoking denicotinized vs. nicotine-containing cigarettes, and found that plasma nicotine levels increased less than 2 ng/ml after smoking the denicotinized cigarette. We have verified that these cigarettes produce less than 2-ng/ml boosts in arterial blood nicotine concentration, and also that they do not increase heart rate, a sensitive index of nicotine delivery in deprived smokers [21].

2.4.2. Controlled puff volume apparatus

Puff volume for both denicotinized and usual-brand cigarettes was controlled with a simple apparatus we validated in previous studies [16]. The device used a glass syringe preloaded with a measured amount of air that was supplied to the burning cigarette with each puff. When subjects took a puff, the syringe barrel slid within the glass housing until the specified volume of air (smoke) had been drawn into the mouth, and no further smoke could be obtained until the device was reset for the next puff. Because subjects had indwelling catheters for nicotine delivery and blood sampling in each arm, the apparatus was held in place with a ring stand situated conveniently in front of the subject, who could take puffs by leaning forward from a semirecumbent position, and drawing from a disposable plastic mouthpiece having a diameter comparable to a cigarette.

2.5. Procedure

The pharmacologic effects of nicotine were delivered without the usual sensory and behavioral cues, using IV nicotine infusions; conversely, the sensory and behavioral components of the smoking habit were conveyed without pharmacologic actions, using denicotinized tobacco smoke. Because there is enormous variability between cigarette smokers in the nicotine dose extracted from cigarettes during ad lib smoking [4], the number of puffs, puff volumes, and interpuff intervals were individualized to match the characteristic topography of each participant. To accomplish this, participants' habitual nicotine intake from cigarette smoking was measured, and then nicotine infusions mimicking the dose and rate of intake were administered. Eighty subjects reported to the laboratory after overnight abstinence for a preliminary baseline session to measure ad lib smoke intake. Self-reported abstinence for this and subsequent sessions was confirmed at the beginning of the session by expired air CO measurement, and subsequently verified by plasma nicotine assay. Usual caffeine consumption was permitted prior to the session.

Ad lib smoking behavior was assessed by measuring the puff volumes, number of puffs taken, and interpuff intervals from subjects' usual brands of cigarettes. To accomplish this, the nicotine intake after ad lib smoking of one cigarette (after overnight abstinence from smoking) was quantified by measuring puff volume, number of puffs, and interpuff intervals, using the smoke delivery apparatus described above. The air-containing syringe was initially filled with 80 cm^3 prior to each puff, and the reading after each puff was recorded, indicating the puff volume inhaled. To calculate the average per-puff dose of nicotine, the smoking pattern was reproduced in the laboratory, and the smoke particulate matter was trapped in Cambridge filters. After extraction with ethanol, a spectrophotometer was used to measure the absorbance of the solution at a wavelength of 400 nm, which is an accurate measure of "tar" concentration [25]. Using published values for the nicotine/tar ratio for each brand of cigarette [5], the nicotine delivery per puff could then be estimated. Subsequently, when each subject reported for the infusion session, s(he) received nicotine (or saline) infusions, in double-blind fashion, using the same dose and rate of administration (rate was calculated in terms of mg nicotine per minute for the continuous nicotine infusion condition and mg/injection for the pulsed nicotine condition). As described above, the interinfusion period was 90 min, and infusions were administered either as pulsed

injections, with each injection delivering a nicotine dose equivalent to one puff, or as a continuous infusion. The total duration of the infusions was equal to the duration of ad lib smoking after overnight abstinence. Number of puffs, mean puff volume, and interpuff interval were also set equal to the values measured during each subject's baseline ad lib smoking session.

2.6. Dependent measures

During the infusion session, the following dependent measures were assessed.

2.6.1. Plasma nicotine concentrations

To verify that the IV nicotine infusions produce dose-related increases in systemic nicotine levels comparable to cigarette smoking, 10-cm^3 samples of venous blood samples were collected before and after each infusion. The samples were centrifuged, packed on dry ice, and shipped from Durham, NC, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay by gas chromatography as described by Jacob et al. [13], modified for use of a capillary column. Limits of quantitation of this assay are 1.0 ng/ml (CV 7.8%) and 10 ng/ml (CV 8.7%) for nicotine and cotinine, respectively.

2.6.2. Smoking withdrawal symptom questionnaire

Before and after each infusion we administered a modified Shiffman–Jarvik questionnaire [27] that we have employed previously in several laboratory studies. It has been sensitive in detecting effects of cigarette deprivation and pharmacologic treatments (e.g., Ref. [32]). The items comprise six subscales: craving (craved a cigarette, would have liked a cigarette, thought of cigarettes, missed a cigarette, had urges to smoke, and, scored oppositely, would have refused a cigarette), negative affect (tense, irritable, and, scored oppositely, calm, content), arousal (wide awake, able to concentrate, and unusually sleepy), somatic symptoms (fluttery feelings in chest, heart beat faster than usual, hands shake, headache, cough, mouth sores, sore throat, heartburn, chest tightness, nausea, bad taste in mouth, upset stomach, and dizziness), appetite (have eaten more than usual, hungrier than usual, craved sweets, and craved salty foods), and habit (missed something to do with the hands, and missed having something in the mouth).

2.6.3. Condition evaluation questionnaire

After each infusion condition, subjects completed a questionnaire previously developed [31] to assess the subjective effects of smoking; items assessed Satisfaction ("Was it satisfying?"; "Was there a good taste?"), Psychological reward ("Did it calm you down?"; "Did it make you feel more awake?"; "Did it reduce your hunger for food?"; "Did it make you feel less irritable?"), Nausea/dizziness ("Did you feel nauseated?"; "Did you feel dizzy?"), Craving relief ("Did it immediately reduce your craving for cigarettes?"), and Enjoyment of airway sensations ("Did you enjoy the sensations in your throat and chest?").

2.6.4. Sensory questionnaire

To obtain detailed information about the sensory properties of cigarette smoke and nicotine, we administered, after each infusion, a sensory questionnaire used in several previous studies, which included items assessing: Estimated nicotine delivery, Similarity to usual brand, and perceived Strength on the tongue, nose, back of mouth and throat, windpipe, and chest.

2.6.5. Mood questionnaire

Additionally, a questionnaire designed to detect mood effects of nicotine and smoking was administered after each infusion, consisting of items that were found in factor analyses to load onto two subscales: Euphoria (exhilaration, pleasurable excitement, comfort, relaxation, and well-being); and Dysphoria (dizziness, lightheadedness, nausea, nervousness, and burning or pain at the IV site).

All items of these questionnaires were rated on seven-point scales labeled as follows: 1 ("not at all"), 2 ("very little"), 3 ("a little"), 4 ("moderately"), 5 ("a lot"), 6 ("quite a lot"), or 7 ("extremely").

2.6.6. Cardiovascular measures

Heart rate and blood pressure were monitored at 1-min intervals immediately prior to and during each infusion using an automated sphygmomanometer (Critikon, Tampa, FL).

2.6.7. Smoking behavior

Subjects' expired air CO concentrations were measured before and after each cigarette using a handheld CO monitor (Vitalograph, Lenexa, KS). Expired air CO concentrations were calculated by subtracting the background (ambient) CO from the peak CO reading. The number of puffs taken from each cigarette were also counted by the research technician, and because the puff volume is controlled, this reflected the total volume of smoke taken into the mouth.

2.7. Statistical analyses

Data analysis was performed using SUPERANOVA and STATVIEW (SAS Institute, Cary, NC). For each parametric variable (including questionnaire scales assessing smoking withdrawal symptoms, ratings of smoking satisfaction and reward), a multivariate approach to repeated measures analysis ANOVA was used, which is generally appropriate regardless of the correlation pattern among repeated measurements. For each dependent measure, an analysis was first conducted using data from the 2 (smoke vs. no-smoke) 3 (nicotine bolus injections vs. continuous nicotine vs. saline) factorial design. Each subject's rate of smoking and rate of nicotine delivery, as determined from the smoking baseline, was used as a covariate in these analyses. Additionally, in assessing the between-subjects

factor of IV nicotine condition, baseline ratings of the usual brand cigarettes were entered as covariates in the analysis. Any significant interactions between factors were followed-up with an analysis of simple effects. Additionally, planned contrasts compared the nicotine bolus injection conditions with the continuous nicotine infusion condition. In the absence of a difference, a subsequent contrast compared the two IV nicotine conditions with the saline condition.

Finally, contrasts were conducted to compare the combination of IV nicotine + denic cigarette to the usual brand cigarette condition; this analysis determined (within the limits of statistical power) whether the rewarding action of a conventional cigarette could be achieved by the combined presentation of the sensory/behavioral and pharmacologic components of cigarette smoking using separate modes of administration.

3. Results

3.1. Subject characteristics

Table 1 shows the subject characteristics, broken down by infusion condition. There were no significant differences between groups in age, years smoked, gender, FTC nicotine, cigarettes/day, baseline expired air CO, Fagerstrom test for Nicotine Dependence score (FTND) [9], or plasma cotinine levels.

3.2. Effects of denicotinized smoke and IV nicotine

In this section, all effects of smoking refer to the denicotinized cigarette. Comparisons with the usual brand cigarette condition will be described in the next section.

3.2.1. Condition evaluation scales

As shown in Fig. 2, satisfaction ratings were significantly higher in the smoking conditions relative to the no-smoking conditions, $F(1,51)=40.79$, $p < 0.0001$. Similarly, ratings of psychological reward, enjoyment of respiratory tract sensations, and craving reduction were significantly higher in the smoking conditions ($p=0.013$, $p=0.0001$, and $p=0.002$, respectively). In contrast, IV nicotine did not affect ratings of satisfaction, psychological reward or enjoyment of respiratory tract sensations ($ps \geq 0.1$ for the contrasts between saline and the two IV nicotine conditions, which did not differ from each other). However, IV nicotine did reduce craving for cigarettes ($p=0.04$), and did increase ratings of nausea and dizziness relative to saline (mean rating of 1.8, SEM = 0.12 vs. a mean of 1.5, SEM=0.11, $p=0.03$).

3.2.2. Smoking withdrawal symptoms

Precondition ratings as well as prepost change scores were examined. There were precondition differences for several of the scales (craving, negative affect, and habit withdrawal) that indicated some carryover from the prior condition. Therefore, we focused on the analysis of prepost condition change scores (see Fig. 3). An effect of nicotine ($p=0.03$) and trend for smoke administration ($p=0.06$) were detected on the prepost condition change in arousal. However, these effects on arousal were limited to subjects who received the high rate of smoke/nicotine administration ($p=0.01$ for IV condition rate interaction). Nicotine and smoke administration both increased subjective arousal for subjects in this group ($p=0.06$ and 0.02, respectively). Change in craving showed no significant differences between conditions; however, habit withdrawal ratings showed a significantly greater reduction after smoking relative to no smoking ($p=0.04$). There was also a trend for smoking to reduce negative affect ratings ($p=0.07$). No effect of IV nicotine was detected on either habit withdrawal or negative affect.

3.2.3. Sensory ratings

Ratings of estimated nicotine delivery were no higher for the denicotinized cigarette than for the no-smoking condition, nor were ratings higher in the nicotine than saline infusion conditions. Ratings of similarity to the usual brand cigarette were significantly higher in the denicotinized cigarette condition than the no-smoking condition ($p=0.03$), as shown in Fig. 4. In contrast, IV nicotine had no effect on ratings of similarity. Airway sensations showed a robust effect of smoke condition, with strength ratings higher when smoking the denicotinized cigarette vs. no smoking, for the tongue ($p=0.0001$), nose ($p=0.002$), back of mouth

Table 1

	IV saline (n = 20)		IV NIC (continuous) (n = 20)		IV NIC (pulsed) (n = 20)		Usual brand (n = 20)	
Subject characteristics	mean	SD	mean	SD	mean	SD	mean	SD
Age	42.6	8.04	40.1	2.07	42.2	8.45	43.7	9.08
Gender	10 m, 10 f		12 m, 8 f		10 m, 10 f		10 m, 10 f	
Cigarettes/day	32.0	11.70	29.4	9.10	28.4	10.56	28.0	7.68
FTC nicotine	0.81	0.25	0.84	0.25	0.77	0.21	0.74	0.20
Years smoked	25.3	6.40	21.0	11.24	24.4	8.75	25.3	8.83
Plasma cotinine (screening)	324.5	22.28	272.0	20.74	315.3	38.21	293.1	18.02
FTND	7.1	1.72	7.1	1.60	6.2	1.82	6.4	2.01

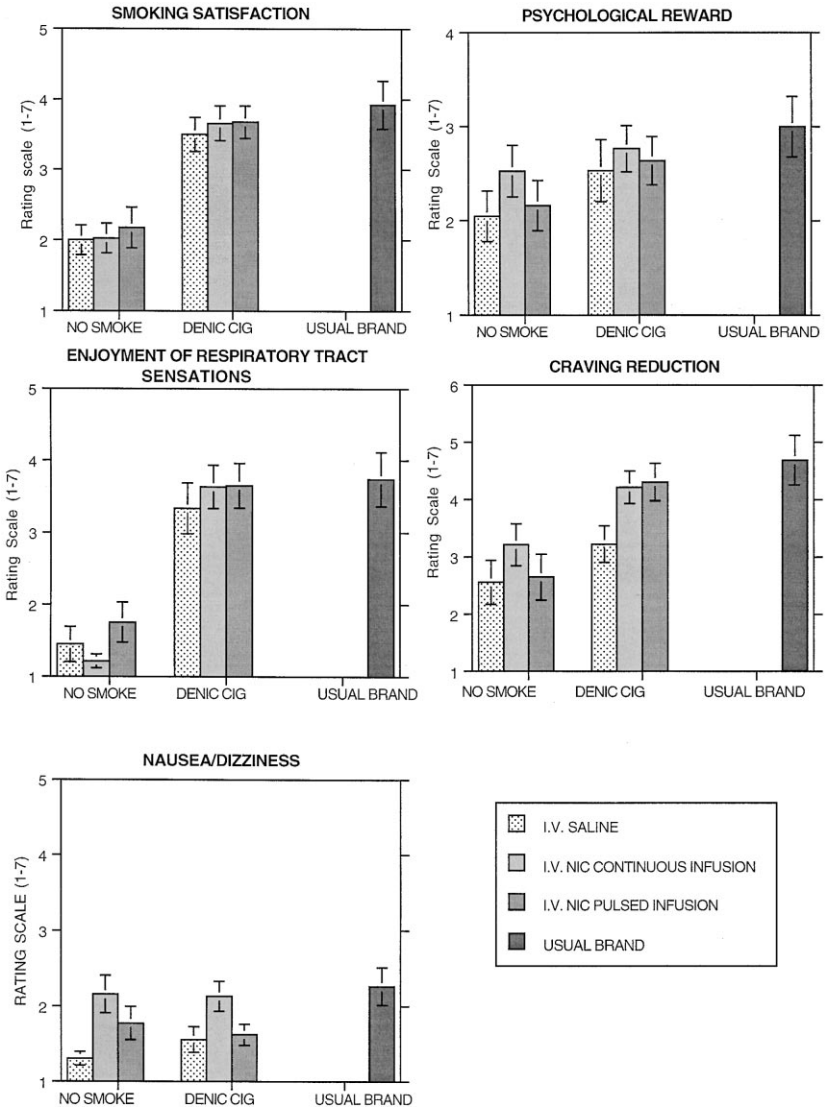


Fig. 2. Mean (± SEM) condition evaluation ratings for the three IV conditions and the different cigarette types.

and throat ($p=0.0001$), windpipe ($p=0.0001$), and chest ($p=0.0001$). Although IV nicotine infusions did not generally produce higher ratings of airway sensations than saline, the pulsed nicotine injections did elicit higher ratings than the continuous infusions, for the nose ($p=0.02$), and there was a similar trend for windpipe sensations ($p=0.07$). For the nose, there was an interaction of IV nicotine rate of smoke/nicotine delivery ($p=0.04$), such that subjects receiving the more rapid IV nicotine delivery reported stronger sensations, even in the absence of smoking.

3.2.4. Euphoria/dysphoria

The analysis of the euphoria factor showed a significant interaction between IV condition, smoke/nicotine delivery rate, and smoking, $F(2,53)=3.49$, $p=0.04$. An analysis of this interaction in terms of simple effects revealed an effect of smoking that was limited to the saline infusion condition and subjects accustomed to a higher than average rate of nicotine intake during ad lib smoking. In this subgroup, smoking a denicotinized cigarette increased ratings of euphoria. IV nicotine did not significantly influence euphoria ratings, and in fact, the ratings were remarkably similar in nicotine and saline infusion conditions (see Fig. 5). To examine the possibility that the failure to detect an effect of nicotine was due to limited statistical power, the confidence interval of the nicotine–saline difference in euphoria ratings was calculated (averaging the two IV nicotine conditions). The upper limit of the 95% confidence interval (one tailed) for a nicotine–saline difference was +0.7 units on the euphoria scale. Thus, any effect of nicotine that may have gone undetected was not likely to be a large effect.

In contrast, the analysis of dysphoria scores showed a significant main effect of IV condition, ($F(2,53)=5.351$, $p=0.003$. Subsequent contrasts indicated that the two IV nicotine conditions were rated higher in dysphoria than the saline control ($p=0.028$, see Fig. 5).

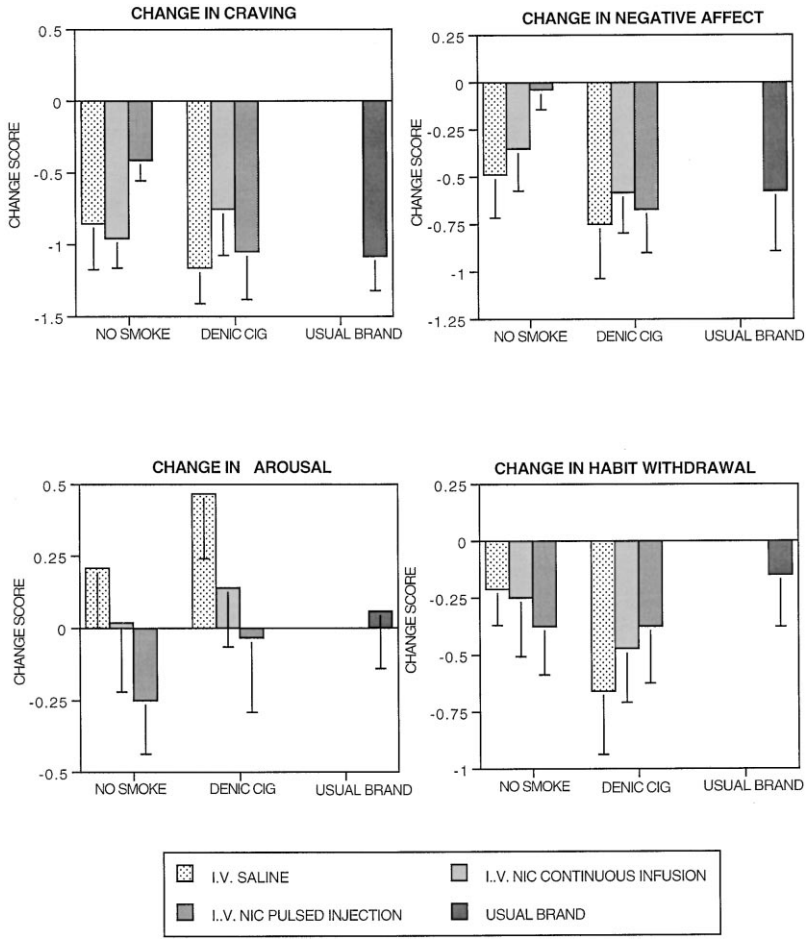


Fig. 3. Mean (±SEM) change in withdrawal symptom ratings (postminus preinfusion) for the three IV conditions and the different cigarette types.

3.2.5. Cardiovascular indices

There was a highly significant effect of nicotine infusion on heart rate boost ($p=0.008$ for the nicotine vs. saline contrast), and a slightly higher boost in the continuous vs. pulsed nicotine condition ($p=0.04$). The mean heart rate boosts were 0.8 bpm (SD=7.35) in the saline condition, 13.1 bpm (SD=10.05) in the continuous nicotine infusion condition, and 8.7 bpm (SD=8.690) in the pulsed IV nicotine condition. Smoking the denicotinized cigarette had no effect on heart rate ($p=0.8$), with a mean heart rate change of 8.1 bpm (SD=9.91) in the smoking conditions vs. 8.4 bpm (SD=10.32) in the no-smoking conditions. There were no significant effects of IV nicotine or smoking on either systolic or diastolic blood pressure.

3.2.6. Smoke/nicotine intake

The prepost infusion boost in expired air CO was, not surprisingly, significantly higher in the smoking conditions ($p=0.0001$); the mean boost was 3.3. ppm (SD=2.51) in the smoking conditions vs. 0.5 ppm (SD=1.09) in the no-smoking conditions. However, there was also a significantly higher CO boost following smoking in the saline condition than in the two IV nicotine infusions ($p=0.01$ for the interaction of infusion condition smoke), possibly reflecting differences in the depth of inhalation after each puff; the infusion conditions did not differ significantly from each other ($p=0.4$); the CO boost was 4.3 ppm (SD=3.20) after smoking in the saline condition, 3.1 ppm (SD=2.12) in the continuous IV nicotine condition, and 2.6 ppm (SD=2.01) in the pulsed IV nicotine condition. As expected, the IV nicotine conditions differed from saline in plasma nicotine boost ($p=0.0008$). The two infusion conditions were very similar to each other ($p>0.1$). The mean nicotine boosts were 0.4 ng/ml (SD=0.83) for saline, 12.2 ng/ml (SD=7.51) for the continuous IV nicotine condition, and 10.4 ng/ml (SD=6.61) for the pulsed nicotine condition. Concurrent smoking of the denicotinized cigarette had no measurable influence on the plasma nicotine boost ($p=0.4$).

3.3. Comparisons of usual brand cigarette with denicotinized cigarette + IV nicotine

A set of contrasts was conducted to assess how well the combination of denicotinized cigarette and pulsed injections of IV nicotine matched the subjective qualities of smoking the usual brand cigarette.

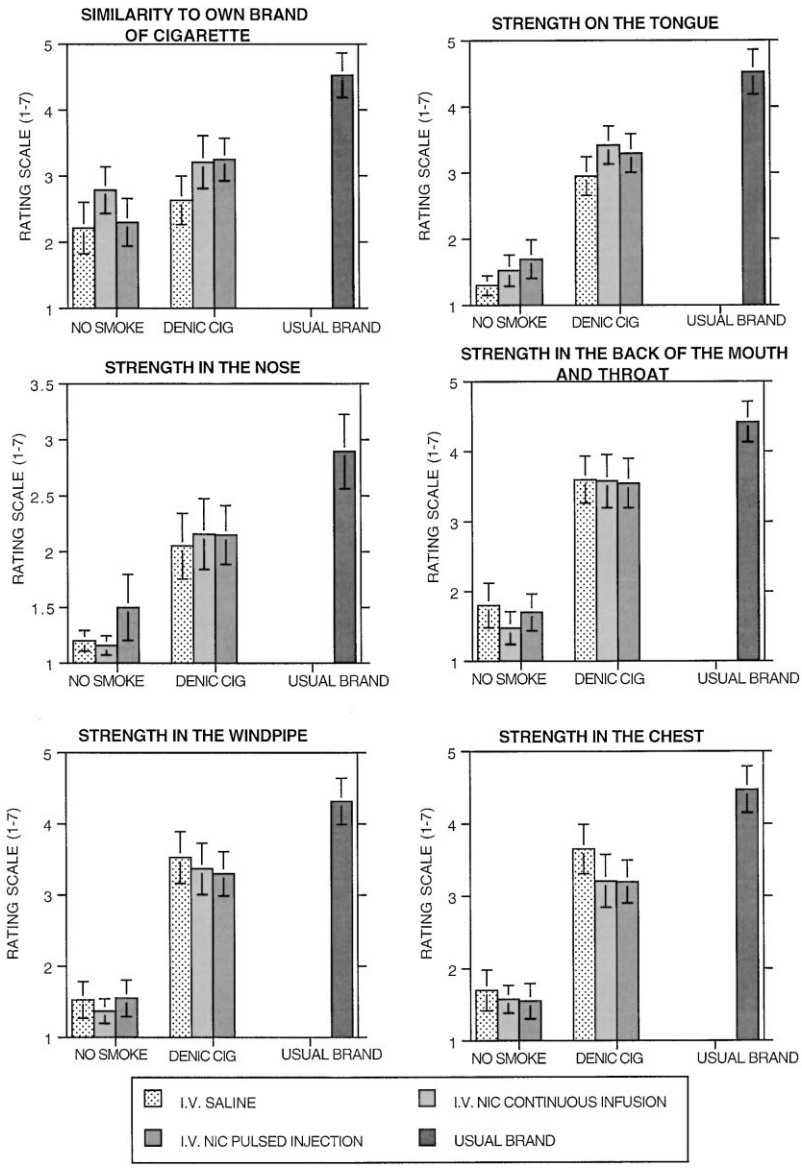


Fig. 4. Mean (± SEM) sensory ratings for the three IV conditions and the different cigarette types.

3.3.1. Condition evaluation scales

None of the differences between the two conditions were significant; the denicotinized cigarette + pulsed IV nicotine condition replicated the ratings of the usual brand cigarette on all of the condition evaluation scales (see Fig. 2).

3.3.2. Smoking withdrawal symptoms

The changes in smoking withdrawal symptoms scales were also very similar in the two conditions ($ps > 0.1$) (see Fig. 3).

3.3.3. Sensory ratings

There was a trend for estimated nicotine ratings to be higher for the usual brand condition ($p = 0.09$); moreover, ratings of similarity to the usual brand were significantly higher in the usual brand cigarette condition ($p = 0.01$). The IV nicotine + denicotinized cigarette received ratings of strength in the respiratory tract similar to those of the usual brand cigarette for the tongue ($p = 0.3$) and nose ($p = 0.8$), but tended to be lower in the back of mouth and throat ($p = 0.06$), and differed significantly in the windpipe ($p = 0.03$) and chest ($p = 0.006$). The usual brand cigarette was rated stronger in the lower respiratory tract regions (see Fig. 4).

3.3.4. Euphoria/dysphoria

Ratings of euphoria and dysphoria also did not differ between the usual brand cigarette condition and the IV nicotine + denicotinized cigarette condition (Fig. 5).

3.3.5. Cardiovascular measures

The heart rate boost following smoking was similar after both conditions (mean boost of 9.8 bpm (SD = 8.8) for the

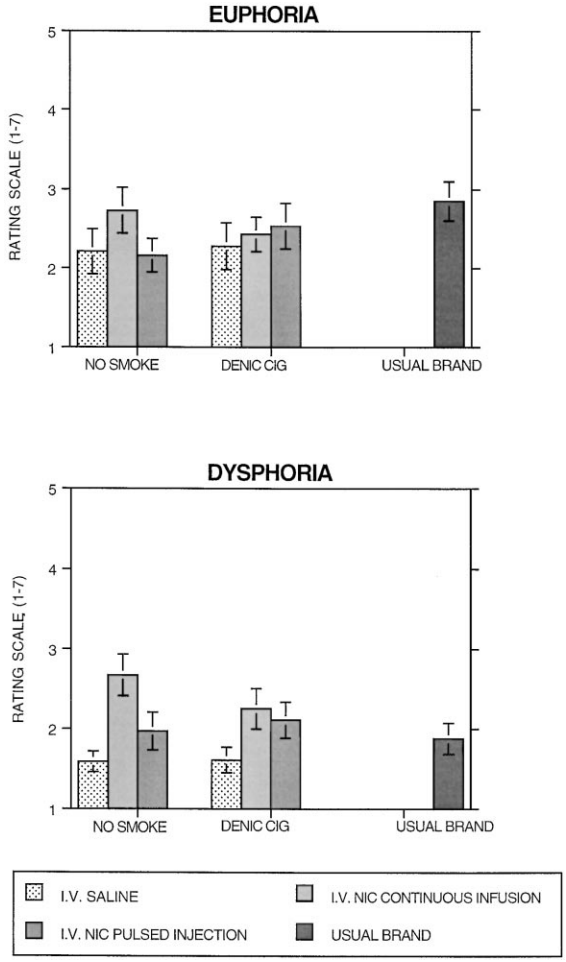


Fig. 5. Mean (±SEM) euphoria/dysphoria ratings for the three IV conditions and cigarette types.

pulsed IV nicotine + denicotinized cigarette condition and 8.1 bpm (SD=7.5) for the usual brand). Similarly, the change in systolic and diastolic blood pressures, though small, did not differ (mean change for the pulsed IV nicotine + denicotinized cigarette condition 5.0 mm Hg/ 6.8 mm Hg (SD=9.6/12.1) vs. +1.0 mm Hg/ 1.3 mm Hg (SD=14.0/7.6).

3.3.6. Smoke/nicotine intake

Expired air CO boosts were comparable in the two conditions (2.6 ppm (SD=2.0) vs. 3.4 ppm (SD=3.3)). However, plasma nicotine boosts differed somewhat ($p = 0.03$), with the IV nicotine + denicotinized cigarette condition producing higher nicotine boosts [8.2 ng/ml (SD=5.90) vs. 5.6 ng/ml (SD=3.30)].

4. Discussion

The main goal of the study was to determine how the pharmacologic actions of nicotine and the sensory/behavioral aspects of cigarette smoking contribute to the immediate subjective effects of cigarette smoking. Overall, the sensory/behavioral aspects presented by smoking a denicotinized cigarette were marked, and replicated many of the immediate subjective responses evoked by smoking the usual brand of nicotine-containing cigarette. Smoking the denicotinized cigarette produced satisfaction, psychological reward, and craving reduction. Moreover, in some smokers the denicotinized cigarette increased ratings of euphoria. Our results thus underscore the importance of sensory/behavioral factors in smoking reward, and show that these effects can be obtained even using an artificial smoking apparatus. In contrast, the effects of IV nicotine were subtle, and the only subjective variables significantly affected were craving reduction and aversion, with IV nicotine receiving higher ratings for craving reduction than saline and producing some mild nausea and dizziness. Thus, although IV nicotine reduced at least one index of smoking withdrawal, which can be viewed as negative reinforcement, it did not produce a significant pleasurable response. While considerable evidence implicates nicotine addiction as an important determinant of smoking, the immediate subjective effects of nicotine, in doses comparable to those obtained by smoking, appear to be mild. The lack of pleasurable responses to IV nicotine is consistent with our previous results [30] as well as with studies by other investigators who have used similar nicotine dosing parameters [15], or slower nicotine infusions [3,17]. In contrast, some previous studies found that subjects reported intense positive and negative effects of IV nicotine [10,14]. However, in these studies nicotine was rapidly administered in large bolus injections instead of in multiple puff-sized doses. While the latter studies demonstrated that it is possible to elicit large subjective effects, studies using dosing parameters more typical of ad lib smoking suggest that reinforcement mechanisms in tobacco dependence do not appear to depend on intense feelings of subjective pleasure elicited by nicotine. The absence of pleasure associated with IV nicotine was not likely due to the aversive effects of the somewhat higher plasma nicotine concentrations than in the usual brand condition, because even in the usual brand cigarette condition ratings of euphoric effects were modest (between "very little" and "a little" on the seven-point rating scales).

It was somewhat surprising that IV nicotine did not substantially affect other measures of smoking withdrawal, such as a negative affect. The plasma nicotine levels produced in our infusion conditions were similar to those typically achieved by cigarette smoking or alternative nicotine replacement methods [3], and clinically, nicotine replacement has often been shown to reduce negative affect (e.g., Ref. [23]). Possibly, despite overnight deprivation from cigarettes, withdrawal symptoms were limited during the short duration of our study, which was also conducted in a laboratory setting. The mean ratings of negative affect were approximately 4, using the same scale that we have used in several previous smoking cessation trials; in these studies, peak withdrawal ratings often exceed 5 in the absence of

nicotine replacement [2,23]. Alternatively, the within-subjects design was susceptible to carryover effects that could have made it more difficult to detect the effects of nicotine.

The boost in venous nicotine levels was comparable using either continuous or pulsed infusions. However, both IV dosing methods produced somewhat higher venous nicotine boosts than in the usual brand cigarette condition. This was likely due to the absence of any breath-hold requirement, resulting in loss of nicotine in exhaled air. Gilbert et al. [6] has shown that a 5-s breath hold after controlled puffing ensures complete nicotine absorption. However, in this study we wanted to interfere minimally with inhalation topography to preserve the enjoyable aspects of smoking. Although it was practical to measure puff volume at the ad lib smoking baseline session and duplicate this parameter during the subsequent infusion session, it would have been more cumbersome to control inhalation volume in an individualized fashion.

The absence of strict control over inhalation may have also been reflected in the higher CO boost following smoking of the denicotinized cigarette in the saline vs. IV nicotine conditions. The absence of nicotine may have driven compensatory smoking behavior in the saline condition, similar to results we reported in previous studies that examined smoking of denicotinized cigarettes while wearing nicotine vs. placebo transdermal patches [20] or nicotine vs. saline infusions [30]. Thus, receiving systemic nicotine limits smoke intake even when the cigarettes do not deliver nicotine, suggesting that compensatory smoking behavior does not depend on the immediate perception of nicotine in the respiratory tract.

The effects of smoking the usual brand of cigarette were closely matched by the combination of IV nicotine infusions and smoking a denicotinized cigarette. Most of the subjective ratings as well as cardiovascular responses were nearly identical in the two conditions. However, one notable difference was the stronger airway sensations elicited by the usual brand cigarette, due to the local irritant effects of nicotine [24]. Although IV nicotine, when administered rapidly, can elicit lung sensations [11], the sensory effects are subtle using dosing parameters that resemble ad lib smoking.

Generally, the continuous IV nicotine infusion produced similar effects as the pulsed injections. Thus, the immediate effects of each puff-sized nicotine "bolus" may not be critical for duplicating many of the subjective effects of cigarette smoking. This finding is consistent with results from a recent study in which we found that arterial nicotine concentrations produced by nicotine inhalation or injection often show a gradual rise over 30–60 s, not dissimilar from what would be produced by a continuous infusion [21].

Our results may also have implications for smoking cessation treatment development. Current nicotine replacement methods do not adequately address the importance of sensory/habit cues to smokers, which may account in part for the high rates of relapse using current treatments [29]. Therefore, new treatments that provide substitutes for these cues need to be devised and evaluated, alone or in the context of standard nicotine replacement methods.

Acknowledgments

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References

[1] Abelin T, Ehrsam R, Buhler-Reichert A, Imhof PR, Muller P, Tommen A, Vesanen K. Effectiveness of a transdermal nicotine system in smoking cessation studies. Methods Find Exp Clin Pharmacol 1989;11:205–14.
[2] Behm FM, Schur C, Levin ED, Tashkin DP, Rose JE. Clinical evaluation of a citric acid inhaler for smoking cessation. Drug Alcohol Depend 1993;31:131–8.
[3] Benowitz NL, Jacob PR. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. J Pharmacol Exp Ther 1990;254:1000–5.
[4] Benowitz NL, Porchet H, Jacob PI. Pharmacokinetics, metabolism, and pharmacodynamics of nicotine. In: Wonnacott S, Russell MAH, Stolerman IP, editors. Nicotine psychopharmacology. Oxford: Oxford Univ. Press, 1990. pp. 112–57.
[5] Federal Trade Commission. Tar, nicotine and carbon monoxide of the smoke of 568 varieties of domestic cigarettes. Washington, D.C.: Federal Trade Commission, 1993.
[6] Gilbert DG, Jensen RA, Meliska CJ. A system for administering quantified doses of tobacco smoke to human subjects: plasma nicotine and filter pad validation. Pharmacol, Biochem Behav 1989;31:905–8.
[7] Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Arch Intern Med 1999;159:2033–6.
[8] Hasenfratz M, Baldinger B, Battig K. Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology (Berlin) 1993; 112:253–8.
[9] Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KL. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict 1991;86:1119–27.
[10] Henningfield J, Goldberg S. Control of behavior by intravenous nicotine injections in human subjects. Pharmacol, Biochem Behav 1983;19:1021–6.
[11] Henningfield JE, Jasinski DR. Pharmacologic basis for nicotine replacement. In: Pomerleau OF, Pomerleau CS, editors. Nicotine replacement: a critical evaluation. New York: Alan R. Liss, 1998. pp. 35–61.
[12] Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal: a replication and extension. Arch Gen Psychiatry 1991;48:52–9.
[13] Jacob P, Wilson M, Benowitz N. Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. J Chromatogr 1981;222:61–70.
[14] Jones RT, Farrell TR, Herning RI. Tobacco smoking and nicotine tolerance. In: Na K, editor. Self-administration of abused substances: methods for study. NIDA Res Monogr Ser. Washington, DC: U.S. Government Printing Office, 1978;18. pp. 202–8.
[15] Kumar R, Cooke EC, Lader MH, Russell MAH. Is nicotine important in tobacco smoking? Clin Pharmacol Ther 1976;21:520–8.
[16] Levin ED, Rose JE, Behm F. Controlling puff volume without dis-

rupting smoking topography. Behav Res Methods Instrum Comput 1989;21:383–6.
[17] Lucchesi BR, Schuster CR, Emley GS. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clin Pharmacol Ther 1967;8:789–96.
[18] Perkins KA, Grobe JE, Stiller RL, Fonte C, Goettler JE. Nasal spray nicotine replacement suppresses cigarette smoking desire and behavior. Clin Pharmacol Ther 1992;52:627–34.
[19] Pomerleau OF, Flessland KA, Pomerleau CS, Hariharan M. Controlled dosing of nicotine via and intranasal aerosol delivery device (INADD). Psychopharmacology (Berlin) 1992;108:519–26.
[20] Rose JE, Behm FM. There is more to smoking than the CNS effects of nicotine. Effects of nicotine on biological systems II. Basel: Burkhäuser Verlag, 1995. pp. 9–16.
[21] Rose JE, Behm FM, Westman EC, Coleman RE. Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction. Drug Alcohol Depend 1999; 56:99–107.
[22] Rose JE, Behm FM, Westman EC, Levin ED, Stein RM, Ripka GV. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. Clin Pharmacol Ther 1994;56:86–99.
[23] Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. Clin Pharmacol Ther 1990; 47:323–30.
[24] Rose JE, Westman EC, Behm FM, Johnson MP, Goldberg JS. Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. Pharmacol, Biochem Behav 1999;62:165–72.
[25] Rose JE, Wu T-C, Djahed B, Tashkin DP. Noninvasive measurement of smokers' tar and nicotine intake. Behav Res Methods Instrum Comput 1987;19:295–9.
[26] Russell MAH, Feyerabend C. Cigarette smoking: a dependence on high-nicotine boli. Drug Metab Rev 1978;8:29–57.
[27] Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology (Berlin) 1976;50:35–9.
[28] U.S.D.H.H.S. The health consequences of smoking: nicotine addiction. . Rockville, MD: Office on Smoking and Health, 1988.
[29] Westman EC, Behm FM, Rose JE. Airway sensory replacement as a treatment for smoking cessation. Drug Dev Res 1996;38:257–62.
[30] Westman EC, Behm FM, Rose JE. Dissociating the nicotine and airway sensory effects of smoking. Pharmacol, Biochem Behav 1996;53:309–15.
[31] Westman EC, Levin ED, Rose JE. Smoking while wearing the nicotine patch: is smoking satisfying or harmful? Clin Res 1992;40:871A.
[32] Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation: a randomized trial with telephone counseling. Arch Intern Med 1993;153:1917–23.

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Individual differences in smoking reward from de-nicotinized cigarettes

Lisa H. Brauer, Frederique M. Behm, James D. Lane, Eric C. Westman, Christine Perkins, Jed E. Rose

Most studies of cigarette smoking and smoking cessation have focused on the psychopharmacological effects of nicotine; relatively few have explored the role of sensory aspects of cigarette smoke. Sensory aspects of cigarette smoke play a role in the maintenance of smoking behavior, and may be particularly important for certain smokers. This paper presents the results of a pooled analysis of nine studies conducted in our laboratory, in order to explore the influence of demographic and smoking-related variables on ratings of de-nicotinized as compared to nicotine-containing cigarettes. A major finding of this analysis is that ratings of smoking derived from de-nicotinized, but not nicotine-containing, cigarettes appear to vary with level of tobacco dependence, suggesting that sensory factors may be more important to highly dependent, as compared to less-dependent, smokers. The implications of these findings for smoking cessation treatment and for future research are discussed.

Introduction

Laboratory and clinical studies of smoking behavior have typically focused on the role of nicotine in the maintenance of smoking and the potential utility of nicotine replacement strategies for smoking cessation, respectively. The emphasis on nicotine, as opposed to other constituents of tobacco, has obvious merit given the large body of evidence that the reinforcing effects of nicotine play a significant role in smoking (reviewed in USDHHS, 1988). However, there is a growing body of evidence suggesting that other aspects of cigarette smoke, namely the sensory effects, also contribute to the maintenance of smoking. To date, sensory aspects of smoking have received relatively little attention in the basic and clinical literature. Understanding the role of sensory and other non-psychopharmacological effects of smoking is important for several reasons. First, clinical studies have demonstrated only modest efficacy of nicotine replacement strategies for smoking cessation (Fagerström, 1988; Hughes & Glaser, 1993; Palmer, Buckley, & Faulds, 1992; Sutherland *et al.*, 1992), and it is important to assess whether the addition of a sensory replacement component could enhance quit rates. Second, sensory replacement may prove useful in particular smokers for whom other forms of smoking cessation treatment have not been effective. Finally, assessing the role of non-psychoactive components of cigarette smoke would aid in our understanding of the relationship between primary and secondary reinforcers (e.g., Rose & Levin, 1991) in cigarette smoking, and in drug addiction generally.

Few studies have directly explored sensory aspects of smoking; however, studies have consistently demonstrated the importance of these factors to the maintenance of smoking. For example, Rose and colleagues have shown in a series of studies that pharmacological blockade of the afferent pathways mediating smoking-

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induced airway sensations significantly reduces smoking satisfaction (Rose, 1988; Rose, Tashkin, Ertle, Zinser, & Lafer, 1985; Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984). These investigators, as well as others, have also shown that replacing the sensory component of smoking with substances including ascorbic and citric acids, capsaicin, black pepper, or refined smoke aerosol significantly reduces craving for cigarettes as well as rates of *ad lib* smoking (Behm & Rose, 1994; Levin, Behm, Carnahan, LeClair, Shipley, & Rose, 1993; Perkins, Grobe, Stiller, Fonte, & Goettler, 1992; Rose & Behm 1987; Rose & Behm 1994; Rose & Behm 1995; Westman, Behm, & Rose, 1995). Finally, it has been shown that treatments that re-create the mouth, throat, and airway sensations of smoking enhance the efficacy of the nicotine patch in smokers attempting to quit (Westman, Behm, & Rose, 1995). When taken together, these findings clearly demonstrate that there is more to smoking than the psychopharmacological effects of nicotine.

One reason for the relative paucity of studies on the sensory effects of smoking is that until relatively recently, there have been few methods available for experimentally separating the pharmacological and sensory components of cigarettes in order to assess their relative roles in maintaining smoking. Methods that were previously used were fraught with limitations related to differences between the experimental manipulation and commercially available cigarettes in the pattern and pharmacokinetics of nicotine administration, the palatability and/or sensory effects of experimental, as compared to commercially available, cigarettes, and the inability to vary nicotine and tar independently.

Recently, cigarettes low in nicotine but with standard levels of tar have become available for directly exploring the role of nicotine and sensory factors in smoking: the Next® cigarette, developed by Philip Morris, Inc.; the University of Kentucky cigarettes; and low nicotine cigarettes by Ultratech Corporation (Philadelphia, PA). These cigarettes are reported to produce sensory effects and taste similar to nicotine-containing brands of cigarettes. The availability of these cigarettes affords a unique opportunity to investigate the sensory and behavioral aspects of smoking, and to serve as a control condition in studies of the effects of nicotine *per se*. Although to date no studies have explored this issue, these cigarettes may have a role in the acute management of early smoking withdrawal symptoms (i.e., craving), when used in combination with nicotine replacement. Moreover, it is possible that sensory replacement strategies may prove useful for particular groups of smokers (e.g., highly dependent smokers).

Only a few studies have compared the effects of de-nicotinized or related types of cigarettes to commercially available cigarettes. Those studies that have been conducted, summarized in Table 1, have produced mixed results. Although the studies are consistent in demonstrating that cigarettes with little or no nicotine can produce smoking satisfaction and craving reduction, they vary in the degree to which the magnitude of these effects was comparable to those of nicotine-containing cigarettes. In an effort to explore a potential source of this variability, namely, individual differences, we conducted a pooled analysis of nine studies from our laboratory, in which the acute subjective effects of Next® cigarettes were compared to subjects' own brands. Acute subjective ratings of drugs have been shown repeatedly to be related to abuse potential (e.g., Fischman & Foltin, 1991), and these variables in particular are likely to relate to the maintenance of smoking.

The data set for the analysis was collected from 142 non-menthol smokers in nine studies, recruited from the Raleigh–Durham–Chapel Hill, NC, area. Each study had similar inclusion and exclusion criteria (e.g., minimum number of cigarettes per day of 15–20, minimum nicotine yield of at least 0.5 mg/cigarette, no medical or psychiatric illnesses) and used similar dependent measures to assess the effects of cigarettes. All of the studies included in the analyses were conducted with the Next® cigarette. Originally manufactured by Philip Morris, Inc., these cigarettes contain tobacco from which the nicotine has been selectively extracted by high-pressure carbon dioxide. They have a taste similar to nicotine-containing brands of cigarette, and the tar delivery, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg; therefore, these cigarettes produce sensory effects similar to those of nicotine-containing cigarettes without providing significant levels of nicotine. All studies were approved by the Duke and/or Veterans Affairs Medical Centers Institutional Review Boards, and informed consent was obtained from all subjects prior to participation.

Methods

The primary dependent measures explored in these analyses were smoking satisfaction and craving reduction obtained from smoking nicotine-containing as compared to de-nicotinized cigarettes. These variables were selected *a priori* as being most relevant to smoking-related reward. Data on satisfaction and craving reduction were gathered from two questionnaires, the Cigarette Evaluation Scale (CES; Westman, Levin, & Rose, 1992), and the Sensory Questionnaire (SQ), which were completed immediately after smoking a cigarette. The CES asks subjects to rate the extent to which the cigarette they just smoked was satisfying, tasted good, made them dizzy, calmed them down, helped them to concentrate, made them feel more awake, reduced appetite, made them nauseous, decreased irritability, produced enjoyable sensations in the throat and chest, and immediately reduced craving for cigarettes, on a Likert-type scale from not at all (1) to extremely (either 5 or 7, depending on study). For the purposes of this analysis, we used data from the last item on this questionnaire as a measure of craving reduction. For one study, data on craving were obtained from pre- to post-smoking changes in the craving subscale score from the

Table 1. Effects of de-nicotinized tobacco cigarettes on ratings of liking and craving relative to nicotine-containing cigarettes

Author	Number of Subjects	Intent to quit	Mean number of cigarettes per day	Mean nicotine yield-usual brand	Design (within- or between-subjects)	Abstinence condition	Smoking pattern	Satisfaction vs. usual brand	Craving reduction vs. usual brand
Hasenfratz, Baldinger, & Battig (1993)	12	No	21.1	0.81	Within	a.m. prior to session	*Ad lib*	Lower	Lower
Rose *et al.* (1994)	12	Yes	28.0	0.91	Within	Overnight	Controlled	Similar	Similar
Baldinger, Hasenfratz, & Battig (1995)	12	No	24.3	Not available	Within	Not available	*Ad lib*	Lower	Lower
Butschky, Baily, Henningfield, & Pickworth (1995)	7	No	26.4	1.15	Within	12 hours	Controlled	Lower	Similar
Lane *et al.* (1995)	18	No	20.9	>0.70	Within	Overnight	*Ad lib*	Lower	Lower
Rose & Behm (1995)	20	Yes	26.8	0.98	Within	Overnight	*Ad lib*	Similar	Similar
Rose, Westman, & Behm (1996)	80	Yes	29.4	0.79	Between	Overnight	Controlled	Similar	Lower
Westman, Behm, & Rose (1996)	6	Yes	28.5	0.98	Within	Overnight	Controlled	Similar	Similar
Gross *et al.* (1997)	10	No	28.3	1.07	Within	Not abstinent	Controlled	Lower	Similar
Rose *et al.* (in progress)	13	Yes	29.4	0.79	Between	Overnight	*Ad lib*	Lower	Lower
Lane *et al.* (unpublished)	27	No	21.7	1.03	Within	Overnight	Controlled	Lower	Lower

Shiffman–Jarvik questionnaire (Shiffman & Jarvik, 1976), because CES data were not available. The SQ asks subjects to rate how much they liked the cigarette they had just smoked and how much it satisfied them, how high in nicotine the cigarette appeared to be, and how similar the cigarette was to their own brand. In addition, the questionnaire presented subjects with a diagram of the respiratory tract and asked them to rate the strength of the cigarette puffs on their tongue, nose, back of mouth and throat, windpipe and chest, on a 1–7 Likert-type scale. For this analysis, we used the mean of the liking and satisfaction ratings as an overall measure of smoking satisfaction. For both questionnaires, data were calculated as difference scores (nicotine-containing minus de-nicotinized cigarette ratings), so that positive ratings indicated more satisfaction or craving reduction from the nicotine-containing cigarette, whereas neutral or negative ratings indicated no difference or higher ratings, respectively, from the de-nicotinized cigarette. Because the results of the separate analyses for craving reduction and smoking satisfaction suggested that these two measures were highly correlated, we calculated the mean of the two ratings and re-analyzed the data with this composite reward rating.

Data analyses were conducted using multiple regression with backward elimination. Five potential predictor variables were entered into the model: study, gender, race, years smoked, and total score on the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994; Pomerleau, Carton, Lutzke, Flessland, & Pomerleau 1994; Tate and Schmitz 1993). Cigarettes per day and nicotine yield of preferred cigarette were not entered as predictor variables because these variables contribute to total FTND score, and would also be explored in subsequent analyses with individual FTND items (see below). Non-significant predictor variables were eliminated one at a time until only significant ($p \leq 0.05$) variables remained in the model. Because FTND score emerged as significant in most models, we conducted follow-up analyses to determine which individual FTND items were related to the composite reward score. The original analytic strategy was repeated with the individual items being entered and backward eliminated as described above.

The analyses conducted on nicotine-containing minus de-nicotinized cigarettes provides information on the relative ratings assigned to the two cigarette types, and gives an estimate of the relative importance of nicotine *per se* to smoking reward. However, these analyses do not address the possibility that individual differences in responses to the different cigarettes types reflect not positive responses to de-nicotinized cigarettes but rather blunted responses to nicotine as a result of tolerance. To address this issue, separate regression analyses were conducted on ratings of each cigarette type.

Results

Subject characteristics

Data from 142 subjects were included in the analysis. Fifty-eight per cent of the subjects were male, and 88% were Caucasian. Their mean age was 36.4 years old (SE = 0.93; range 18–65). Subjects smoked an average of 24.5 (SE = 0.70; range 10–60) cigarettes per day of a mean nicotine yield of 0.9 (SE = 0.02; range 0.5–1.7) mg when smoked by FTC criteria. They had smoked for an average of 19 years (SE = 0.92; range 1–48) at the time of participation in the study, and had average FTND scores of 5.5 (SE = 0.16; range 1–10).

Cigarette ratings

As a group, subjects reported substantial reward (i.e., the mean of craving reduction and smoking satisfaction ratings) from both nicotine-containing and de-nicotinized cigarettes, but, as expected, ratings were highest after smoking cigarettes containing nicotine [mean (SE) of 4.05 (0.15) for nicotine-containing-cigarettes vs. 3.36 (0.14) for de-nicotinized cigarettes; one-way ANOVA, $F(1,137) = 23.69$, $p = 0.0001$]. Interestingly, the final regression model indicates that there were significant individual differences in cigarette ratings, with some individuals assigning approximately equal ratings to the two kinds of cigarettes (see below), and others reporting greater reward from nicotine-containing cigarettes. Cigarette ratings are summarized in Table 2.

Regression model: NIC–DENIC

Of the five original potential predictors, including total FTND score, entered into the first model, only three predictors, FTND score, gender and study, remained significant in the final model. There were no significant effects of race or years smoked. The final model was as

Table 2. Mean (SE) cigarette ratings by gender and FTND score

Ratings	Males	Females	FTND<6	FTND≥6
DENIC	3.7 (0.2)	3.2 (0.2)	3.0 (0.2)	3.7 (0.2)
NIC	4.2 (0.2)	4.1 (0.2)	4.0 (0.2)	4.3 (0.2)
NIC-DENIC	0.5 (0.2)	0.9 (0.2)	1.0 (0.2)	0.4 (0.2)

Table 3. Mean (SE) cigarette ratings by study

Study	DENIC	NIC	NIC-DENIC
Rose & Behm (1995)	3.8 (0.2)	4.3 (0.3)	0.5 (0.2)
Westman *et al.* (1996)	5.2 (0.6)	5.0 (0.5)	–0.2 (0.7)
Rose *et al.* (1994)[a]	1.5 (0.2)	1.7 (0.3)	0.2 (0.3)
Lane *et al.* (1995)	2.9 (0.4)	5.5 (0.4)	2.6 (0.5)
Lane *et al.* (unpublished)	3.4 (0.3)	4.7 (0.3)	1.3 (0.3)
Rose *et al.* (unpublished)	3.0 (0.3)	2.8 (0.3)	–0.1 (0.2)
Rose *et al.* (submitted)	4.3 (0.3)	4.5 (0.3)	0.2 (0.3)
Brauer, Behm, Westman, Patel, & Rose (1999)	4.5 (0.3)	4.6 (0.3)	0.1 (0.2)
Brauer *et al.* (in preparation)	2.6 (0.4)	3.9 (0.4)	1.3 (0.6)

[a] Cigarettes were rated on a scale of 1–5, rather than 1–7.

follows: FTND: $F(1,120) = 6.20$, $p = 0.014$, beta = –0.174; study: $F(8,120) = 6.40$, $p = 0.0001$; gender: $F(1,120) = 5.54$, $p = 0.020$, beta (male) = 0.00, beta (female) = 0.622; $r^2 = 0.345$. Several interesting findings emerged from this analysis. First and most interestingly, there was a significant negative correlation between the difference in ratings between nicotine-containing and de-nicotinized cigarettes (NIC–DENIC) and FTND scores, such that more highly dependent subjects assigned more similar ratings to the two cigarette types than less-dependent smokers, who obtained more reward from nicotine-containing cigarettes. When expressed as a median split, subjects with high dependence, defined as a total FTND score of ≥6, had an average NIC–DENIC difference of 0.42 (0.18), as compared to those with low to moderate dependence (FTND<6), who had a mean difference of 1.04 (0.24). Lower scores in the highly dependent group reflect more indifference to the two cigarette types, in that very similar ratings were assigned whether the cigarettes contained nicotine or not.

Second, cigarette ratings also tended to vary as a function of gender. On average, males were more indifferent to the effects of nicotine than females. The mean NIC–DENIC rating for males was 0.53 (0.18), whereas for females the mean rating was 0.93 (0.24). Thus, males assigned relatively less import to the psychopharmacological effects of nicotine than did females. Interestingly, there was no gender×FTND interaction for this measure.

The effects of study were difficult to characterize along a single dimension. Mean ratings for each cigarette type as a function of study are presented in Table 3.

Regression model: DENIC only

A separate regression analysis for DENIC ratings only suggests that the basis for this FTND effect is ratings of DENIC cigarettes, rather than diminished responses to nicotine. When the same backward elimination process was conducted for DENIC ratings, only FTND ($F(1,127) = 5.61$, $p = 0.019$, beta = 0.158) and study ($F(8,127) = 6.07$, $p = 0.0001$) emerged as significant predictors. Data from a mean split analysis demonstrate that, as expected, highly dependent subjects assigned de-nicotinized cigarettes a mean rating of 3.72 (0.20), as compared to less-dependent subjects, who assigned a mean rating of 2.98 (0.19).

When explored in the context of DENIC ratings only, there was no significant gender effect [mean for females = 3.16 (0.23) vs. mean for males = 3.67 (0.17)]. Nevertheless, the direction of the gender difference, with females liking de-nicotinized cigarettes less than males, is consistent with the results of the previous analysis.

Regression model: NIC only

Regressions for NIC ratings only support the notion that group differences in tolerance to the effects of nicotine does not account for our findings. Of the predictor variables entered into the regression, only study emerged as significant ($F(8,130) = 10.09$, $p = 0.001$; see Table 3).

Regression model with individual FTND items

Based on the obvious import of FTND scores to ratings of cigarette reward, we conducted an additional analysis to determine which individual FTND items most predicted significant reward from smoking-related sensory cues (i.e., de-nicotinized cigarettes). Using the regression approach described above, we examined the difference score (NIC–DENIC) with respect to the following FTND items [scoring]: (1) How long after waking do you smoke your first cigarette? [within 5 min = 3; 6–30 min = 2; 30–60 min = 1; greater than 60 min = 0]; (2) Do you find it difficult to refrain from smoking in places where it is forbidden? [yes = 1; no = 0]; (3) Which cigarette of the day would you most hate to give up? [first cigarette of the day = 1; all other cigarettes = 0]; (4) How many cigarettes do you smoke per day? [greater than 31 = 3; greater than 21 but les than 30 = 2; greater than 11 but less than 20 = 1]; (5) Do you smoke more in the morning than during the rest of the day? [yes = 1; no = 0]; (6) Do you smoke even when you are ill? [yes = 1; no = 0].

NIC–DENIC

In the first analysis, of NIC–DENIC differences, two FTND items, Question 3 (which cigarette of the day would you most hate to give up; $F(1,132) = 5.99$, $p = 0.016$, beta = −0.721) and Question 4 (cigarettes/day; $F = 5.02$, $p = 0.027$; beta = −0.446) were significantly related to ratings of smoking reward ($r^2 = 0.068$). For Question 3, the mean rating for subjects who scored 1 (first cigarette of the day) was 0.46 (0.16), and the mean for those who scored 0 (all other cigarettes) was 1.09 (0.27), indicating that for subjects who most hated to give up the first cigarette of the day, ratings for the NIC and DENIC cigarettes were highly similar, whereas the remaining subject ratings for NIC cigarettes were significantly higher. To the extent that most missing the first cigarette of the day is considered an index of relatively higher dependence, these findings are consistent with the notion that more dependent subjects are more indifferent to nicotine-containing vs. de-nicotinized cigarettes than less dependent subjects.

A similar pattern emerged for Question 4 ratings. Ratings were nominalized in order to obtain mean values. Mean ratings in each category are as follows: score = 0 (smoke fewer than 11 cigarettes per day; $n = 4$), mean = −0.50 (0.35); score = 1 (smoke 11–19 cigarettes per day; $n = 58$), mean 1.09 (0.24); score = 2 ($n = 61$; smoke 21–30 cigarettes per day), mean = 0.60 (0.19); score = 3 (smoke greater than 31 cigarettes per day; $n = 15$), mean = −0.13 (0.40). Thus, with the exception of the small number of subjects who smoked fewer than 11 cigarettes per day, NIC–DENIC ratings were negatively correlated with cigarettes per day. Again, these findings are consistent with the notion that more highly dependent subjects place relatively less value on nicotine *per se* than do less dependent smokers.

DENIC only

A separate regression analysis with DENIC-only ratings yielded different results. In this analysis, only Question 1 (how soon after waking do you smoke your first cigarette?) was significantly related to cigarette ratings ($F = 5.78$, $p = 0.018$, $r^2 = 0.041$, beta = 0.378). Mean ratings were as follows: score = 0 (greater than 60 min), mean = 1.38 (0.18); score = 1 (30–60 min), mean = 3.21 (0.31); score = 2 (6–30 min), mean 3.64 (0.20); score = 3 (within 5 min), mean = 3.43 (0.25). These results indicate that subjects who smoked within 30 min of awakening were more likely to assign higher ratings of smoking reward than those who did not.

NIC only

No FTND items emerged as significant predictors of cigarette ratings.

Discussion

With each puff of cigarette smoke, smokers inhale over 4000 chemicals, each having potentially distinctive subjective effects. Given this fact, it is perhaps naive to expect that only the psychopharmacological effects of nicotine motivate smoking behavior. Indeed, the results of several previous studies confirm the critical role of smoking-related sensory cues. For example, we have shown that de-nicotinized cigarettes produce substantial craving reduction and smoking satisfaction (Rose & Behm, 1995). Interestingly, the results of this analysis indicate that the degree to which sensory factors maintain smoking may differ among smokers. Our analyses demonstrate a significant relationship between ratings of smoking reward and FTND scores, indicating that more dependent smokers rely more heavily on sensory cues than do less dependent smokers. In contrast, less dependent subjects appear to rely more heavily on the direct effects of nicotine.

The reasons why more dependent smokers might rate de-nicotinized and nicotine-containing cigarettes similarly may relate to the more prolonged and intensive associations of smoking-related sensory cues with the psychopharmacological effects of nicotine (see Rose & Levin, 1991). That is, with more prolonged and intensive pairing between the direct CNS effects of nicotine and the sensory effects of cigarette smoke, the ability of the sensory elements of smoke to induce conditioned reinforcing effects strengthens. If this were the case, then sensory effects of cigarette smoke, in their own right, would be rewarding. Alternatively, these results may reflect more extensive tolerance development to the effects of nicotine in heavier, more dependent smokers. That is, as the extent of acute or (perhaps) chronic tolerance to nicotine increases, the incremental effects of nicotine in cigarette smoke are less pronounced. As this occurs, the psychopharmacological effects of nicotine would likely become relatively less important in maintaining smoking. Although it is possible that the development of chronic tolerance contributes to the findings reported here, our analyses with DENIC ratings alone and NIC ratings alone clearly indicate that the secondary reinforcing effects of smoking-related sensory cues play a role in the maintenance of smoking in highly dependent smokers. The notion that conditioned reinforcers can contribute to drug-taking and/or withdrawal symptoms has been shown in previous studies with both animal and human subjects (e.g., Childress, McLellan, & O'Brien, 1986; O'Brien, Childress, McLellan, Ehrman, & Ternes, 1988; Stewart & Eikelboom, 1987). For example, O'Brien and colleagues have repeatedly shown that cues associated with the administration of opiates can increase drug craving (Childress *et al.*, 1986; O'Brien *et al.*, 1988). These findings underscore the complex nature of smoking and other drug use and emphasize the fact that substitution for or blockade of the central psychopharmacological effects of drugs may not be sufficient to reduce drug taking.

Another interesting finding in this study relates to the gender differences observed in this study. On average, women had greater NIC–DENIC differences, and lower scores on ratings of de-nicotinized cigarettes alone. These results suggest that women assign more import to the direct psychopharmacological effects of nicotine than to the secondary reinforcing (i.e., sensory) effects, whereas men assign more equal relevance to nicotine and sensory cues. This pattern of results goes counter to those previously reported by Perkins and colleagues (e.g., 1992, 1996), who have shown in laboratory studies that women rate the sensory aspects of smoking as more salient than men. Perkins and others have used these results to suggest that perhaps nicotine replacement therapies are less effective for women because women rely less heavily on the psychopharmacological effects of nicotine than on other aspects of cigarette smoke. In contrast, our results suggest that perhaps nicotine is more salient to women, and that nicotine replacement therapies fail because there is insufficient nicotine replacement in this population. However, before we make this assertion with confidence, more prospective studies with de-nicotinized cigarettes should be conducted with respect to gender differences. The studies of Perkins and colleagues have primarily explored other routes of administering sensory impact (e.g., nicotine nasal spray and nicotine inhaler), which also deliver additional nicotine. Thus, the extent to which their findings would extend to smoking-related sensory cues is unclear.

The final models resulting from our analyses indicated that ratings also varied as a function of study. It is not clear why study was significant in our models, but several possibilities exist. First, it is possible that the studies varied with respect to motivation to quit smoking. Indeed, some of the studies included in the analysis were laboratory studies in which subjects were paid to participate and did not have to quit smoking, whereas others were smoking cessation trials. However, since subjects were not directly queried about their intentions to quit, it did not seem prudent to include this variable in the model. Second, the studies undoubtedly varied in terms of the context in which smoking took place. For example, in some studies subjects smoked through a controlled smoking apparatus, and in others they smoked *ad lib*. Third, the studies differed in terms of their purpose, and this may have influenced how smoking was measured or the importance of the cigarette rating data to the overall design. For instance, in one study, the antinociceptive effects of nicotine were of primary interest (Lane *et al.*, 1995), whereas others were specifically designed to compare cigarette types as was done in this analysis. Other, as yet undefined, differences between studies may also have contributed to our findings. Future studies should prospectively manipulate some of these parametric dimensions in an effort to characterize and systematize within-and between-subjects variability in response to de-nicotinized cigarettes.

The findings described in this paper have important implications, both for laboratory studies of smoking and for the development of effective smoking cessation strategies. One implication for laboratory studies is that the role of sensory and motor components of smoking cannot be ignored, and should be rigorously controlled with de-nicotinized cigarettes or similar technology. For instance, studies attempting to explore nicotine regulation by providing smoking preloads, or studies assessing nicotine preference using cigarettes, need to consider carefully the possible influence of sensorimotor factors in their data. For example, Behm and Rose (1994) have shown that capsaicin-enhanced low tar and nicotine cigarettes substantially reduce craving for cigarettes by mimicking respiratory tract cues associated with cigarette smoking.

Another finding that may have relevance for future studies is the fact that ratings of craving reduction and smoking satisfaction seem to co-vary – indeed, this is the reason that we elected to use a composite reward variable in the present analyses. A regression analysis of satisfaction vs. craving reduction ratings showed a very strong correlation between these factors ($r = 0.53$). A similar relationship has been shown in a previous paper (Behm & Rose, 1994). The fact that these cigarette ratings co-vary supports the idea that smokers may smoke to relieve withdrawal symptoms, rather than merely for enjoyment. That is, it is possible that smoking satisfaction is derived largely from craving reduction, and that the measures explored in these studies are one and the same. However, it is likely that craving reduction and smoking satisfaction represent separate constructs; it is possible to reduce craving with manipulations that do not impact upon satisfaction (e.g., nausea).

The findings described here also suggest that future laboratory studies need to explore the basis for compensatory increases or decreases in smoking following alterations in the nicotine or tar content of cigarettes. To date, no studies have systematically explored this question by allowing subjects to smoke de-nicotinized tobacco (as opposed to herbal or lettuce) cigarettes over a prolonged period of time. A study to examine this issue is currently underway. Although the prevailing opinion is that smokers alter smoking topography based on changes in nicotine delivery, the data described here suggest that subjects may also attempt to regulate, to some extent, the sensory impact or quality experienced. Nicotine itself is a local irritant, and in addition stimulates nicotine receptors in the respiratory tract, and thus nicotine dose is related to the intensity of airway sensations (Herskovic, Rose, & Jarvik, 1986; Rose & Hickman, 1988). However, tar also plays a role in sensory impact by modulating the sensory effects of nicotine, and contributes to the taste, aroma, and airways sensations of smoking. Therefore, smokers may seek a particular ratio of nicotine to tar, as reflected in the intensity and quality of sensory cues. Studies exploring pharmacological or behavioral manipulations that decrease craving in the laboratory may be useful in developing strategies for alleviating craving for cigarettes that occurs during smoking cessation attempts.

The small number of published studies exploring the role of sensory factors in smoking underscores the need for more laboratory research into sensory effects of smoking. Many questions remain unanswered, despite their importance to theories of smoking reward in general and to smoking cessation efforts. For instance, the mechanism by which these cigarettes reduce craving should be explored. In addition, attempts should be made to replicate the findings of currently published studies with a variety of different procedures, dependent measures, and populations. It also remains to be determined whether brand loyalty may underlie lower ratings of satisfaction of de-nicotinized cigarettes in some individuals. Finally, future laboratory studies should attempt to replicate the relationship between level of tobacco dependence and importance of sensory aspects of smoking. In particular, it will be important to determine whether the responses after a single cigarette, as assessed in this analysis, would persist over a larger number of cigarettes. The fact that Next® and similar products have not fared well in the marketplace suggests that the effect reported here may be short-lived.

The findings of this analysis also provide useful insight into aspects of smoking that should be taken into account in smoking cessation strategies. The fact that sensory factors play an important role in smoking helps to explain the lack of more robust effects of nicotine replacement therapies for smoking cessation. Transdermal or buccal administration of nicotine may provide many of the central effects of nicotine that smokers seek, and may also reduce some of the cognitive, subjective and physiological symptoms of cigarette withdrawal; however, these routes of administration do not produce the important airway sensations smokers seek. Although de-nicotinized cigarettes do not exactly reproduce the airway sensations of commercially available cigarettes, they produce substantial smoking satisfaction and craving reduction, and may enhance the withdrawal relief provided by nicotine replacement. Although it would be counterproductive to suggest that smokers switch to these cigarettes for a prolonged period of time, it may be fruitful to provide a limited number of these cigarettes to smokers during cessation attempts, for use in conjunction with nicotine replacement therapy. This strategy may be particularly effective during early abstinence, and in highly dependent smokers. By using this strategy, smokers could be weaned from the pharmacological effects of nicotine with the expectation that the conditioned rewarding effects of airway stimulation would subsequently extinguish. Alternatively, other forms of nicotine replacement, such as the nicotine inhaler, which include a sensory component, may be useful.

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References

Baldinger B, Hasenfratz M, Battig K. 1995. Switching to ultralow nicotine cigarettes: effects of different tar yields and blocking of olfactory cues. *Pharmacology, Biochemistry and Behavior* 50:233–239.

Behm F, Rose J. 1994. Reducing craving for cigarettes while decreasing smoke intake using capsaicin-enhanced low tar cigarettes. *Experimental and Clinical Psychopharmacology* 2:143–153.

Brauer LH, Behm FM, Westman EC, Patel P, Rose JE. 1999. Naltrexone blockade of nicotine effects in cigarette smokers. *Psychopharmacology* 143: 339–346.

Butschky M, Baily D, Henningfield J, Pickworth W. 1995. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology, Biochemistry and Behavior* 50:91–96.

Childress AR, McLellan AT, O'Brien C. 1986. Role of conditioning factors in the development of drug dependence. *Psychiatric Clinics of North America* 9:413–425.

Fagerström K. 1988. Efficacy of nicotine chewing gum: a review. In: Pomerleau O, Pomerleau C, eds. *Nicotine Replacement: A Critical Evaluation*. New York: Alan R. Liss, pp. 109–128.

Fischman MW, Foltin RW. 1991. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *British Journal of Addiction* 86:1563–1570.

Hasenfratz M, Baldinger B, Battig K. 1993. Nicotine or tar titration in cigarette smoking behavior? *Psychopharmacology* 112:253–258.

Heatherton T, Kozlowski L, Frecker R, Fagerström K. 1991. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction* 86:1119–1127.

Herskovic J, Rose J, Jarvik M. 1986. Cigarette desirability and nicotine preference in smokers. *Pharmacology, Biochemistry and Behavior* 24:171–175.

Hughes J, Glaser M. 1993. Transdermal nicotine for smoking cessation. *Journal of Health Behavior Education and Promotion* 17:25–31.

Kozlowski L, Porter C, Orleans C, Pope M, Heatherton T. 1994. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. *Drug and Alcohol Dependence* 34:211–216.

Lane J, Lefebvre J, Rose J, Keefe F. 1995. Effects of cigarette smoking on perception of thermal pain. *Experimental and Clinical Psychopharmacology* 3:140–147.

Levin E, Behm F, Carnahan E, LeClair R, Shipley R, Rose J. 1993. Clinical trials using ascorbic acid aerosol to aid smoking cessation. *Drug and Alcohol Dependence* 33:211–223.

O'Brien C, Childress AR, McLellan AT, Ehrman R, Ternes JW. 1988. Types of conditioning found in drug-dependent humans. In Ray, BA, ed. *Learning Factors in Substance Abuse*. National Institute on Drug Abuse Research Monograph 84. Washington DC: US Department of Health and Human Services, pp. 44–61.

Palmer K, Buckley M, Faulds D. 1992. Transdermal nicotine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. *Drugs* 44:498–529.

Perkins K. 1996. Sex differences in nicotine versus nonnicotine reinforcements as determinants of tobacco smoking. *Experimental and Clinical Psychopharmacology* 4:166–177.

Perkins KA, Grobe JE, Stiller RL, Fonte C, Guettler JE. 1992. Nasal spray nicotine replacement suppresses cigarette smoking desire and behaviour. *Clinical Pharmacology: Therapeutics* 52:627–634.

Pomerleau C, Carton S, Lutzke M, Flessland K, Pomerleau O. 1994. Reliability of the Fagerström Tolerance Questionnaire and the Fagerström Test for Nicotine Dependence. *Addictive Behaviors* 19:33–39.

Rose J. 1988. The role of upper airway stimulation in smoking. In: Pomerleau O, Pomerleau C, eds. *Nicotine Replacement: A Critical Evaluation*. New York: Alan R. Liss, pp. 95–106.

Rose J, Behm F. 1987. Refined cigarette smoke as a method for reducing nicotine intake. *Pharmacology, Biochemistry and Behavior* 28:305–310.

Rose J, Behm F. 1994. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug and Alcohol Dependence* 34:225–229.

Rose J, Behm F. 1995. There is more to smoking than the CNS effects of nicotine. In: Clarke P, Quik M, Adlkofer F, Thuray K, eds. *Effects of Nicotine on Biological Systems II. Advances in Pharmacological Sciences*. Basel: Birkhauser Verlag, pp 239–246.

Rose J, Behm F, Westman E, Levin E, Stein R, Lane J, Ripka G. 1994. Combined effects of nicotine and mecamylamine in attenuating smoking satisfaction. *Experimental and Clinical Psychopharmacology* 2:328–344.

Rose J, Hickman C. 1988. Citric acid aerosol as a potential smoking cessation aid. *Chest* 92:1005–1008.

Rose J, Levin E. 1991. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *British Journal of Addiction* 86:605–609.

Rose J, Tashkin D, Ertle A, Zinser M, Lafer R. 1985. Sensory blockade of smoking satisfaction. *Pharmacology, Biochemistry and Behavior* 23:289–293.

Rose J, Westman E, Behm F. 1996. Comparative effects of intravenous nicotine and de-nicotinized cigarette smoke. Presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Washington D.C.

Rose J, Zinser M, Tashkin D, Newcomb R, Ertle A. 1984. Subjective response to cigarette smoking following airway anesthetization. *Addictive Behaviors* 9:211–215.

Shiffman S, Jarvik M. 1976. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology* 50:35–39.

Stewart J, Eikelboom R. 1987. Conditioned drug effects. In Iverson LL, Iverson SD, Snyder SH, eds. *Handbook of Psychopharmacology*, Volume 19. New York: Plenum.

Sutherland G, Stapleton JA, Russell MAH, Jarvis MJ, Hajek P, Belcher M, Feyerbend C. 1992. Randomized controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 340:324–329.

Tate J, Schmit J. 1993. A proposed revision of the Fagerström Tolerance Questionnaire. *Addictive Behaviors* 18:135–143.

USDHHS. 1988. *The Health Consequences of Smoking: A Report of the Surgeon General*. Rockville: Public Health Service.

Westman E, Behm F, Rose J. 1995. Airway sensory replacement combined with nicotine replacement for smoking cessation: a randomized, placebo-controlled trial using a citric acid inhaler. *Chest* 107:1358–1364.

Westman E, Behm F, Rose J. 1996. Dissociating the nicotine and airway sensory effects of smoking. *Pharmacology, Biochemistry and Behavior* 53:309–315.

Westman E, Levin E, Rose J. 1992. Smoking while wearing the nicotine patch: Is smoking satisfying or harmful? *Clinical Research* 40:871A.

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Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes

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Tobacco smoking is associated with many health risks, all of which are decreased by smoking cessation. Tobacco companies are marketing novel products (e.g., Phillip Morris' Accord®, R.J. Reynolds' Eclipse®) intended to reduce these risks. Evaluation of these products is necessary to determine if they increase, decrease, or fail to change smoking's health risks. This study examines the acute effects of the Accord® system on cigarette smokers; the study extends a previous preliminary evaluation by controlling for the system's eight-puff/cigarette limit, smokers' brand preference, and the act of smoking. Smokers of light or ultra-light cigarette brands (≥10 cigarettes/day, 16 men and 16 women) participated in this within-subjects protocol. Prior to each of the four, Latin-square ordered, approximately 2.5-h sessions, subjects abstained from smoking for at least 8 h. In each session, subjects smoked eight puffs, at 30-min intervals, from either their own brand of cigarettes, a marketed brand that was not their own, de-nicotinized tobacco cigarettes, or the novel smoking system. Subjective and physiological effects were assessed regularly. Results confirmed previous observations that the withdrawal suppression, CO intake, and tachycardia produced by the novel system are all less than that produced by normally marketed cigarette brands, even controlling for the system's eight-puff limitation and for brand preference. Incomplete withdrawal suppression may increase smoking frequency, thus potentially offsetting any decreased risks associated with Accord® use. Laboratory studies of the acute effects of novel smoking systems are an important part of a comprehensive evaluation program.

Introduction

Cigarette smoking costs an estimated 418,690 American lives and $100 billion in annual health care expenses (CDC, 1994). Many of the health risks of smoking are directly attributable to carcinogenic smoke constituents (e.g., Hecht & Hoffman, 1988; Denissenko, Pao, Tang, & Pfeifer, 1996); carbon monoxide (CO) exposure during smoking is also unhealthy (Benowitz, 1997; Kuller & Radford, 1983). Smoking cessation is the optimal method of decreasing these risks: population models suggest that universally effective cessation would reduce the expected mortality attributable to cigarette smoking by as much as 75% (Russell *et al.*, 1998).

As an alternative to cessation, tobacco companies are marketing novel products intended to reduce smoking's lethal effects (Holzman, 1999). For example, R.J. Reynolds' Eclipse® system heats tobacco and 'may reduce the risks of smoking-associated cancers and lower the risk of lung disease' (Weiss, 2000). Phillip Morris has developed a novel smoking system, the Accord®, that is intended to reduce secondhand smoke and that may decrease the mutagenicity and cytotoxicity associated with normal tobacco smoke (Terpstra, Reininghaus, & Solana, 1998). Because real or implied claims of decreased lethality associated with novel systems may cause some smokers to

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change brands rather than quit, these systems deserve close scrutiny.

In a preliminary evaluation of the Accord® (Buchhalter & Eissenberg, 2000) conflicting results related to the potential decreased lethality of this system were reported. Compared to normally marketed cigarettes, carbon monoxide (CO) intake from Accord® was greatly reduced, which may have some health benefits. Relative to normally marketed brands that increased heart rate by an average of 11.4 bpm, Accord® use produced small (but reliable) heart rate increases (i.e., 3.5 bpm), suggesting less nicotine delivery. However, relative to a smoker's own brand, this system failed to suppress tobacco withdrawal fully, suggesting that users may increase their smoking frequency. The small sample size of this preliminary study (N=10) may have skewed the CO and/or heart rate results and limited the study's generalizability. Moreover, the study did not control for smokers' brand preference and the novel system's eight-puff limit.

This study had two goals: (1) to extend the preliminary evaluation of the Accord® by including a much larger sample size and controls for brand preference, the system's eight-puff limit, and smoke inhalation and (2) to describe a methodology for evaluating the acute effects of novel smoking systems. To achieve these goals, 32 smokers participated in four Latin-square ordered sessions in which they smoked either the Accord®, their own brand of cigarettes, a brand of cigarette that was not their own, or de-nicotinized tobacco cigarettes. Participants completed four eight-puff smoking bouts in each 2.5-h session, with a 30-min interval between each bout. Subject-rated and physiological measures, as well as puff topography variables, were assessed periodically within each session. Based on preliminary results, we hypothesized that the Accord® would fail to suppress withdrawal fully, as compared to smokers' own and not own brands. We further hypothesized that CO and heart rate increases produced by the Accord® would be less than those of normally marketed cigarettes. However, assuming that the Accord® delivers pharmacologically active nicotine doses, we hypothesized that the heart rate increases it produced would be greater than those produced by de-nicotinized cigarettes.

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Method

Subjects and setting

Advertisements and word-of-mouth were used to recruit 16 women (one non-white) and 16 men (two non-white) for participation in this IRB-approved study. Volunteers were excluded from participation if they reported previous Accord® experience, past or current cardiovascular disorders, current pregnancy or breastfeeding, current attempts at smoking cessation or reduction, and/or regular use of Merit Ultra Light® cigarettes. Merit Ultra Light® smokers were excluded because this brand was selected arbitrarily for use in the 'not own' brand condition.

Volunteers were included if they were 18–60 years of age (mean=25.9 years, SEM=1.4), reported that they smoked 'light' or 'ultra-light' cigarettes regularly (Accord® is marketed to this population), smoked 10 or more king-sized, non-mentholated cigarettes daily (mean=20.6 cigarettes/day, SEM=0.8), and provided a breath sample > 7 ppm CO at screening (mean=21.1 ppm, SEM=1.7). On average, participants had smoked their current number of cigarettes per day for 6.6 years (SEM=0.7) and were mildly nicotine dependent, as indicated by a mean score of 4.7 (SEM=0.2) on the Fagerström (1978) nicotine tolerance questionnaire. They reported an average of two past quit attempts (SEM=0.4), and 8/32 subjects reported previous use of a pharmacotherapy for smoking cessation. Men and women did not differ on body mass index [women's mean=23.5, SEM=1.3; men's mean=25.7, SEM=1.2; $F(1,32)$=1.6, n.s.] or on any demographic characteristic related to cigarette smoking. All subjects provided written, informed consent before and were paid $160 after their participation.

Materials

The Accord® system consists of a handheld device and specially constructed 'cigarettes'. The device contains a battery, eight heating elements, and a display. The 'cigarettes' are 62 mm long, 8 mm in diameter, and consist of 7 mm of filter plug, 30 mm of a hollow tube, and 25 mm of paper-encased, pressed tobacco wrapped around a plug of tobacco leaf. These 'cigarettes' are not lit, but inserted into a hole in the handheld chamber, with approximately 21 mm of the filter portion exposed. Insertion puts the paper-encased tube of pressed tobacco in contact with the surrounding heating elements. When a smoker puffs on the exposed filter, one of the heating elements heats a portion of the pressed tobacco; subsequent puffs heat other portions until the maximum of eight puffs has been reached. The peak temperature attained by the novel system (about 600°C) is less than that attained by a conventional cigarette (about 950°C; Terpstra *et al.*, 1998). The Accord® (Phillip Morris, Richmond, VA) delivers 0.20 mg nicotine by the FTC method while subjects' own brand of cigarettes delivered, on average, 0.75 mg nicotine, the not own brand (Merit Ultra Light®; Phillip Morris, Richmond, VA) delivered 0.40 mg nicotine, and the de-nicotinized cigarettes (Ultratech Corporation, Lafeyette Hill, PA) delivered 0.07 mg nicotine (Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999). Subjects were aware when they were using the Accord®; opaque tape was used on the other cigarette types to blind the subjects (but not the experimenter).

Subject-rated measures

All subject-rated measures were computerized. Visual analog scale (VAS) items consisted of a word or phrase centered above a horizontal line anchored on the left with

'not at all' and on the right with 'extremely'. Subjects responded to these items by moving a mouse-controlled cursor to any point on the line and clicking, thus producing a vertical mark on the horizontal line; this mark could be further adjusted if necessary. The score for each scale was the distance of the vertical mark from the left anchor, expressed as a percentage of the total length of the horizontal line. The VAS items used in this study were derived from previous research describing tobacco withdrawal symptomatology (e.g., Hughes & Hatsukami, 1986) and included 'Urges to smoke', 'Irritability/frustration/anger', 'Anxious', 'Difficulty concentrating', 'Restlessness', 'Hunger', 'Impatient', 'Craving a cigarette/nicotine', 'Drowsiness', 'Depression/feeling blue', and 'Desire for sweets'. Another measure of subjective effects was the Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991), which consists of 32 smoking-related items that are rated on a seven-point scale ranging from 0 (strongly disagree) to 6 (strongly agree). The QSU yields two factors defined by previous factor analysis: Factor 1 (intention to smoke) and Factor 2 (anticipation of relief from withdrawal).

Physiological measures

Heart rate and skin temperature were monitored continuously (Noninvasive Patient Monitor 507E, Criticare Systems, Waukesha, WI) and were recorded every 20 s. CO was measured before and at least 5 min after each cigarette using a breath CO monitor (Vitalograph, Lenaxa, KS).

Puff topography measurement

As described elsewhere (Eissenberg, Adams, Riggins, & Likness, 1999), topography data collection was computerized (Plowshare Technologies, Baltimore, MD). Cigarettes were smoked through a mouthpiece that was connected to a pressure transducer, and pressure changes created by an inhalation were amplified, digitized, and sampled at a rate of 1000 Hz. Software converted signals to airflow (ml/sec) and integrated the data over time for each puff, producing several measures including puff volume, duration, and interpuff interval (IPI).

Procedure

Subjects were screened, provided informed consent, and were acclimated to the testing environment, equipment, and questionnaires at least 1 day before participating. At least 8 h of objectively verified cigarette abstinence (i.e., CO level of <10 ppm) was required before each of the four approximately 2.5-h experimental sessions, and each session was separated by at least 24 h. For 28 subjects, each of the four sessions began at approximately the same time of day (e.g., all in the morning or all in the afternoon); for the remaining four subjects, scheduling difficulties led to as many as two sessions occurring at a different time of day (i.e., two in the morning and two in the afternoon). Because of the study's within-subjects design, no effort was made to control time of session onset across subjects.

Thirty minutes before the start of each session, baseline CO was assessed and physiological data recording commenced. Each experimental session started with the first of four smoking bouts. Smoking bouts, which were separated by 30 min, consisted of pre-smoking CO and subjective effect measurement, eight self-paced puffs from the type of cigarette assigned to that session, and post-smoking subjective effect and CO measurement (at least 5 min after the eighth puff; mean=5.6 min; SEM=0.09). Subjects puffed from the same cigarette type (Accord®, own brand, not own brand, or de-nicotinized) within a session, but cigarette type varied across the sessions; order was determined by Latin-square. The number of puffs taken within each smoking bout was counted manually.

Data analysis

Prior to analysis, physiological data (except CO) were averaged to produce a single value for each measure for each of four pre-smoking periods (10 min prior to smoking) and four smoking periods (time during which subjects were actually smoking; Buchhalter & Eissenberg, 2000). Topography data were examined for errors of measurement that might occur if a pressure differential was detected when subjects were not smoking (e.g., tapping the cigarette). These errors were removed using two decision rules (Eissenberg *et al.*, 1999): (1) puffs of less than 5 ml were removed arbitrarily, and (2) after applying rule 1, all puffs less than or greater than two standard deviations from the mean were removed. Remaining data for each of the four cigarettes were averaged for each subject using all remaining values for puff volume, duration, and IPI.

All data were entered into a mixed analysis of variance (ANOVA) with subject sex as a between-subject factor and cigarette type (Accord®, own brand, not own brand, de-nicotinized), cigarette number (1–4), and time (for subject-rated and physiological data) as the within-subjects factors. For all repeated measures factors, significance levels were adjusted for violations of the sphericity assumption using Huynh–Feldt corrections. The mean square error terms for the overall interaction were used to conduct Tukey's honestly significant difference test; comparisons for which $p<0.05$ were reported as significant.

Results

Subjective measures

Results of the statistical analyses for subjective measures are shown in Table 1. Main effects and interactions involving subjects' sex are omitted because no measure showed a significant main effect and only one measure showed a significant interaction involving sex (i.e., type

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Table 1. Statistical analysis results for subjective effects and physiological measures collected during four smoking bouts

	Type[a]		Num[a]		Time[b]		Type×Num[c]		Type×Time[a]		Num×Time[a]		Type×Num ×Time[c]	
	F	P	F	P	F	P	F	P	F	P	F	P	F	P
Subjective effects														
VAS items														
Urges to smoke	10.98	<0.001	62.43	<0.001	90.47	<0.001	0.67	n.s.	5.21	<0.01	38.84	<0.001	3.28	<0.01
Irritability/frustration/anger	2.08	n.s.	18.91	<0.001	11.58	<0.01	0.60	n.s.	3.11	<0.05	4.12	<0.05	1.41	n.s.
Anxious	1.11	n.s.	21.39	<0.001	19.10	<0.001	0.76	n.s.	2.24	n.s.	23.64	<0.001	1.02	n.s.
Difficulty concentrating	0.80	n.s.	9.28	<0.001	6.90	<0.05	2.30	<0.05	1.65	n.s.	3.16	<0.05	2.24	<0.05
Restlessness	1.10	n.s.	11.33	<0.001	12.22	<0.01	0.54	n.s.	1.30	n.s.	10.19	<0.001	0.55	n.s.
Hunger	2.32	n.s.	5.93	<0.01	10.83	<0.01	1.76	n.s.	0.60	n.s.	6.45	<0.01	0.69	n.s.
Impatient	1.43	n.s.	12.93	<0.001	11.58	<0.01	0.66	n.s.	3.42	<0.05	13.38	<0.001	1.64	n.s.
Craving a cigarette/nicotine	11.73	<0.001	47.14	<0.001	85.84	<0.001	1.11	n.s.	10.16	<0.001	35.11	<0.001	1.86	n.s.
Drowsiness	0.59	n.s.	0.07	n.s.	9.15	<0.01	1.66	n.s.	0.72	n.s.	0.27	n.s.	1.42	n.s.
Depression/feeling blue	0.14	n.s.	8.26	<0.01	5.28	<0.05	0.28	n.s.	1.54	n.s.	0.85	n.s.	0.61	n.s.
Desire for sweets	0.73	n.s.	0.60	n.s.	3.61	n.s.	0.82	n.s.	2.40	n.s.	1.16	n.s.	1.09	n.s.
Tiffany–Drobes QSU														
Factor 1	11.21	<0.001	63.65	<0.001	122.82	<0.001	1.57	n.s.	10.31	<0.001	4.43	<0.01	1.05	n.s.
Factor 2	7.33	<0.01	44.50	<0.001	64.10	<0.001	0.98	n.s.	4.55	<0.01	12.87	<0.001	1.68	n.s.
Physiological measures														
Heart rate	25.81	<0.001	7.91	<0.01	38.93	<0.001	5.22	<0.001	18.68	<0.001	34.30	<0.001	7.71	<0.001
Expired air CO	70.65	<0.001	274.53	<0.001	296.05	<0.001	95.98	<0.001	87.47	<0.001	3.94	<0.05	0.89	n.s.
Skin temperature	1.84	n.s.	65.32	<0.001	35.25	<0.001	2.73	<0.01	0.49	n.s.	7.69	<0.001	2.16	<0.05

[a] df=3, 90.
[b] df=1, 30.
[c] df=9, 270.

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by cigarette by sex interaction for 'Craving a cigarette/nicotine', $F(9,270)=2.55$, $p<0.05$). Given that there were 90 separate F tests involving this between-subjects factor, this interaction may represent a Type I error. In contrast to the between-subjects factor, there were many measures on which significant main effects and interactions involving within-subjects factors were observed. The most relevant interactions are those involving cigarette type and time, as they indicate that the effects of smoking depended upon the type of cigarette used; interactions involving cigarette number indicate that magnitude of observed smoking effects depended on how many cigarettes had been smoked at that measurement time point.

There were several measures for which significant cigarette type by time or cigarette type by cigarette number by time interactions were observed, including: the 'Urges to smoke', 'Irritability/frustration/anger', 'Difficulty concentrating', 'Impatient', and 'Craving a cigarette/nicotine' VAS items, and both factors of the Tiffany-Drobes QSU. Figure 1 shows the results of the two measures on which the largest F ratio for the type by time interaction was observed; data are displayed for each cigarette type before and after 32 subjects (collapsed across subjects' sex) took eight puffs in each of the four smoking bouts. As can be seen in the figure's top panel, scores for 'Craving a cigarette/nicotine' were high and similar across cigarette types before the first cigarette was smoked, as might be expected from smokers who had remained cigarette abstinent for at least 8 h. Not surprisingly, taking eight puffs from each cigarette type reduced self-reported craving significantly in all conditions (i.e., a significant pre-post difference, all ps<0.05, Tukey's HSD). However, the magnitude of these reductions depended on cigarette type, with the greatest reductions in subjective craving observed when subjects took their first eight puffs from normally marketed brands (i.e., own and not own brand cigarettes). Indeed, as the figure shows, self-reported craving was significantly lower after the first, second, third, and fourth eight-puff smoking bouts when subjects used either of the two normally marketed cigarette brands relative to when they used the novel system (ps<0.05, Tukey's HSD).

A similar pattern of results was observed for the other VAS measures on which a cigarette type by time interaction was observed. For example, relative to baseline scores, significant reductions of self-reported 'Irritability/frustration/anger' were observed after all smoking bouts when subjects used normally marketed cigarettes, after the second, third, and fourth smoking bouts when subjects used de-nicotinized cigarettes, but only after the fourth bout with Accord® (ps<0.05, Tukey's HSD). The magnitude of these reductions was greatest after subjects took the first eight puffs from normally marketed brands (own=45.8% and not own=54.3% reduction from pre-smoking levels) relative to when they used the Accord® for the first time (7.0%).

Figure 1 (bottom panels) shows the data from the QSU Factor 1. Data from this more standardized measure mirror those from the VAS; scores were high before any

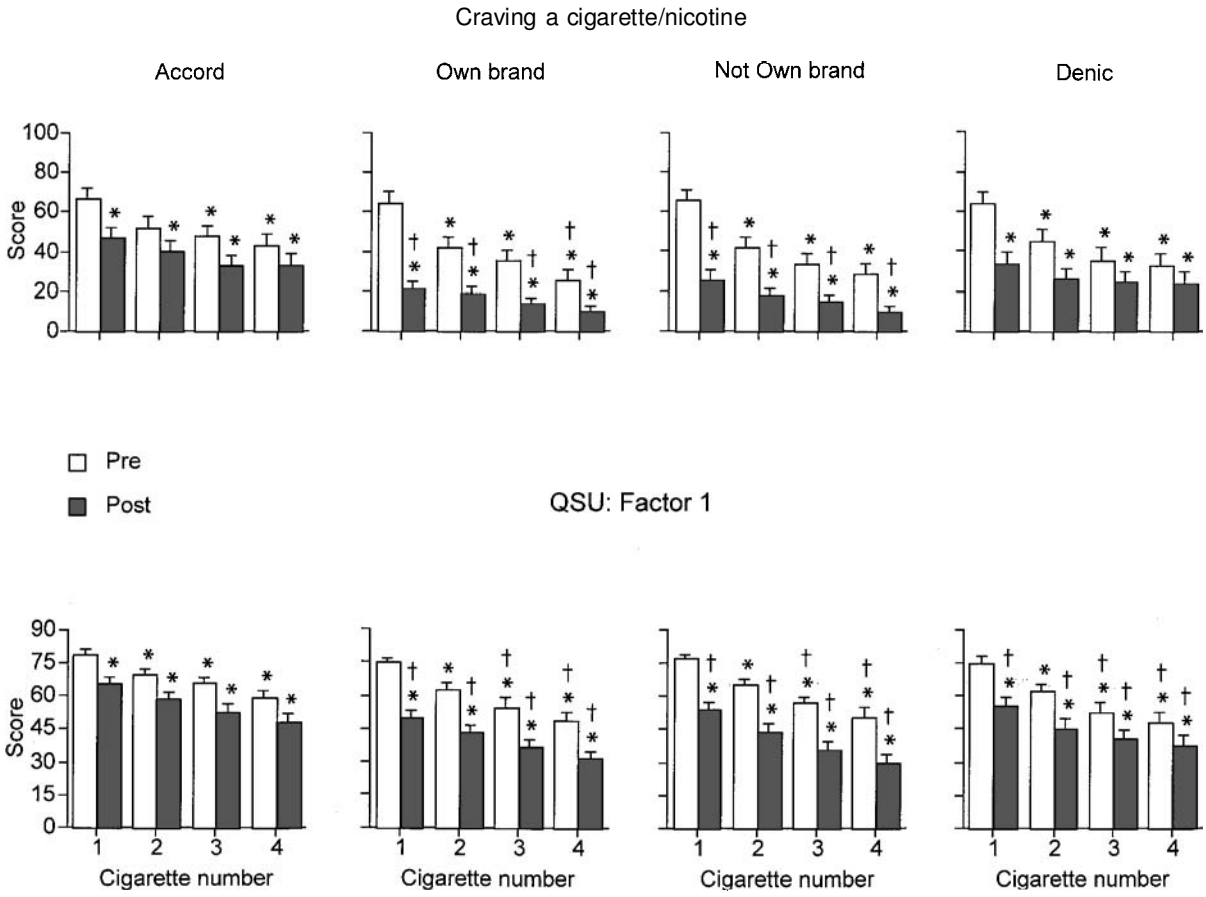


Figure 1. Averaged data (plus one SEM) from 32 subjects on the 'Craving a cigarette/nicotine' VAS (top panels) and Factor 1 of the Tiffany–Drobes (1991) Questionnaire of Smoking Urges (bottom panels) when subjects were using the novel Accord® system (Novel), their own brand of cigarette (Own), a brand of cigarettes that was not their own brand (Not Own), or De-nicotinized cigarettes (Denic). The *y*-axis shows maximum possible score for each scale. Open bars are data collected before an eight-puff smoking bout, filled bars are data collected after a smoking bout. * Indicates a significant difference from baseline (i.e., before the first cigarette), † indicates a significant difference from the Accord® at that time point (all *p*s<0.05, Tukey's HSD).

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smoking occurred, were reduced by smoking each type of cigarette, and the greatest reductions in scores were observed when subjects smoked either of the two normally marketed brands of cigarettes. On this measure, the reduction (relative to pre-smoking levels) was nearly identical when subjects smoked de-nicotinized cigarettes (26.1%) relative to own (33.0%) and not own (30.0% reduction) brands; there was only a 17.0% reduction when subjects puffed from the Accord®. For each of the four smoking bouts, post-smoking scores were significantly lower for own, not own, and de-nicotinized brands relative to the novel system (all *p*s<0.05, Tukey's HSD). A virtually identical pattern of results was observed for the QSU Factor 2.

A cigarette number by time interaction was observed on several other VAS measures, including 'Anxious', 'Restlessness', and 'Hunger'. Inspection of the data revealed that, independent of cigarette type, the magnitude of the post-smoking decreases was greatest after the first smoking bout, with much smaller decreases observed after other bouts. For example, for the 'Anxious' VAS, post-smoking scores decreased by 49.7% after the first smoking bout, 27.8% after the second, 23.4% after the third, and 22.5% after the fourth smoking bout. Only the decrease observed after the first smoking bout was statistically significant.

On measures where no interactions were observed, main effects of time indicate that smoking, independent of cigarette type or number, reduced scores. As Table 1 shows, main effects of time were observed for 'Drowsiness' and 'Depression/feeling blue'. No significant main effects or interactions were observed on only one measure: the 'Desire for sweets' VAS.

Physiological measures

Table 1 displays statistical analysis results for all physiological measures. Main effects and interactions involving subject sex are not shown: a main effect of smokers' sex was observed for heart rate [$F(1,30) = 4.2$, $p<0.05$]. On average, women's heart rate was faster (mean = 75.0 bpm, SEM = 1.9) than men's (mean = 69.6 bpm, SEM = 1.9). More importantly, heart rate depended upon cigarette type, number, and assessment time (see Table 1). Figure 2 (top panels) shows the data for this significant interaction for the 32 subjects. For the novel system, the first eight-puff smoking bout significantly increased heart rate, relative to pre-smoking

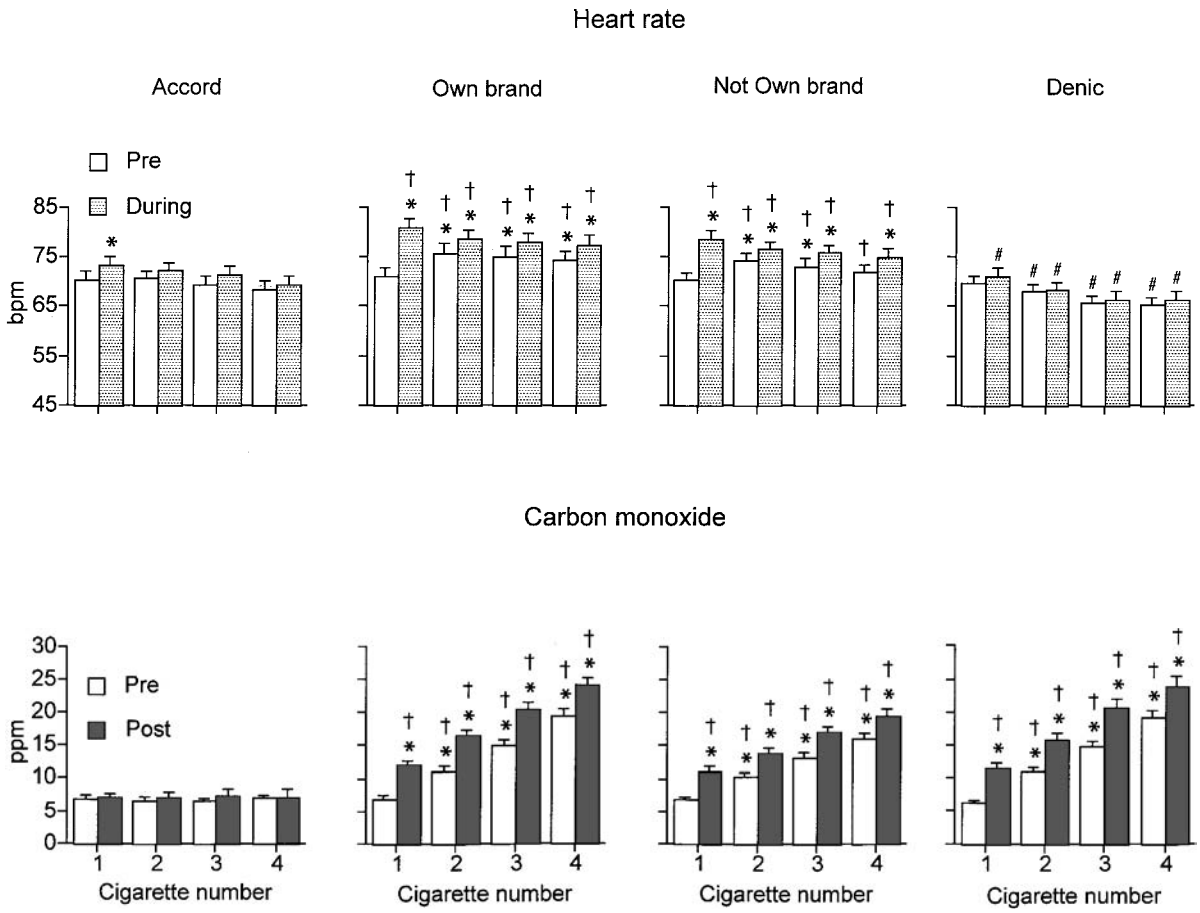


Figure 2. Averaged data (plus one SEM) from 32 subjects on the heart rate (top panels), and expired air CO (bottom panels) when they were using the novel Accord® system (Novel), their own brand of cigarette (Own), a brand of cigarettes that was not their own brand (Not Own), or De-nicotinized cigarettes (Denic). Open bars are data collected before an eight-puff smoking bout, stippled bars are data collected during a smoking bout (heart rate) and black bars are data collected at least 5 min after a smoking bout (CO). # Indicates that heart rate was significantly lower when smoking de-nicotinized cigarettes relative to the other three conditions. In all other respects the figure is identical to Figure 1.

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values ($p<0.05$, Tukey's HSD), though heart rate was not significantly elevated at any other time point during that session. When subjects were smoking normally marketed brands, heart rate increased significantly after the first smoking bout and then remained elevated relative to pre-smoking levels. Indeed, as the figure shows, heart rate increases produced by normally marketed cigarette brands were significantly greater relative to those produced by Accord®. Heart rate never increased significantly when subjects smoked de-nicotinized cigarettes, and was significantly lower at every time after the baseline measurement, relative to the other three smoking conditions.

Expired air CO also depended upon cigarette type, number, and time. A CO level below 10 ppm was required to begin a session; the average pre-smoking CO level collapsed across all conditions was 6.8 ppm. However, as seen in Figure 2 (bottom panels), CO levels rose reliably whenever subjects used the two normally marketed cigarette brands or de-nicotinized cigarettes. No significant CO increase was observed when subjects used the novel smoking system. After the four eight-puff smoking bouts were completed, the novel smoking system produced significantly lower post-smoking CO levels (mean=7.2 ppm; SEM=0.3) compared to those produced by own brand (mean=24.1 ppm, SEM=1.2), not own brand (19.6 ppm, SEM=0.9), or de-nicotinized cigarettes (mean=23.9 ppm, SEM=1.5; all ps<0.05, Tukey's HSD).

Skin temperature decreased significantly (relative to pre-smoking values) with all cigarette types, with the most pronounced decreases seen after subjects puffed from normally marketed cigarettes. For example, after the first smoking bout, the average decreases of the greatest magnitude were seen for the own (mean=1.1°C) and not own brands (mean=1.2°C) relative to the Accord® (mean=0.7°C) or the de-nicotinized cigarettes (mean=0.8°C).

Topography measures

Measurement error resulted in topography data from one man and two women not being collected; thus topography results reflect data from 29 (rather than 32) subjects. Women's puffs were smaller [$F(1,27)=10.01$, $p<0.01$; mean volume=46.5 ml, SEM=3.6] and shorter [$F(1,27)=9.31$, $p<0.01$; mean duration=1.5 s, SEM=0.1] relative to men's (mean volume=62.3 ml, SEM=3.5;

mean duration=2.0 s, SEM=0.1). Also, a cigarette type by number interaction was observed for both puff volume and duration [$F(9,243)>3.56$, $ps<0.01$]. The source of these interactions was primarily the second, third, and fourth bouts with the de-nicotinized cigarettes, where subjects took smaller, shorter puffs relative to the other conditions. Also, main effects of cigarette type [$F(3,81)=14.35$, $p<0.001$] and number [$F(3,81)=3.18$, $p<0.05$] were observed for IPI. For this measure, collapsed across cigarette number and time, IPI was significantly shorter when subjects used the Accord® (mean=20.0 s, SEM=1.3), relative to own (mean=30.2 s, SEM=2.7) and not own brands (mean=29.4 s, SEM=2.3) but not relative to de-nicotinized cigarettes (mean=25.4 s, SEM=1.9). Collapsed across cigarette type and time, IPI was shortest with de-nicotinized cigarettes (mean=24.9 s, SEM=1.8) relative to Accord® (mean=25.5 s, SEM=1.7), own (mean=27.0 s, SEM=2.2) and not own brands (mean=27.8 s, SEM=2.1).

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Discussion

Smoking cessation is the most effective method of reducing the well-known health risks of smoking. As an alternative to cessation, the tobacco industry appears to support harm reduction, primarily through their development of purportedly less lethal novel smoking systems. However, the effectiveness of these systems as a means of harm reduction is an empirical question. Ideally, the question would be answered before novel smoking systems of unknown lethality are made available to the approximately 48 million US tobacco smokers (CDC, 1999).

In the current evaluation of one such novel smoking system, as in preliminary work (Buchhalter & Eissenberg, 2000), withdrawal suppression, CO intake, and tachycardia produced by Phillip Morris' Accord® were less than those produced by normally marketed cigarette brands. These results suggest that the system does not suppress acute tobacco withdrawal fully and that this effect is due neither to the system's eight-puff limitation nor to smokers' brand preference. We speculate that the inability of this system to suppress withdrawal fully is related, in part, to its low nicotine delivery but may also be related to the fact that it fails to deliver many stimuli that are usually associated with smoking (e.g., sight and smell of tobacco smoke). Clearly such stimuli are important in tobacco-withdrawal suppression, as de-nicotinized cigarettes can suppress withdrawal for up to 24 h (e.g., Baldinger, Hasenfratz, & Battig, 1995).

Smokers' CO intake when using the novel system was lower than that observed when they smoked normally marketed cigarettes. This result suggests a potential benefit for Accord® users, as CO is a causative agent in cardiovascular disease (Benowitz, 1997; Kuller & Radford, 1983) and fetal tobacco syndrome (Nieburg, Marks, McLaren, & Remington, 1985). In the current study, four eight-puff smoking bouts with the novel system did not produce a significant increase in CO levels, though a 2–3-fold increase was observed after the same exposure to normally marketed cigarettes. However, any potential advantage may be offset if incomplete withdrawal suppression results in increased smoking. Thus, these results highlight a clear need for controlled investigations of novel smoking systems that take into account the behavior of the smoker as well as the constituents of the smoke. Such studies may be most valuable if non-industry investigators conduct them before a novel system is brought to market and if their results are made available for scientific review.

Nicotine administration produces dose-related tachycardia (e.g., Jones, Garrett, & Griffiths, 1999), and this effect was observed after a single, eight-puff smoking bout with the novel smoking system or either of the two normally marketed cigarette brands. De-nicotinized cigarettes did not produce a reliable heart rate increase. These results suggest that smokers extract pharmacologically active nicotine doses when using the novel smoking system. However, the heart rate increase observed during the first Accord® smoking bout was less than that observed when smoking either of the two normally marketed brands, consistent with its lower FTC nicotine yield (i.e., 0.20 mg), suggesting less nicotine delivery. Nicotine dose delivered via tobacco may be influenced by a variety of factors (e.g., filter dynamics, buccal nicotine absorption) and is best determined by the analysis of nicotine levels in the plasma.

The de-nicotinized cigarette condition allowed another demonstration of placebo-induced withdrawal suppression in tobacco users (e.g., Baldinger *et al.*, 1995; Butschky, Bailey, Henningfield, & Pickworth, 1995; Fant, Henningfield, Nelson, & Pickworth, 1999; Gire & Eissenberg, 2000). In this case, de-nicotinized cigarettes were as effective as normally marketed cigarettes in suppressing acute withdrawal symptomatology on some measures (e.g., the QSU Factor 1). This placebo-induced withdrawal suppression is thought to arise from smoking-related stimuli that gain their withdrawal suppressing capability via classical conditioning, wherein tobacco-related stimuli (e.g., taste, smell of smoke, sight of lit cigarette, etc.) become associated with nicotine delivery (e.g., Gire & Eissenberg, 2000; Rose, Behm, & Levin 1993). Other factors, such as non-nicotine mediated MAO-B inhibition (Fowler *et al.*, 1998) may also contribute to the effect.

Results from puff topography measurement in this study were consistent with past observations. For example, as has been frequently reported (e.g., Battig, Buzzi, & Nil, 1982; Eissenberg *et al.*, 1999; Moody, 1980), women took smaller and shorter puffs than men. Also, when using the novel smoking system, smokers puffed with greater frequency (i.e., shorter inter-puff intervals) than when smoking a normally marketed cigarette brand. As suggested previously (Buchhalter & Eissenberg, 2000), this difference may be a behavioral manifestation of the incomplete withdrawal suppression provided by the novel system.

This study included controls for many factors, but also had some potential limitations, such as the use of smokers of light and ultra-light cigarettes who were naïve to the Accord® and no control for menstrual cycle phase. Smokers of light and ultra-light cigarettes were used because they are the target audience for the Accord®. Accord®'s ability to suppress withdrawal may be less in smokers who regularly use cigarettes with stronger flavor and/or greater FTC tar and nicotine yields. Experience with a novel smoking system may influence its subjective effects as users become more adept at extracting nicotine and/or more familiar with the stimuli associated with it. Menstrual cycle phase may influence women's reports of nicotine/tobacco withdrawal symptomatology (e.g., Pomerleau, Garcia, Pomerleau, & Cameron, 1992). However, a recent study found no effects of cycle phase on withdrawal symptomatology and concluded that 'laboratory smoking abstinence studies in women may not need to tightly control for cycle phase' (Allen, Hatsukami, Christianson, & Nelson, 1999).

A final feature of the current study is the laboratory environment in which it was conducted. This environment is ideal for controlled evaluation of the acute effects of novel smoking systems, though it does not supplant more naturalistic methods. Laboratory evaluations can identify important safety concerns such as incomplete withdrawal suppression (suggesting a compensatory increase in smoking frequency), greater cardiovascular risks, and increased exposure to harmful smoke constituents such as CO and nicotine. These results could identify potentially harmful products and might suggest extreme caution in bringing these products to market. Thus the laboratory methodology reported here represents one facet of an as-yet-undetermined comprehensive evaluation program that could be used to ensure the veracity of any implied or explicit claims regarding the decreased lethality of novel smoking systems.

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References

Allen SS, Hatsukami DK, Christianson D, Nelson D. 1999. Withdrawal and pre-menstrual cycle in short-term smoking abstinence: effects of menstrual cycle on smoking abstinence. *Nicotine and Tobacco Research* 1:129–142.

Baldinger B, Hasenfratz M, Battig K. 1995. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. *Human Psychopharmacology* 10:127–136.

Battig K, Buzzi R, Nil R. 1982. Smoke yield of cigarettes and puffing behavior in men and women. *Psychopharmacology* 76:139–148.

Benowitz N. 1997. The role of nicotine in smoking-related cardiovascular disease. *Preventive Medicine* 26:412–417.

Buchhalter AR, Eissenberg T. 2000. Preliminary evaluation of a novel smoking system: effects on subjective and physiological measures and on smoking behavior. *Nicotine and Tobacco Research* 2:39–43.

Butschky MF, Bailey D, Henningfield JE, Pickworth WB. 1995. Smoking without nicotine delivery decreases withdrawal in 12-hr abstinent smokers. *Pharmacology, Biochemistry and Behavior* 50:91–96.

Centers for Disease Control. 1994. Medical-care expenditures attributable to cigarette smoking – United States, 1993. *Morbidity and Mortality Weekly Report* 43:469–471.

Centers for Disease Control. 1999. Cigarette smoking among adults – United States, 1997. *Morbidity and Mortality Weekly Report* 48:993–996.

Denissenko MF, Pao A, Tang M, Pfeifer GP. 1996. Preferential formation of benzo[*a*]pyrene adducts at lung cancer mutational hotspots in P53. *Science* 274:430–432.

Eissenberg T, Adams C, Riggins EC III, Likness M. 1999. Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. *Nicotine and Tobacco Research* 1:317–324.

Fagerström KO. 1978. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behavior* 3:235–241.

Fant RV, Henningfield JE, Nelson RA, Pickworth WB. 1999. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tobacco Control* 8:387–392.

Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, MacGregor R, Alexoff D, Wolf AP, Warner D, Cilento R, Zezulkova I. 1998. Neuropharmacological actions of cigarette smoke: Brain monoamine oxidase B (MAO B) inhibition. *Journal of Addictive Diseases* 17:23–34.

Gire JT, Eissenberg T, 2000. Placebo control study of acute smokeless tobacco abstinence in young adult men. *Psychology of Addictive Behaviors*, 14:356–366.

Hecht SS, Hoffmann D. 1988. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 9:875–884.

Holzman D. 1999. Safe cigarette alternatives? Industry critics say 'not yet'. *Journal of the National Cancer Institute* 91:502–504.

Hughes JR, Hatsukami, DK. 1986. Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry* 43:289–294.

Jones HE, Garrett BE, Griffiths RR. 1999. Subjective and physiological effects of intravenous nicotine and cocaine in cigarette smoking cocaine abusers. *Journal of Pharmacology and Experimental Therapeutics* 288:188–197.

Kuller LH, Radford EP. 1983. Epidemiological bases for the current ambient carbon monoxide standards. *Environmental Health Perspectives* 52:131–139.

Moody PM. 1980. The relationships of quantified human smoking behavior and demographic variables. *Social Science and Medicine* 14A:49–54.

Nieburg P, Marks JS, McLaren NM, Remington PL. 1985. The fetal tobacco syndrome. *The Journal of the American Medical Association* 253: 2998–2999.

Pickworth WB, Fant RV, Nelson A, Rohrer MS, Henningfield JE. 1999. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine and Tobacco Research* 1:357–364.

Pomerleau CS, Garcia AW, Pomerleau OF, Cameron OG. 1992. The effects of menstrual phase and nicotine abstinence on nicotine intake and on biochemical and subjective measures in women smokers: a preliminary report. *Psychoneuroendocrinology*, 17:627–638.

Rose JE, Behm FM, Levin ED. 1993. Role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacology, Biochemistry and Behavior* 44:891–900.

Russell LB, Carson JL, Taylor WC, Milan E, Dey A, Jagannathan R. 1998. Modeling all-cause mortality: projections of the impact of smoking cessation based on the NHEFS. NHANES I epidemiologic follow-up study. *American Journal of Public Health* 88:630–636.

Terpstra PM, Reininghaus W, Solana RP. 1998. Evaluation of an electrically heated cigarette. *Toxicologist* 42:295.

Tiffany ST, Drobes DJ. 1991. The developmental and initial validation of a questionnaire on smoking urges. *British Journal of Addiction* 86:1467–1476.

Weiss R. 2000. RJR to heavily market new cigarette. *The Washington Post* April 19, 2000.

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ORIGINAL INVESTIGATION

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Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking

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Abstract *Rationale:* The relative contribution of sensory and pharmacological variables in regulating craving and smoking remains unclear. Rapid smoking procedures and denicotinized cigarettes can be used to further disentangle these factors, and to explore the relationship between craving and smoking. *Objective:* The present study examined the role of nicotine and sensory cues in mediating craving and smoking, and the relationship between craving and smoking. *Methods:* Participants (n=15) engaged in one session each of rapid smoking (up to nine cigarettes with puffs taken every 6 s) and normal paced smoking with nicotinized and denicotinized cigarettes (total of four sessions). During the next 3 h, craving and withdrawal assessments and smoking opportunities were scheduled every 15 min. Plasma nicotine levels were measured at baseline, immediately and 15 min after the smoking interventions, and subsequently at the time when the participant first chose to smoke. *Results:* Craving ratings were equally suppressed immediately after all conditions. After self-paced conditions, both types of cigarettes produced equivalent effects on latency to smoke. Latency to smoke was significantly longer after rapid smoking of nicotinized cigarettes compared to all other conditions. Finally, changes in craving were associated with choices to smoke. *Conclusions:* The sensory cues associated with smoking suppressed craving ratings regardless of the smoking pace or nicotine content. Only at high doses did nicotine levels play an additional role in acutely suppressing smoking behavior. Small elevations in craving ratings were associated with choices to smoke.

Keywords Rapid smoking · Craving · Cigarette smokers · Sensory cues · Nicotine content

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Introduction

There is growing recognition that craving and withdrawal from cigarettes can be mediated by non-nicotine and contextual factors (Rose et al. 1985, 1993, 1999; Rose and Behm 1987; Rose and Levin 1991; Gross et al. 1997). Non-nicotine factors include the acute sensory effects of smoking, such as its taste, smell, sensations produced in the airway and lungs, the hand and mouth activity involved in smoking, as well as any other contextual cues associated with smoking. Several methodological advances have allowed researchers to more clearly partition sensory and contextual factors from the direct effects of nicotine. For example, denicotinized cigarettes mimic many of the sensory effects associated with smoking (Robinson et al. 2000). Interestingly, single denicotinized cigarettes produce similar acute suppression of craving and withdrawal when compared to regular cigarettes (Baldinger et al. 1995; Butschky et al. 1995; Gross et al. 1997; Pickworth et al. 1999; Robinson et al. 2000). These results suggest that sensory effects can play a critical role in the control of craving and withdrawal responses of smokers. Therefore, further evaluation of the relative contribution of sensory and pharmacological effects of cigarettes to craving and withdrawal suppression is warranted.

In a previous study Houtsmuller and Stitzer (1999) reported that rapid smoking of nicotinized cigarettes produced a profound and long-lasting suppression of craving. Rapid smoking procedures entail smoking a large amount in a short period of time (Hall et al. 1979). Because the rapid smoking procedure exaggerates the impact of both pharmacological and sensory effects of smoking, the model might be useful for examining further

the role of pharmacological versus sensory effects in craving suppression. Thus, the main goal of the current study was to compare the effects of rapid smoking using nicotine-containing and denicotinized cigarettes. We were interested in the contribution of sensory factors versus nicotine to symptoms produced by rapid smoking, the extent of craving suppression, and the latency to resume voluntary smoking. In order clearly to partition sensory and pharmacological factors, we used nicotinized and denicotinized cigarettes that were identical except for the nicotine content. We expected that nicotine intake would contribute to the acute suppression of smoking and that latency to smoke would be longer after rapid smoking of nicotine containing cigarettes than after denicotinized cigarettes. Inclusion of self-paced smoking conditions allowed us to test the above hypotheses and to examine the effects of nicotine content on craving and subsequent smoking when nicotine intake occurs under more naturalistic conditions. Under self-paced smoking conditions we did not expect to see differences between effects of nicotine-containing and denicotinized cigarettes. Finally, we did not expect a significant difference between the self-paced conditions and rapid smoking of the denicotinized cigarettes.

An additional goal of the present study was to explore further the relationship between craving and smoking after a rapid smoking intervention. Drug craving is a clinically prominent feature of drug dependence, but its relationship to drug seeking behavior, particularly on a moment-to-moment basis, is uncertain. Several laboratory studies suggest that craving self-reports are not a reliable predictor of self-administration of nicotine (Nemeth-Coslett and Henningfield 1986; Perkins et al. 1997; Houtsmuller and Stitzer 1999) or cocaine (Fischman et al. 1990; Foltin and Fischman 1994; Dudish-Poulsen and Hatsukami 1997). However, research also suggests that craving reports and tobacco smoke self-administration are correlated (Willner et al. 1995), and that craving ratings predict relapse to smoking (Shiffman et al. 1996; Killen and Fortmann 1997; Catley et al. 2000). Indeed, many smokers cite craving as the most difficult obstacle in their attempts to quit (Seidman and Covey 1999). In order to examine further the relationship between craving and smoking, we scheduled both craving assessments and smoking opportunities at frequent short (15 min) intervals following experimental interventions (Sayette et al. 2000). Frequent assessments provided a concurrent assessment of the time course of changes in craving reports and smoking choices at different levels of craving, as induced by the rapid versus self-paced smoking manipulation.

Materials and methods

Participants

Fifteen heavy smokers (>15 cigarettes per day, expired CO at intake >15 ppm) between 18 and 55 years old participated in this study. All participants were screened medically before participation. Exclusion criteria included medical or psychiatric illness that would significantly interfere with the study, abnormal ECG, pregnancy, and drug abuse as assessed by self-report and urinalysis (enzyme-multiplied immunoassay technique, Behavioral Pharmacology Research Unit Laboratory, Baltimore, Md., USA). Participants included eight females and seven males; 7% were African-American, 13% Asian, and 7% Hispanic. Mean age was 35 years, mean number of cigarettes smoked per day was 25, and mean expired CO at intake was 25 ppm. Participants were informed that the study investigated how people react to different amounts of nicotine and different patterns of smoking, and that they would be required to smoke intensively as directed. The local Institutional Review Board approved the study, and all participants gave informed consent.

General session procedures

Participants participated in four outpatient laboratory sessions at the Behavioral Pharmacology Research Unit. Sessions were separated by at least 48 h and were conducted in a well-ventilated room.

At the beginning of each session participants smoked one of their own brand of cigarettes to ensure standardization of the time since the last cigarette across sessions and participants. Thirty minutes later, one of four smoking interventions started (rapid or self-paced smoking of nicotinized cigarettes, and rapid or self-paced smoking of denicotinized cigarettes). Sessions were scheduled in a different order for each participant. For 3 h after the smoking intervention, craving assessments were scheduled every 15 min followed by a 1-min interval during which the participant could accept or decline the opportunity to smoke a cigarette. The latency to the first accepted smoking opportunity, and the total number of cigarettes smoked during the post-intervention period were recorded. Puff topography equipment also recorded detailed measures of smoking during the post-intervention period.

Physiological data, subjective measures and blood samples were collected throughout the session. Subjective questionnaires were selected to assess tobacco withdrawal and craving, side effects of the smoking interventions, and cigarette effects.

Smoking interventions

Participants smoked standardized cigarettes during the smoking interventions. The nicotinized cigarettes had a nicotine yield of 1.1 mg (FTC), and the denicotinized cigarettes had a nicotine yield of 0.07 mg (FTC). Cigarettes were obtained from Ultratech Corporation (Lafayette Hill, Pa., USA), and are described elsewhere (Pickworth et al. 1999).

In the two rapid smoking interventions, participants smoked up to nine cigarettes, puffing every 6 s. A 5-min break was scheduled after each set of three cigarettes. An audible cue prompted participants to puff, and a research assistant monitored compliance. Participants experiencing nausea and/or vomiting could choose not to smoke all three cigarettes of each set, but were asked to smoke at least one puff at the beginning of the subsequent smoking period.

In the two self-paced interventions, participants smoked one cigarette at a self-regulated pace during each of three 5-min smoking periods. Five-minute breaks separated the smoking periods. Participants who chose not to smoke after a break were asked to smoke one puff.

The duration of the rapid and self-paced interventions was equivalent unless nausea and/or vomiting prevented the participant from smoking at the necessary interval.

During the 3-h post-intervention period, participants were given smoking opportunities every 15 min. For one minute, the computer screen indicated that participants could accept a smoking opportunity. Opportunities were accepted by using the mouse to click a region of the computer screen that read “yes.” Participants could then smoke one of their own brand of cigarettes at a self-regulated pace.

Participant-rated measures

Questionnaires were administered via computer at regular intervals during each session. The Withdrawal Symptoms Questionnaire (WSQ; Hughes and Hatsukami 1986), the Nicotine Effects Visual Analog Scale (VAS, Houtsmuller and Stitzer 1999), and a Desire to Smoke VAS (derived from Schuh and Stitzer 1995) were administered at baseline, at each 5-min break during the smoking intervention, immediately after the smoking intervention, and immediately before each of the 1-min smoking opportunities offered during the 3-h post-intervention period. The Questionnaire of Smoking Urges (QSU; Tiffany and Drobes 1991) and the Shiffman-Jarvik Smoking Withdrawal Questionnaire (Shiffman and Jarvik, 1976) were administered at baseline, after the smoking intervention and at 1-h intervals during the 3-h post-intervention period. The Cigarette Effect Questionnaire (Gross et al. 1997) was administered after each cigarette a participant smoked during the session.

The QSU consists of 32-items designed to assess urges and cravings to smoke in cigarette smokers. The items were presented as 7-point scales where 1 indicates strongly disagree and 7 indicates strongly agree. Based on factor analysis, the items can be divided into two subscales, one that represents craving for the positive effects of the cigarette (factor 1), and one that represents anticipation of relief from withdrawal (factor 2). The Shiffman-Jarvik is a 25-item questionnaire that assesses withdrawal symptomatology in smokers. The items were presented as 7-point scales, where 1 indicates very definitely and 7 indicates very definitely not. The items were divided into five subscales based on factor analysis: Craving, Psychological Discomfort, Physical Symptoms, Stimulation/Sedation, and Appetite. The WSQ, derived from Hughes and Hatsukami (1986), also assesses nicotine withdrawal and consists of 13 items: "Urges to smoke", "Irritable", "Anxious", "Difficulty concentrating", "Restless", "Impatient", "Excessive hunger", "Tremor", "Heart racing", "Sweating", "Dizziness", "Craving cigarettes", "Insomnia/disturbed sleep", "Increased eating", "Drowsiness", "Headache", "Bowel or stomach problems", and "Depressed".

The Nicotine Effects VAS consisted of items assessing nicotine effects ("Nausea," "Clammy skin", "Dizziness", "Light headed", "Burning throat", "Tingling sensations", and "Heart racing"), and the Desire to smoke VAS consisted of four items: "How pleasant would a cigarette be right now?", "How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking", "How much do you need to smoke right now, just for relief?", and "How much do you want to smoke right now?" Visual analog scales were presented on a computer screen as a 100-point horizontal line, anchored on the left side with "not at all" (Desire to smoke scales) or "none" (Nicotine effect scales) and on the right side with "very much" (Desire to smoke scales) or "severe" (Nicotine effects scales). Participants moved the cursor at 1-mm intervals along the line with a mouse, and pressed the button when the cursor was at the appropriate point to indicate their response to the item presented. The Cigarette Effect VAS was anchored with "not at all" on the left and "extremely" on the right. The scale assessed smoking satisfaction and the effects of the cigarette using the items: "Pleasant", "Unpleasant", "Like taste", "Dislike taste", "Smoke versus air" (anchored with "mostly smoke" to "mostly air"), "Harsh", "Strength", "High in nicotine", "Like drug effect", "Dislike drug effect", "Satisfying", "More awake", "More calm", "Easier to concentrate", and "Less irritable". Scores on all VAS could range from 0 to 100.

Physiological measures

Heart rate and blood pressure were measured every 5 min using automated equipment (Sentry II, NBS Medical, Costa Mesa, Calif., USA). Plasma was extracted from the blood samples and analyzed for the presence of nicotine (gas chromatography; LabStat, Toronto, Canada). Blood draws occurred before the first baseline cigarette, 1 min and 15 min after the smoking interventions, and immediately before the first accepted smoking opportunity. No blood was collected from one of the participants; therefore results are shown for 14 participants. Expired air CO was measured using a Micro II Smokerlyzer (Bedfont Instruments Ltd, Kent, UK). CO measurements were taken before and after the pre-session cigarette, before and after each of the three smoking periods, at 15-min intervals during the 3-h post-intervention period, and after each accepted smoking opportunity.

Smoking measures

All cigarettes were smoked through a smoking topography measurement system described elsewhere (Zacny et al. 1986, 1987). Puff duration, volume, and inter-puff interval were recorded using this system and an Apple IIe microcomputer. The system was used to ensure that participants were complying with the smoking interventions during each session. With the exception of number of puffs taken, we were not able to record the topography measures for analysis.

Data analysis

Data were analyzed using ANOVA with factors "smoking pace" and "nicotine content." Where appropriate, "time" was also a factor. Tukey post hoc tests were used when significant main or interaction effects were found. Repeated measures data were adjusted for sphericity by Huyn-Feldt corrections. All statistical tests were considered significant at $P<0.05$. The effects of the smoking procedures on the participant-rated measures were examined in several ways: (a) the pre-intervention measures were compared to the post-intervention measures, (b) the measures obtained during each smoking procedure were compared across conditions, and (c) the measures obtained after each smoking procedure were compared across conditions. The physiological measures obtained during the four smoking conditions were also evaluated across condition. Finally, craving levels were examined at each measurement time point in relation to the decision to smoke or not smoke using the craving item score from the WSQ. These data were analyzed using a mixed-model repeated-measures ANCOVA with smoking pace, nicotine content, and time as fixed factors, and the decision to smoke as a random factor (GlimMix, SAS, Cary, N.C., USA). The GlimMix modeling program is a repeated measures analysis for dichotomous data (i.e. the decision to smoke).

Results

During the rapid smoking intervention, participants smoked an average of 7.7 (±0.38) nicotinized cigarettes and 8.7 (±0.27) denicotinized cigarettes out of a total of nine possible cigarettes. During the self-paced smoking intervention, where three cigarettes were allowed, participants smoked an average of 2.8 (±0.16) nicotinized cigarettes and 3 (±0.03) denicotinized cigarettes.

Validation of the smoking interventions: physiological measures

Figure 1 shows expired air CO and nicotine levels before and after the interventions. For CO, there was a significant effect of smoking pace [$F(1,14)=38.2$, $P<9.001$] and of nicotine content [$F(1,14)=19.9$, $P<0.001$] on CO level. Post hoc comparisons showed that all interventions

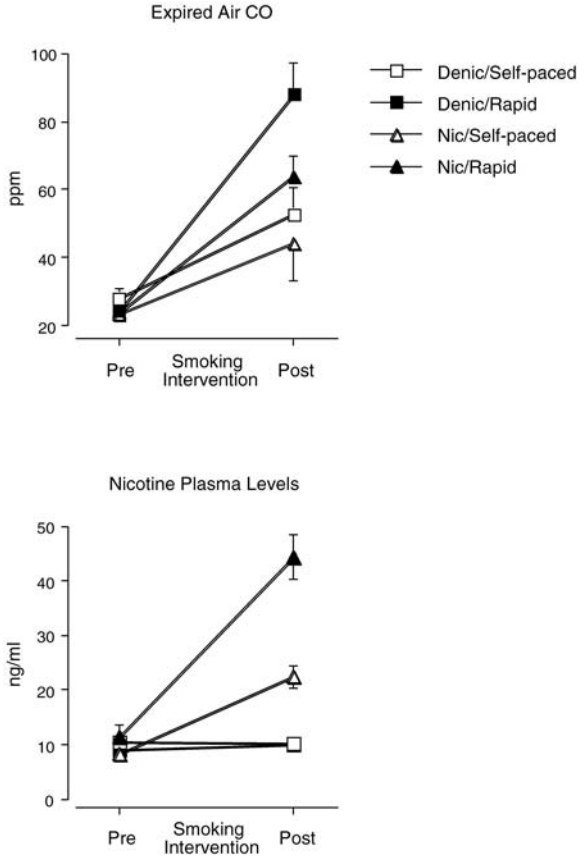


Fig. 1 Mean expired air CO (n=15) and plasma nicotine levels (n=14) before and after the smoking interventions. *Vertical lines* indicate SE

significantly increased CO levels, and that CO was significantly higher after rapid smoking than after self-paced smoking. Denicotinized cigarettes significantly increased CO more than nicotinized cigarettes. This result may be due in part to differences in inhalation variables or simply to the lower number of cigarettes smoked in the nicotinized compared to the denicotinized condition (means presented above).

For nicotine plasma concentration, there was a main effect of cigarette nicotine content [$F(1,13)=76.8$, $P<0.001$] and a Smoking pace×Nicotine content interaction [$F(1,13)=68.3$, $P<0.001$]. Post hoc analyses showed that both nicotinized conditions produced significantly higher plasma levels than both denicotinized conditions. Rapid smoking of nicotinized cigarettes produced higher levels than self-paced smoking. Nicotine levels after self-paced smoking were significantly higher after nicotinized cigarettes versus denicotinized cigarettes.

There was a main effect of smoking pace [$F(1,14)=14.1$, $P<0.05$], but not of nicotine content on heart rate. Mean heart rate was 79.1 (±2.25) under the self-paced conditions versus 85.4 (±2.00) under the rapid smoking conditions. There were no significant main or interaction effects of conditions on blood pressure.

Validation and effects of the smoking interventions: self-report measures

As shown in Table 1, rapid smoking of nicotinized cigarettes significantly increased all ratings of nicotine effect VAS items while rapid smoking of denicotinized cigarettes significantly increased ratings of "nausea", "dizziness", "light-headed", "burning throat", "heart racing", and "headache". The effects of the smoking interventions on ratings of "nausea" and "dizziness" are presented in Fig. 2. The effects of nicotine content on "nausea" depended on smoking pace [Smoking pace×Nicotine content interaction, $F(1,14)=15.93$, $P=0.001$], which was also the case for "dizziness" [Smoking pace×Nicotine content interaction, $F(1,14)=17.02$, $P=0.001$]. Post hoc tests indicated that after rapid smoking of both nicotinized and denicotinized cigarettes ratings of "nausea" and "dizziness" significantly increased. The effect on both items was more pronounced for the nicotinized cigarettes.

Table 1 Direct symptomatic effects of smoking interventions. The mean baseline rating was subtracted from the mean post-intervention reading (n=15). Higher values reflect greater effects for the Analog Side Effect Scale, and higher negative numbers indicate greater effects for the Shiffman-Jarvik

	Rapid smoking		Self-paced smoking	
	Nicotinized	Denicotinized	Nicotinized	Denicotinized
Analog side effect				
Nausea	63.03*	19*	1.3	4.9
Clammy skin	33.83*	10.7	0.33	–0.26
Dizziness	69.17*	27.77*	3.4	2.37
Light headed	67.3*	30.3*	3.6	4.5
Burning throat	52*	58.43*	8.2	20.9*
Tingling	55.7*	14.1	3.9	0.14
Heart racing	53.2*	23.83*	2.87	2.53
Headache	29.43*	23.77*	5.13	4.7
Shiffman-Jarvik				
Psychological discomfort	–5.9*	–3*	–0.8	–1.1
Physical symptoms	–8.1*	–4.3*	–0.4	–1.1
Stimulation/sedation	3.2	0.7	1.2	0.4
Appetite	1.8*	0.9	0.3	0.2

*$P<0.05$ post-intervention value compared to the baseline value

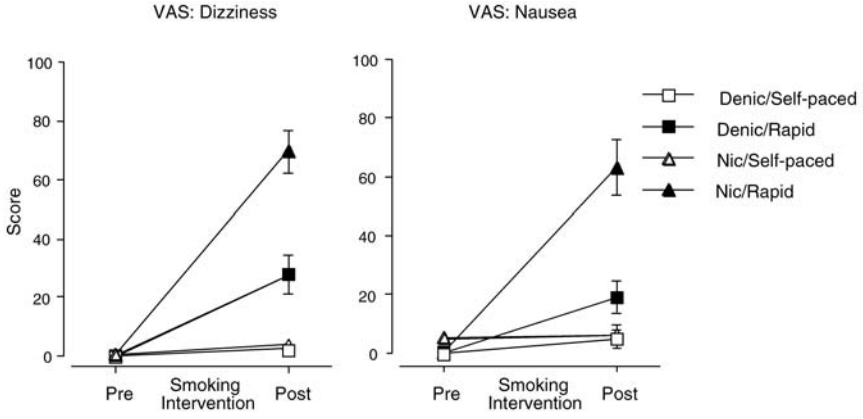


Fig. 2 Mean ratings of "nausea" and "dizziness" before and after the smoking interventions (n=15). *Vertical lines* indicate SE

Table 2 Effects of smoking on craving reports. The mean baseline rating was subtracted from the mean post-intervention reading (n=15). Negative values reflect craving suppression for the WSQ, Schuh Stitzer, and QSU, and positive numbers indicate craving suppression for the Shiffman-Jarvik

	Rapid smoking		Self-paced smoking	
	Nicotinized	Denicotinized	Nicotinized	Denicotinized
WSQ				
Urge	–1.1*	–0.72*	–0.83*	–0.8*
Craving cigarettes	–0.87*	–0.73*	–0.87*	–0.73*
Schuh-Stitzer				
Pleasant	–42.53*	–39.3*	–39.1*	–37.7*
Pleasure	–41*	–39.4*	–38.8*	–34.2*
Relief	–29.47*	–31.6*	–33.2*	–23.8*
Want	–36.73*	–33.7*	–33.1*	–33.6*
Shiffman-Jarvik				
Craving	16.3*	13*	11.5*	11.2*
QSU				
Factor 1	–36.5*	–34.9*	–32.2*	–32.1*
Factor 2	–18.9*	–17.5*	–12.5*	–12.6*

*P<0.05 post-intervention value compared to the baseline value

As shown in Table 2, reports of craving were significantly suppressed after all four interventions. ANOVA revealed a significant effect of Time for the WSQ items "Urges to smoke" [F(1,14=35.9, P<0.001) and "Craving cigarettes" [F(1,14)=30.73, P<0.001], and the VAS items "How pleasant would a cigarette be right now?" [F(1,14)=28.0, P<0.001], "How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking?" [F(1,14)=22.75, P<0.001], "How much do you need to smoke right now, just for relief?" [F(1,14)=14.2, P=0.002], and "How much do you want to smoke right now?" [F(1,14)=19.7, P<0.001]. The interventions also had similar effects on the craving factor derived from the Shiffman-Jarvik Questionnaire [F(1,14)=65.41, P<0.001], and two craving factors derived from the QSU [factor 1: F(1,14)=49.09, P<0.001; factor 2: F(1,14)=15.97, P<0.001].

Cigarette ratings

Table 3 shows participants' ratings of the nicotinized and denicotinized cigarettes under each smoking condition. Importantly, participants did not rate the cigarettes differently on "high in nicotine" or in "strength" under either smoking pace condition. However, after self-paced smoking, post hoc tests showed that the denicotinized cigarette was rated as significantly more unpleasant, and the taste and drug effect were more disliked than the nicotinized cigarette.

Effects on smoking behavior

Mean latency to smoke, total number of cigarettes smoked, and cigarettes smoked per hour once smoking was resumed after the interventions are presented in Fig. 3. ANOVA revealed a significant main effect of smoking pace on latency to smoke [F(1,14)=37.05, P<0.001], number of cigarettes smoked [F(1,14)=36.2, P<0.001], number of puffs [F(1,14)=13.13, P<0.05], and on cigarettes smoked per hour [F(1,14)=7.3, P<0.05]. Analyses also showed an interaction between smoking pace and nicotine content on number of cigarettes smoked [F(1,14)=7.7, P<0.05], and on cigarettes smoked per hour [F(1,14)=4.9, P<0.05].

Post hoc tests identified significant contrasts between the conditions. In terms of differences between the rapid smoking conditions, the latency to the first cigarette after rapid smoking of nicotinized cigarettes was significantly

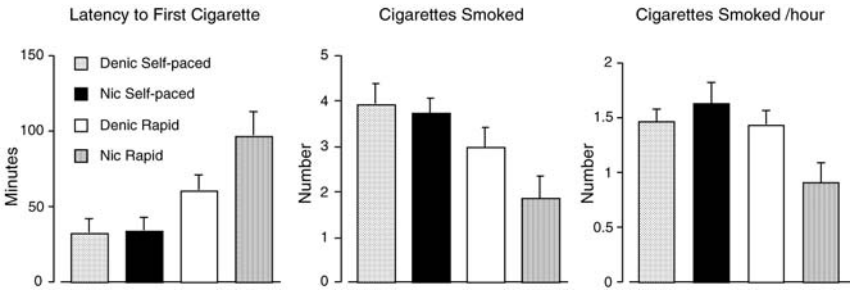


Fig. 3 Effects of smoking interventions on subsequent smoking. Shown are mean latency to smoke, total number of cigarettes smoked, and cigarettes smoked per hour once smoking was resumed after the interventions (n=15). *Lines above the bars* indicate SE

Table 3 Mean cigarette ratings during each intervention (n=15). Means with different superscripts indicate significantly different values based on post hoc tests (P<0.05). Means with the same superscript indicate no significant difference

	Rapid smoking		Self-paced smoking	
	Nicotinized	Denicotinized	Nicotinized	Denicotinized
Cigarette effect				
Pleasant	0.0[a]	1.6[a,c]	23.1[b]	14.1[b,c]
Unpleasant	97.0[a]	95.2[a]	56.5[b]	79.2[c]
Like taste	2.5[a]	3.3[a]	20.9[a]	8.7[a]
Dislike taste	96.7[a]	94.6[a]	70.3[b]	89.0[a,c]
Smoke versus air	20.3[a]	21.8[a]	25.0[a]	26.1[a]
Harsh	97.5[a]	90.3[a]	68.2[b]	82.7[a,b]
Strength	89.9[a]	91.6[a]	71.5[b]	72.0[b]
High in nicotine	87.8[a]	83.4[a]	67.6[b]	64.8[b]
Like drug effect	2.8[a]	16.2[a,b]	30.0[b]	19.8[a,b]
Dislike drug effect	92.2[a]	89.0[a]	54.0[b]	71.3[c]
Satisfying	3.5[a]	7.0[a]	24.3[b]	14.1[a,b]
More awake	33.0[a,b]	51.1[a]	32.0[a,b]	26.1[b]
More calm	12.2[a]	18.1[a]	22.5[a]	21.1[a]
Easier to concentrate	13.6[a]	22.8[a]	26.2[a]	21.6[a]
Less irritable	11.1[a]	23.2[a]	16.6[a]	18.8[a]

longer than after rapid smoking of denicotinized cigarettes (97±15.8 and 61±10.8 min). In addition, participants smoked significantly fewer cigarettes after rapidly smoking nicotinized compared with denicotinized cigarettes (1.8±0.42 and 2.9±0.41 cigarettes), and took fewer puffs after the nicotinized cigarettes (22±6.3 and 36±4.7 puffs). The difference in cigarettes smoked per hour once smoking resumed (0.9±0.19 and 1.4±0.13) was not significantly different.

After the self-paced interventions, there were no significant differences between nicotinized and denicotinized cigarettes in either the latency to smoke (34±9.9 and 33±9.5 min), number of cigarettes smoked (3.7±0.33 and 3.7±0.41), total number of puffs during the session (40±4.2 and 43±5.5 puffs), or cigarettes smoked per hour (1.6±0.19 and 1.5±0.11).

Finally, post hoc tests showed that compared to the self-paced conditions, only rapid smoking of nicotinized cigarettes produced a significantly longer latency to resume smoking. The latency after rapid and after self-paced smoking of denicotinized cigarettes did not differ significantly. However, significantly fewer cigarettes were smoked after rapid smoking of denicotinized cigarettes compared to the self-paced denicotinized condition. Lastly, the rate of cigarettes smoked per hour was significantly higher after self-paced versus rapid smoking of nicotinized cigarettes.

Blood levels and craving reports prior to smoking

A final plasma sample was taken immediately before the first accepted smoking opportunity. Means were 19.9 (±2.8), 13.9 (±1.7), 7.0 (±0.76), and 11.0 (±1.38) ng/ml for each for the rapid nicotinized, self-paced nicotinized, rapid denicotinized, and self-paced denicotinized conditions, respectively. As expected, there was a significant main effect of nicotine content on plasma level [F(1,13)=35.46, P<0.001]. Post hoc analysis showed that the plasma level after rapid smoking of nicotinized cigarettes was significantly higher than all of the other interventions. Also, plasma nicotine levels were significantly higher after self-paced smoking of the nicotinized cigarettes compared to rapid smoking of the denicotinized cigarettes.

Craving levels were measured immediately prior to the first accepted smoking opportunity. Means on the "craving cigarettes" item of the WSQ did not differ significantly between rapid nicotine, rapid denicotinized, self-

paced nicotine and self-paced denicotinized conditions (1.0±0.1, 1.2±0.14, 0.7±0.16, and 0.9±0.17, respectively).

To assess the correlation between craving ratings and the decision to smoke, mean craving ratings from the "craving cigarette" item of WSQ were calculated. One mean was calculated when participants refused a smoking opportunity, and another was calculated when they accepted a smoking opportunity during the 3 h experimental session. Craving ratings were collapsed across experimental conditions and participants since there were no significant differences in craving ratings across conditions at the time smoking was initiated. The unadjusted means were 0.16 (±0.10) when participants refused, and 0.91 (±0.18) when they accepted a smoking opportunity. A rating of 0 on the WSQ indicates "none," and a rating of 1 indicates "mild." ANCOVA revealed that craving ratings were significantly higher when participants accepted a smoking opportunity compared to when they refused an opportunity [$F(1,610)=69.97$, $P<0.001$].

Discussion

The rapid smoking procedure exaggerates the impact of both pharmacological and sensory effects of smoking and thus provides a unique opportunity to examine the role of nicotine versus sensory effects on smoking behavior. The present study showed that rapid smoking of nicotinized cigarettes produced profound reductions in cigarette craving reports and, compared to self-paced conditions, substantially prolonged latency to smoking resumption. Nicotine increased the latency to smoking resumption after rapid smoking: the latency to smoke was significantly longer after rapid smoking of nicotinized versus denicotinized cigarettes. The role of sensory factors was examined by comparing rapid and self-paced smoking of denicotinized cigarettes. The latency to smoke after rapid smoking of denicotinized cigarettes was roughly 27 min longer compared to both self-paced conditions, but this difference was not significant. However, participants smoked fewer cigarettes after rapid smoking than after self-paced smoking of denicotinized cigarettes. Taken together, these results support a role for both nicotine and sensory effects in the control of smoking behavior. Indeed, the differences in smoking behavior after rapid smoking of denicotinized cigarettes would not necessarily be predicted if the resumption of smoking was controlled purely by pharmacological factors. Only after delivery of high doses of nicotine in the rapid smoking condition was there evidence that nicotine played an additional role in acutely suppressing smoking behavior. Similarly, Rose et al. (1985) found that the sensory factors associated with smoking can influence smoking satisfaction in the short term, and that nicotine may play an additional role in the sustained effects of smoke intake on subsequent smoking behavior. It is also likely that the increased smoking latency following the rapid smoking procedures was in part related to the aversive effects of rapid smoking (nausea, dizziness). These symptoms were more intense and prolonged following rapid smoking of nicotine-containing cigarettes than they were in any other condition (Table 1; Fig. 2).

The present study also demonstrated that self-paced smoking of nicotinized and denicotinized cigarettes produces equivalent effects on subsequent craving (Table 2) and smoking behavior (Fig. 3). These findings replicate and extend previous research showing that the sensory effects associated with smoking can suppress craving (Rose et al. 1985; 1993, 1999; Rose and Behm 1987; Rose and Levin 1991; Gross et al. 1997). Equivalent effects on craving measures were observed for nicotinized and denicotinized cigarettes despite the fact that nicotine plasma levels were higher immediately after smoking nicotinized cigarettes (Fig. 1). Self-report measures suggest that participants did not reliably discriminate the difference in cigarette nicotine content (Table 3), indicating that the results reported are based on the presence versus absence of nicotine with few expectancy effects involved. Finally, the latency to smoke after the self-paced smoking interventions did not differ depending on nicotine content (Fig. 3). This extends previously published research showing similarities in smoking and subjective effects of nicotinized versus denicotinized cigarettes (Baldinger et al. 1995; Butschky et al. 1995; Gross et al. 1997; Pickworth et al. 1999; Robinson et al. 2000). The similarities in craving suppression and smoking behavior following self-paced smoking of both nicotinized and denicotinized cigarettes were probably due to respondent conditioning processes. That is, the sensory cues produced by the denicotinized cigarettes have been associated repeatedly with the direct effects of nicotine, and thus become conditioned reinforcing stimuli that are able to suppress smoking and subjective reports of craving (Rose and Levin 1991).

We attempted to equate nicotinized and denicotinized cigarettes in all respects possible. With the exception of four items, all of the participant-rated measures were equivalent when compared within each smoking pace condition (Table 3). After self-paced smoking the denicotinized cigarette was rated as significantly more unpleasant, and the taste and drug effect were more disliked than the nicotinized cigarette. It may be that the absence of sensory and gustatory aspects of nicotine was responsible for these differences. Indeed, Behm and Rose (1994) suggest that the sensory effects of nicotine in the respiratory tract may be significant in terms of craving suppression, and they may also contribute to the reinforcing effects of a cigarette. It would be of interest to introduce ingredients into the denicotinized cigarette, such as capsaicin, that further mimic the sensory profile of nicotinized cigarettes. The benefit of using a denicotinized cigarette with a nearly identical sensory profile is that most, if not all, of the sensory effects will be decoupled from the direct effects of nicotine, and these sensory variables may thereby undergo extinction. Rose and associates have discussed how such cigarettes may be used in a treatment context as part of a cigarette fading

procedure. In other words, the nicotine content in a cigarette could be gradually reduced, while the sensory characteristics would be maintained. Such an approach could be combined with nicotine replacement devices that mitigate other aspects of nicotine withdrawal, such as negative affect and drowsiness (Behm and Rose 1994; Westman et al. 1996).

Although craving ratings did not differ across conditions at the time smoking was resumed, the present study did reveal an overall relationship between craving ratings and choices to smoke. Craving ratings were slightly but significantly higher when a smoking opportunity was accepted (0.91) rather than declined (0.16). Thus even modest elevations in craving may indicate that smoking is likely. One implication of this finding is that differences in craving ratings may not predict differences in smoking if craving ratings are above some minimum, threshold level. For example, even "low" and "high" craving ratings may engender equivalent amounts of smoking (Dudish-Poulsen et al. 1997; Houtsmuller and Stitzer 1999). It is therefore arguable that apparent dissociations between craving and smoking may result from a ceiling effect in terms of craving ratings, particularly as most studies seek to elevate craving. This suggestion would also be consistent with the observation that smoking was resumed in the present study at relatively low mean craving levels. The finding that small increases in craving are associated with choices to smoke may be limited to situations where smokers are provided free access to cigarettes. In clinical contexts, where numerous contingencies are present to abstain from smoking, craving levels associated with choices to smoke would probably be much higher.

The present study provides new insights into the role of nicotine versus sensory cues in the regulation of smoking behavior and lends further support to the importance of sensory cues. Specifically, when cigarettes are smoked at a self-regulated pace, differences in cigarette nicotine content produce no difference in subsequent craving suppression and smoking behavior. Only at higher doses does nicotine play an additional role in suppressing craving and smoking. This study continues to support the value of denicotinized cigarettes to disentangle the sensory and pharmacological effects of smoking. Furthermore, the results also suggest that denicotinized cigarettes could have therapeutic value when used alone or in conjunction with nicotine replacement therapies.

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References

Baldinger B, Hasenfratz M, Bättig K (1995) Effects of smoking abstinence and nicotine abstinence on heart rate activity and cigarette craving under field conditions. Hum Psychopharmacol 10:127–136

Behm FM, Rose JE (1994) Reducing craving for cigarettes while decreasing smoke intake using capsaicin-enhanced low tar cigarettes. Exp Clin Psychopharmacol 2:143–153

Butschky MF, Bailey D, Henningfield J, Pickworth WB (1995) Smoking without nicotine delivery decreases withdrawal in 12-hr abstinent smokers. Pharmacol Biochem Behav 50:91–96

Catley D, O'Connell KA, Shiffman S (2000) Absentminded lapses during smoking cessation. Psychol Addict Behav 14:73–76

Dudish-Poulsen SA, Hatsukami DK (1997) Dissociation between subjective and behavioral responses after cocaine stimuli presentations. Drug Alcohol Depend 47:1–9

Fischman MW, Foltin RW, Nestadt G, Pearlson GD (1990) Effects of desipramine maintenance on cocaine self-administration in humans. J Pharmacol Exp Ther 253:760–770

Foltin RW, Fischman MW (1994) Effects of buprenorphine on the self-administration of cocaine by humans. Behav Pharmacol 5:79–89

Gross J, Lee J, Stitzer ML (1997) Nicotine-containing versus denicotinized cigarettes: Effects on craving and withdrawal. Pharmacol Biochem Behav 57:159–165

Hall RG, Sachs DPL, Hall SM (1979) Medical risk and therapeutic effectiveness of rapid smoking. Behav Ther 10:249–259

Houtsmuller EJ, Stitzer ML (1999) Manipulation of cigarette craving through rapid smoking: efficacy and effects on smoking behavior. Psychopharmacology 142:149–157

Hughes JR, Hatsukami DK (1986) Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 43:289–294

Killen JD, Fortmann SP (1997) Craving is associated with smoking relapse: findings from three prospective studies. Exp Clin Psychopharmacol 5:137–142

Nemeth-Coslett R, Henningfield JE (1986) Effects of nicotine chewing gum on cigarette smoking and subjective and physiologic effects. Clin Pharmacol Ther 39:625–630

Perkins KA, Grobe J, Fonte C (1997) Influence of acute smoking exposure on the subsequent reinforcing value of smoking. Exp Clin Psychopharmacol 5:277–285

Pickworth WB, Fant RV, Nelson RA, Rohrer MS, Henningfield JE (1999) Pharmacodynamic effects of new de-nicotinized cigarettes. Nicotine Tobacco Res 1:357–364

Robinson M, Houtsmuller E, Moolchan ET, Pickworth WB (2000) Placebo cigarettes in smoking research. Exp Clin Psychopharmacol 8:326–332

Rose JE, Behm F (1987) Refined cigarette smoke as a method for reducing nicotine intake. Pharmacol Biochem Behav 28:305–310

Rose JE, Levin ED (1991) Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br J Addict 86:605–609

Rose JE, Tashkin DP, Ertle A, Zinser MC, Lafer R (1985) Sensory blockade of smoking satisfaction. Pharmacol Biochem Behav 23L:289–293

Rose JE, Behm FM, Levine ED (1993) The role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacol Biochem Behav 44:891–900

Rose JE, Westman EC, Behm FM, Johnson MP, Goldberg JS (1999) Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. Pharmacol Biochem Behav 62:165–172

Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG (2000) The measurement of drug craving. Addiction 95:189–210

Schuh KJ, Stitzer ML (1995) Desire to smoke during spaced smoking intervals. Psychopharmacology 120:289–295

Seidman DF, Covey LS (1999) Helping the hard-core smoker: a clinician's guide. Erlbaum, Mahwah, NJ

Shiffman SM, Jarvik ME (1976) Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology 50:35–39

Shiffman SM, Hickox M, Paty JA, Gnys M, Kassel JD, Richards TJ (1996) Progression from a smoking lapse to relapse: prediction from abstinence violation effects, nicotine dependence, and lapse characteristics. J Consult Clin Psychol 64:993–1002

Tiffany ST, Drobes DJ (1991) The development and initial validation of a questionnaire of smoking urges. Br J Addict 86:1467–1476

Westman EC, Behm FM, Rose JE (1996) Dissociating the nicotine and airway sensory effects of smoking. Pharmacol Biochem Behav 53:309–315

Willner P, Hardman S, Eaton G (1995) Subjective and behavioural evaluation of cigarette cravings. Psychopharmacology 118:171–177

Zacny JP, Stitzer ML, Yingling JE (1986) Cigarette filter vent blocking: effects on smoking topography and carbon monoxide exposure. Pharmacol Biochem Behav 25:1245–1252

Zacny JP, Stitzer ML, Brown FJ, Yingling JE, Griffiths RR (1987) Human cigarette smoking: effects of puff and inhalation parameters on smoke exposure. J Pharmacol Exp Ther 240:554–564

Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes

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ABSTRACT

Aims Cigarette smoking causes cancer and disease, yet people find quitting difficult due to aversive symptoms that accompany tobacco abstinence. Understanding how to suppress these symptoms is critical in developing effective smoking cessation treatments. Pharmacologically, pure nicotine suppresses tobacco abstinence symptoms partially, and non-nicotine, smoking-related stimuli suppress these abstinence symptoms fully, at least for 24 hours. The current study was designed to clarify the impact of smoking-related stimuli on tobacco withdrawal, and to explore the duration of their ability to suppress withdrawal in smokers.

Design Three double-blind, within-subjects, Latin square-ordered, 5-day conditions in which participants smoked nicotinized, denicotinized or no cigarettes.

Setting Out-patient laboratory at Virginia Commonwealth University.

Participants Thirteen women and 19 men.

Measurements Subjective, physiological and performance measures were collected daily and compliance with study conditions was verified objectively.

Findings Smoking-related stimuli are sufficient for suppressing some symptoms of tobacco abstinence over a 5-day period [i.e. Questionnaire of Smoking Urges (QSU) factor 1, 'Desire for sweets', 'Hunger' and 'Urges to smoke'], while in this study a combination of nicotine and smoking-related stimuli suppressed other symptoms (i.e. 'Difficulty concentrating', 'Increased eating', 'Restlessness' and 'Impatient').

Conclusions These results indicate that, while some tobacco abstinence symptoms may be suppressed with nicotine, suppressing others may also require strategies that address the absence of smoking-related stimuli.

KEYWORDS Abstinence, stimuli, symptom, suppression, tobacco.

INTRODUCTION

Tobacco smoking causes cancer and respiratory and cardiovascular disease (e.g. [1–3]). These negative health effects are attributable to the carcinogenic and toxic constituents in tobacco smoke [2,4,5] that smokers could avoid by quitting. Quitting smoking is difficult because of the aversive symptoms that accompany tobacco abstinence [6–8]. Effective smoking cessation treatments suppress these aversive symptoms, and thus increase the likelihood of permanent cessation.

Symptoms of tobacco abstinence include physical complaints (e.g. headache, increased hunger), negative mood, decreased arousal and increased cigarette craving/smoking urges [9–11]. Tobacco abstinence is also associated with decrements in attention and/or cognitive

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function [12] and physiological signs, including decreased heart rate and increased skin temperature, electroencephalogram (EEG) and weight [13–15]. Smoking during a quit attempt suppresses most of these aversive abstinence symptoms completely, and can thus lead to relapse. Understanding the factors that contribute to these abstinence symptoms is vital in order to determine the best interventions for suppressing them.

One factor that contributes to tobacco abstinence symptoms is a physical dependence on tobacco-delivered nicotine. Nicotine is a mild psychomotor stimulant, and pharmacologically pure nicotine can suppress tobacco abstinence symptoms partially [12,16,17]. Generally, abstinence symptoms that are produced by drug deprivation and suppressed by drug administration indicate an underlying level of physical dependence on the drug [18,19]. Thus, many investigators conclude that smokers are dependent on nicotine, and that tobacco abstinence symptoms reflect this underlying nicotine dependence. [19] For this reason, many smoking interventions focus on the administration of nicotine (i.e. nicotine replacement therapy: NRT [20,21]) as a means of suppressing tobacco abstinence symptoms with the goal of permanent smoking cessation.

NRT is an effective cessation pharmacotherapy: it increases quit rates an average of 1.4 times, compared to placebo [22]. However, absolute abstinence rates are low; only 7% of smokers who use NRT during a cessation attempt remain abstinent at 6 months [22]. To the extent that suppression of aversive tobacco abstinence symptoms is critical in preventing relapse, low absolute abstinence rates suggest that nicotine alone may not be sufficient to suppress these abstinence symptoms effectively. Understanding which abstinence symptoms are suppressed by nicotine and which are suppressed by other factors is critical in improving intervention effectiveness.

The relative influence of nicotine versus other factors on tobacco abstinence symptoms has been addressed empirically. For example, pharmacologically pure nicotine supports physical dependence [23] although, relative to tobacco abstinence symptoms, nicotine abstinence symptoms are less numerous and intense [24]. The more numerous and intense symptoms reported by abstaining smokers may reflect the combined influence of nicotine and non-nicotine factors.

One non-nicotine factor that may contribute to the severity of tobacco abstinence is the absence of smoking-related stimuli. This notion is supported by the finding that tobacco abstinence symptoms can be suppressed by smoking denicotinized cigarettes [25–29]. 'Placebo-induced withdrawal suppression' [30] challenges the idea that the absence of nicotine causes all tobacco abstinence symptoms. However, demonstrations of placebo-induced withdrawal suppression have been limited to a 24-hour evaluation period (e.g. [25]). Thus the long-term role that smoking-related stimuli play in suppressing tobacco abstinence effects is unknown. If placebo-induced withdrawal suppression is a long-term phenomenon, addressing the role of smoking-related stimuli in treatment may increase the efficacy of current interventions (e.g. [31]).

The present study was designed to clarify the impact of smoking-related stimuli on tobacco withdrawal, and explore the duration of placebo-induced withdrawal suppression in cigarette smokers. All participants completed three 5-day, double-blind, out-patient conditions, in which they smoked no cigarettes, denicotinized cigarettes or nicotine-containing cigarettes *ad libitum*. Subject-rated, performance and physiological measures were collected on days 1–5 of each condition and compliance with condition restrictions was verified objectively. This design allowed observation of tobacco abstinence symptoms during 5 days of no smoking, and a comparison of the symptoms that were suppressed when smokers were using placebo (denicotinized) or active (nicotine-containing) cigarettes over the 5-day period. Thus, the symptom specificity and duration of placebo-induced withdrawal suppression was revealed. Identification of abstinence symptoms that are suppressed by smoking-related stimuli (i.e. denicotinized cigarettes) may help in the development of more comprehensive and efficacious cessation interventions.

METHOD

Participants and setting

Thirteen women (four non-white) and 19 men (six non-white) completed this IRB-approved, three-condition, double-blind, Latin square-ordered, within-subjects study. Participants were included if they were aged 18–50 years (mean = 24.8, SD = 7.1), provided a breath sample ≥15 parts/million CO (mean = 26.6, SD = 13.4) and smoked ≥15 king-sized cigarettes/day (mean = 20.7, SD = 4.0) for the past 2 years (mean = 6.0, SD = 4.4). Participants were moderately nicotine dependent (i.e. Fagerström nicotine tolerance questionnaire, mean = 5.4, SD = 1.7 [32]) and smoked cigarettes that yielded, on average, 0.9 mg nicotine and 12.4 mg tar [33]. Individuals were excluded if they had a history of chronic health problems or psychiatric conditions, were currently pregnant or breastfeeding, or reported smoking cessation efforts. All participants signed an IRB-approved informed consent form, in which all study procedures were described. The consent form also explained that the cigarettes provided in the two smoking conditions 'contain

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tobacco and may or may not taste and feel the same as your usual brand', and that participants 'may smoke as many of these cigarettes as you want'.

Materials

Depending upon condition, participants smoked nicotinized (NIC), denicotinized (DENIC) or no cigarettes. The NIC and DENIC cigarettes were developed and manufactured for the National Institute on Drug Abuse by Lifetech Corporation (Lafayette Hill, PA, USA). The smoke of the NIC cigarettes yielded 0.6 mg nicotine and 10.0 mg tar, while the smoke of the DENIC cigarettes yielded 0.07 mg nicotine and 12.1 mg tar [27]. These DENIC cigarettes do not deliver nicotine, but suppress withdrawal in short-term laboratory studies [26,27,34].

Outcome measures

Compliance measures

Compliance in all conditions was monitored using daily expired air CO (BreathCO, Vitalograph, Lenexa, KS, USA) and thrice-weekly semiquantitative analysis of urinary cotinine, a nicotine metabolite (Nicalert®; Nymox, Maywood, NJ, USA); participants also returned used cigarette butts as an index of smoking behavior. Urine samples were also stored at −70°C for later quantitative analysis of cotinine level (GC/MS; LOQ = 5 ng/ml). GC/MS is a sensitive and specific measure of smoking [35,36].

Subjective, performance, and physiological measures

Daily, computerized, subjective measures consisted of visual analog scales (VAS [9]), the Questionnaire of Smoking Urges (QSU [11]) and the Direct Effects Scale (DES [37]). VAS items were presented above a horizontal line with anchors on the left ('not at all') and right ('extremely'). Subjects used a mouse to produce a vertical mark on the horizontal line. Scores are the distance of the vertical mark from the left anchor, expressed as a percentage. VAS items describe tobacco/nicotine withdrawal symptoms: 'Urges to smoke', 'Irritability/frustration/anger', 'Anxious', 'Difficulty concentrating', 'Restlessness', 'Hunger', 'Impatient', 'Craving a cigarette/nicotine', 'Insomnia/disturbed sleep', 'Increased eating', 'Drowsiness', 'Depression/feeling blue', and 'Desire for sweets'. The QSU consists of 32 seven-point (each scored 0–6), Likert-scale items, and yields two empirically derived factors: factor 1 (intention to smoke) and factor 2 (anticipation of relief from withdrawal). The DES consists of 15 VAS items: 'Are the cigarettes pleasant?', 'Do the cigarettes taste good?', 'Do the cigarettes make you dizzy?', 'Do the cigarettes calm you down?', 'Do the cigarettes help you concentrate?', 'Do the cigarettes make you feel more awake?', 'Do the cigarettes reduce your hunger for food?', 'Do the cigarettes make you sick?', 'Do the cigarettes taste like your own brand of cigarettes?', 'Do the cigarettes feel like your own brand of cigarettes?', 'Do the cigarettes feel as mild as your own brand of cigarettes?', 'Do you like the cigarettes?' and 'Do you dislike the cigarettes?'.

The Digit Symbol Substitution Test (DSST [38]) is a performance measure sensitive to nicotine/tobacco withdrawal [39] and consists of randomly selected digits appearing on the center of a video screen. Participants used the numeric keypad to reproduce a geometric pattern associated with a digit, according to the digit code presented at the top of the screen, and completed as many patterns as possible during the 90-second task presentation. Data collected include the number of trials attempted and the number of correct trials completed.

Each day, resting heart rate (HR) and skin temperature (TEMP) were recorded every 20 seconds for 30 minutes, and blood pressure (BP; systolic and diastolic) was recorded every 3 minutes (Monitor 507E, Criticare Systems, Waukesha, WI, USA).

Procedure

Participants completed three 5-day (Monday–Friday) conditions in which they smoked NIC, DENIC or no cigarettes (they smoked their own brand on weekends). Subjective, physiological and performance measures, and expired CO samples were assessed daily; during smoking conditions, DES and cigarette butt data were collected on days 2–5. Semiquantitative urinary cotinine analyses were performed on days 1 (Monday), 3 (Wednesday) and 5 (Friday). On days 3 and 5, CO and semiquantitative urine cotinine data were used to assess compliance with smoking restrictions; compliance was reinforced monetarily (i.e. $30 on day 3 and $70 on day 5). For example, when participants were in the no smoking condition, compliance was verified with decreases in CO and semiquantitative urinary cotinine levels, relative to day 1. Participants who failed to comply with condition restrictions once could try once more but were withdrawn if they failed more than once. For all study days, time of day (i.e. a.m. or p.m.) was constant within subjects but could vary across subjects. In addition to the 32 participants described above, another seven individuals entered the study but were withdrawn for repeated non-compliance and another 17 entered but withdrew voluntarily, seven during the no smoking condition, eight during the DENIC condition and two during the NIC condition; these individuals' data are excluded from all analyses. Analyses of demographic data revealed that there were no differences between the 32 completers and the 24 non-completers in general characteristics (e.g. education level or body mass

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index), or characteristics related specifically to cigarette, alcohol or marijuana use. Participants who completed the study earned a total of $400.

Data analysis

Resting HR, TEMP and BP data collected in the final 15 minutes of each day were averaged, and all outcome measures were analyzed using a condition × day repeated-measures analysis of variance (ANOVA; collapsed across gender because only three of 57 possible interactions involving this factor were significant). The levels of condition and day varied according to measure. For urinary cotinine data, there were three levels of condition (i.e. NIC, DENIC and no smoking) and two levels of day (i.e. days 1 and 5; day 3 samples were used to assess compliance, but were not analyzed quantitatively due to the relatively high cost of the quantitative assay). For cigarette butt data, there were two levels of condition (NIC and DENIC) and four levels of day (2–5). For CO, subjective, performance and physiological data, there were three levels of condition (i.e. NIC, DENIC and no smoking) and five levels of day. For all analyses, significance levels were adjusted for violations of the sphericity assumption using Huynh–Feldt corrections. Significant main effects and interactions were analyzed using Tukey's Honestly Significant Difference (HSD) post hoc test using the mean square error terms for the interaction; comparisons for which $P < 0.05$ were reported as significant.

RESULTS

Study completion was contingent upon condition compliance as described below. Subjective, performance and physiological measures are critical for dissociating the role of nicotine alone (in the DENIC condition) from the combination of nicotine and smoking-related stimuli (in the no smoking condition) on tobacco abstinence effects.

Compliance measures

Quantitative urine cotinine analysis available after study completion revealed that, in the no smoking condition, levels decreased from day 1 to day 5 for all participants. In the DENIC condition, cotinine level decreased from day 1 to day 5 for 31 participants. However, one participant showed an increase from day 1 to day 5 (851–1427 ng/ml), indicative of non-compliance. This participant's data were excluded from all subsequent analyses.

For the 31 remaining participants, significant condition by day interactions were observed for three compliance measures: CO [F (8240) = 19.2, $P < 0.01$], quantitative urinary cotinine [F (2,60) = 28.4, $P < 0.01$] and butt count [F (3,87) = 6.6, $P < 0.01$]. In the no smoking condition, participants' CO (Fig. 1, top) decreased significantly across days 2–5, relative to day 1 (Ps < 0.05; Tukey's HSD). On average, across the 5 days of this condition, CO dropped by 95.0%. No significant changes in CO were observed over time when participants smoked either nicotinized or denicotinized cigarettes. On days 4 and 5, CO levels were lower when participants smoked denicotinized compared to nicotinized cigarettes (Ps < 0.05; Tukey's HSD).

Quantitative urinary cotinine did not change significantly over time when participants smoked nicotinized cigarettes (see Fig. 1, bottom). In this condition, mean urinary cotinine level decreased by 15.5% from day 1 to day 5. When participants smoked denicotinized cigarettes or no cigarettes, their urinary cotinine levels decreased significantly from day 1 to day 5 (Ps < 0.05, Tukey's HSD), with an 89.5% mean decrease observed in the denicotinized cigarette condition, and a 95.0% mean decrease in the no smoking condition. On day 5, urinary cotinine levels were significantly greater in the nicotinized cigarette condition, relative to the denicotinized and no smoking conditions (Ps < 0.05; Tukey's HSD). Day 5 urinary cotinine levels did not differ significantly between the denicotinized and no smoking conditions.

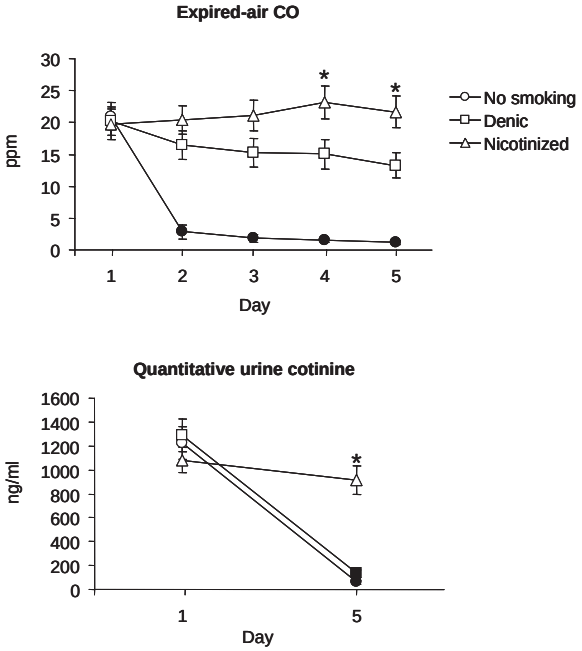


Figure 1 Averaged data (± 1 SEM) from 31 subjects for expired air carbon monoxide (top) and quantitative urine cotinine (bottom) during three 5-day conditions in which they smoked nicotinized (triangles), denicotinized (squares) or no cigarettes (circles). Filled symbols represent significant differences from baseline (day 1), and asterisks indicate significant differences between the NIC and DENIC conditions on that day. All Ps < 0.05; Tukey's HSD

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Cigarette butt counts on days 2–5 did not vary significantly over time within either smoking condition. Cigarette butt counts were significantly lower on all days of the denicotinized cigarette condition (day 2 mean = 10.7, SD = 5.2; day 3 mean = 9.9, SD = 4.4; day 4 mean = 8.5, SD = 5.1; day 5 mean = 9.1, SD = 5.9), compared to the nicotinized cigarette condition (day 2 mean = 14.9, SD = 6.4; day 3 mean = 15.1, SD = 6.6; day 4 mean = 17.3, SD = 6.8; day 5 mean = 17.4, SD = 7.3; *P*s < 0.05; Tukey's HSD).

Subjective, performance and physiological measures

Statistical results for subjective, performance and physiological measures are presented in Table 1. Significant condition × day interactions indicate that results observed across condition days depended upon whether participants were smoking nicotinized, denicotinized or no cigarettes: a significant interaction was observed on many withdrawal-related subjective effect items, including QSU factors 1 and 2, and VAS items assessing urges to

Table 1 Effects of condition, day and condition × day interactions on withdrawal symptoms.

	Condition			*Day*			*Condition × day*		
	F	*P*	ω^2	*F*	*P*	ω^2	*F*	*P*	ω^2
Subjective measures									
Withdrawal									
QSU Factor 1	13.94	<0.001	0.32	6.37	<0.01	0.18	4.57	<0.01	0.13
QSU Factor 2	8.65	<0.01	0.22	8.62	<0.001	0.22	5.82	<0.001	0.16
Urges to smoke	15.32	<0.001	0.34	2.19	NS	0.07	2.56	<0.05	0.08
Irritability/frustration/anger	6.55	<0.01	0.18	10.65	<0.001	0.26	2.84	<0.05	0.08
Anxious	8.72	<0.001	0.23	6.13	<0.01	0.17	1.80	NS	0.06
Difficulty concentrating	12.30	<0.001	0.29	7.92	<0.001	0.21	3.72	<0.01	0.11
Restlessness	12.27	<0.001	0.29	8.90	<0.001	0.23	4.19	<0.001	0.12
Hunger	13.65	<0.001	0.31	7.33	<0.001	0.20	1.92	NS	0.06
Impatient	13.96	<0.001	0.32	12.22	<0.001	0.29	4.73	<0.001	0.14
Craving a cigarette	10.42	<0.001	0.26	9.51	<0.001	0.24	4.64	<0.001	0.13
Insomnia	2.17	NS	0.07	2.74	<0.05	0.08	1.87	<0.05	0.06
Increased eating	23.93	<0.001	0.44	16.98	<0.001	0.36	6.72	<0.001	0.18
Drowsiness	4.66	<0.05	0.14	2.40	NS	0.07	0.90	NS	0.03
Depression/feeling blue	1.75	NS	0.06	2.92	<0.05	0.09	1.11	NS	0.04
Desire for sweets	11.75	<0.001	0.28	4.73	<0.01	0.14	4.96	<0.01	0.14
Sensory characteristics									
Satisfying	119.87	<0.001	0.80	0.59	NS	0.02	1.99	NS	0.06
Pleasant	108.92	<0.001	0.78	0.31	NS	0.01	3.20	<0.05	0.10
Taste good	77.70	<0.001	0.72	1.96	NS	0.06	3.78	<0.05	0.11
Dizzy	0.00	NS	0.00	1.92	NS	0.06	0.93	NS	0.03
Calm you down	34.85	<0.001	0.54	0.76	NS	0.03	0.19	NS	0.00
Help you concentrate	26.19	<0.001	0.47	0.41	NS	0.01	0.35	NS	0.01
Feel more awake	26.33	<0.001	0.47	0.10	NS	0.00	0.88	NS	0.03
Reduce hunger	19.38	<0.001	0.39	2.33	NS	0.07	0.65	NS	0.02
Make you sick	11.20	<0.01	0.27	4.31	<0.05	0.13	1.74	NS	0.06
Taste like own brand	41.00	<0.001	0.58	5.29	<0.01	0.15	5.50	<0.01	0.16
Feel like own brand	55.33	<0.001	0.65	2.49	NS	0.08	2.64	NS	0.08
Harsh as own brand	5.44	<0.05	0.15	0.48	NS	0.02	0.21	NS	0.00
Mild as own brand	17.12	<0.001	0.36	0.48	NS	0.02	0.99	NS	0.03
Like the cigarettes	92.55	<0.001	0.76	0.78	NS	0.03	2.25	NS	0.07
Dislike the cigarettes	90.26	<0.001	0.75	1.17	NS	0.04	1.83	NS	0.06
Performance measures									
DSST percentage correct	1.41	NS	0.05	0.21	NS	0.00	0.63	NS	0.02
Physiological measures									
Systolic blood pressure	0.03	NS	0.00	2.14	NS	0.07	2.29	<0.05	0.07
Diastolic blood pressure	0.35	NS	0.01	11.32	<0.001	0.27	1.52	NS	0.05
Skin temperature	2.00	NS	0.06	2.64	<0.05	0.08	0.61	NS	0.02
Heart rate	13.58	<0.001	0.31	17.15	<0.001	0.36	2.51	<0.05	0.08

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smoke, irritability/frustration/anger, difficulty concentrating, restlessness, impatience, craving, insomnia, increased eating, and desire for sweets. These data showed a general pattern: relative to baseline, scores increased most in the no smoking condition (except 'Insomnia' and 'Depression/feeling blue'). Two distinctive patterns of findings also emerged, as described below.

One pattern was observed on QSU factor 1 (intention to smoke) and VAS measures 'Desire for sweets', 'Hunger' and 'Urges to smoke': mean scores increased over time when participants were not smoking, but did not increase over time when participants smoked either denicotinized or nicotinized cigarettes. One representative measure, QSU factor 1, is displayed in Fig. 2 (top). Relative to day 1, mean scores increased 33.5% after 4 days of no smoking ($P < 0.05$). No significant increases were observed when participants were smoking either nicotinized or denicotinized cigarettes. The same pattern was seen for the 'Urges to smoke' VAS. When participants were not smoking, ratings of 'Urges to smoke' increased significantly from day 1 (mean = 57.4, SD = 20.9) to day 2 (mean = 73.9, SD = 20.0), and remained 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; *P*s < 0.05). When participants were smoking nicotinized or denicotinized cigarettes, ratings of 'Urges to smoke' did not vary significantly from day 1 (NIC mean = 53.1, SD = 25.5; DENIC mean = 51.5, SD = 22.6) to day 5 (NIC mean = 49.5, SD = 21.9; DENIC mean = 48.3, SD = 29.3; *P*s > 0.05). With minor differences, a similar pattern was seen for 'Hunger' and 'Desire for sweets'. Again, mean scores increased from baseline during 4 days of no smoking (*P*s < 0.05) and, generally, scores did not increase significantly from baseline when participants were smoking either nicotinized or denicotinized cigarettes. However, when participants were smoking denicotinized cigarettes, there was a significant increase in ratings of 'Hunger' from day 1 (mean 30.2, SD = 20.9) to day 5 (mean = 43.6, SD = 26.0; $P < 0.05$) and on 'Desire for sweets' from day 1 (mean = 22.1, SD = 28.0) to days 4 (mean = 35.6, SD = 37.7) and 5 (mean = 34.0, SD = 35.4; *P*s < 0.05). Because increases on these measures were observed when participants were not smoking, and suppressed when participants smoked denicotinized cigarettes, these measures may assess something other than nicotine withdrawal.

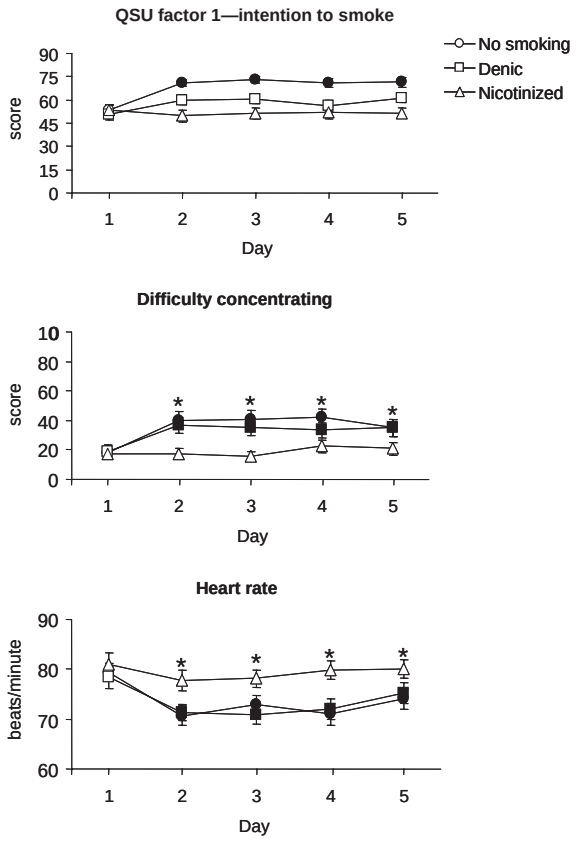


Figure 2 Averaged data (± 1 SEM) from 31 subjects on factor 1 of the Tiffany–Drobes Questionnaire of Smoking Urges [11] (top), the visual analog scale item assessing difficulty concentrating (middle) and heart rate (bottom). In all other respects, the figure is identical to Fig. 1

A different pattern was observed for measures of 'Increased eating', 'Restlessness', 'Impatient' and 'Difficulty concentrating': mean scores increased over time when participants were not smoking and when they were smoking denicotinized cigarettes, while scores did not increase when participants smoked nicotinized cigarettes. Figure 2 (middle) shows that when participants did not smoke, mean scores for the 'Difficulty concentrating' VAS item increased by 127.8% from day 1 to day 2 and remained elevated. Similarly, when participants were in the denicotinized cigarette condition, scores increased by 94.7% from day 1 to day 2 and remained elevated. However, when participants were in the nicotinized cigarette condition, scores for the 'Difficulty concentrating' VAS item increased only 18.8% from day 1 to day 5. A similar pattern of results was observed for the VAS item 'Restlessness'. When participants did not smoke or smoked denicotinized cigarettes, item scores increased significantly from day 1 (no smoking mean = 19.1, SD = 22.6; DENIC mean = 16.5, SD = 20.9) to day 2 (no smoking mean = 39.4, SD = 31.2; DENIC mean = 34.1, SD = 26.7), and remained elevated across days 3 (no smoking mean = 43.7, SD = 31.2; DENIC mean = 36.3, SD = 29.4), 4 (no smoking mean = 47.8, SD = 32.8; DENIC mean = 36.1, SD = 26.9) and 5 (no smoking mean = 42.4, SD = 34.2; DENIC mean = 37.3, SD = 32.1; *P*s < 0.05). However, when participants smoked nicotinized cigarettes, their scores on 'Restlessness' did not vary from day 1 (mean = 21.5, SD = 25.6) to day 5

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(mean = 19.2, SD = 24.2). Because increases on measures of 'Difficulty concentrating', 'Restlessness', 'Increased eating' and 'Impatient' were apparent when participants were not smoking, and were not suppressed when participants smoked denicotinized cigarettes, these measures may assess nicotine withdrawal.

Less clear patterns were observed on measures of 'Craving a cigarette/nicotine', 'Anxious', 'Irritability/frustration/anger' and the QSU factor 2 (anticipation of relief from withdrawal). Scores were increased significantly on most days, relative to baseline, when participants abstained from smoking (Ps < 0.05). Significantly increased scores also were observed occasionally, compared to baseline, when participants smoked denicotinized cigarettes (Ps < 0.05). On most days, scores for these measures were suppressed fully when participants smoked nicotinized cigarettes relative to when they abstained from smoking (Ps < 0.05). For example, when participants were in the non-smoking condition, mean scores for the QSU factor 2 increased from 17.1 (SD = 10.2) on day 1 to 28.0 (SD = 12.8) on day 2, and remained elevated during days 3 (mean = 29.0, SD = 14.1), 4 (mean = 29.3, SD = 13.9) and 5 (mean = 28.8, SD = 14.5). When participants were in the denicotinized cigarette condition, mean scores for the QSU factor 2 showed a similar, but less pronounced pattern as in the no smoking condition. Scores increased from 17.9 (SD = 12.8) on day 1–24.3 (SD = 13.6) on day 2, and remained moderately elevated on days 3 (mean = 24.9, SD = 12.4), 4 (mean = 22.6, SD = 13.1) and 5 (mean = 25.0, SD = 15.0). In the nicotinized condition, no changes in scores were evident across days 1 (mean = 18.7, SD = 11.6), 2 (mean = 18.4, SD = 12.1), 3 (mean = 17.0, SD = 13.3), 4 (mean = 18.7, SD = 12.8) and 5 (mean = 17.8, SD = 12.1). A similar pattern was observed for 'Craving a cigarette/nicotine', 'Anxious', and 'Irritability/frustration/anger', making uncertain the extent to which these measures assess nicotine withdrawal.

Statistical results for DES items are presented in Table 1. Significant condition × day interactions were observed for the items: 'Are the cigarettes pleasant?', 'Do the cigarettes taste good?' and 'Do the cigarettes taste like your own brand of cigarettes?'. When participants were smoking denicotinized cigarettes, ratings of 'taste good' were significantly lower on days 4 (mean = 2.2, SD = 4.3) and 5 (mean = 2.0, SD = 4.6) compared to days 2 (mean = 4.6, SD = 7.2) and 3 (mean = 4.2, SD = 8.2; Ps < 0.05). When participants were smoking nicotinized cigarettes, ratings of 'taste good' were significantly higher on days 3 (mean = 47.1, SD = 27.7) and 4 (mean = 46.9, SD = 26.1) compared to day 2 (mean = 39.3, SD = 29.0; $P < 0.05$). Ratings of 'taste good' were significantly higher when participants were smoking nicotinized cigarettes, compared to denicotinized cigarettes across all days (Ps < 0.05). Similarly, when participants were smoking nicotinized cigarettes, ratings of 'taste like own brand' increased by 31.3% from day 2 to day 5 ($P < 0.05$). However, scores did not change significantly over time, relative to baseline, when participants were smoking denicotinized cigarettes, increasing only 2.4% from day 2 to day 5. Relative to when participants were smoking denicotinized cigarettes, ratings were significantly more positive on all assessment days when participants smoked nicotinized cigarettes (Ps < 0.05). A comparable pattern was found for all remaining DES items with significant condition main effects.

As seen in Table 1, no significant main effects or interactions were observed for the DSST measure 'percentage correct', diastolic blood pressure or skin temperature. However, significant interactions were observed for heart rate and systolic blood pressure. As can be seen in Fig. 2 (bottom), when participants abstained from smoking, or smoked denicotinized cigarettes, heart rate was lower relative to baseline and relative to when participants smoked nicotinized cigarettes (Ps < 0.05). For example, when participants were not smoking, heart rate decreased 11.1% from day 1 to day 2 and remained lower across the 5-day study period. Similarly, when participants smoked denicotinized cigarettes, heart rate decreased 9.2% from day 1 to day 2 and remained reduced. Relative to baseline, significant changes in heart rate were not observed when participants smoked nicotinized cigarettes. Decreases in heart rate (and also systolic blood pressure, on which a similar pattern was observed) may indicate nicotine withdrawal during tobacco abstinence.

DISCUSSION

Tobacco smoking causes disease and death [3]. However, most smokers find quitting difficult, due to tobacco abstinence symptoms [6–8]. Understanding withdrawal symptom etiology is critical if effective interventions are to be developed to treat them. Much research has been based on the assumption that nicotine dependence is responsible for all tobacco abstinence symptoms. The validity of this assumption is challenged by the fact that smoking-related stimuli alone—without nicotine—can suppress tobacco abstinence symptoms, at least for a 24-hour period [25]. To the extent that non-nicotine, smoking-related stimuli alone can suppress tobacco abstinence symptoms indefinitely, the role of nicotine in treating these symptoms is uncertain.

Results from this study indicate that smoking-related stimuli are sufficient for suppressing some symptoms of tobacco abstinence over a 5-day period (i.e. QSU factor 1,

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'Desire for sweets', 'Hunger' and 'Urges to smoke'). That is, for these symptoms, denicotinized and nicotinized cigarettes were equally effective in suppressing withdrawal. Interestingly, craving for cigarettes has been identified previously as a withdrawal symptom that could be suppressed by non-nicotine stimuli (i.e. citric acid inhaler (e.g. [40]).

In contrast, in this study the combination of smoking-related stimuli and nicotine was required to suppress other symptoms associated with 5 days of tobacco abstinence (i.e. 'Difficulty concentrating', 'Increased eating', 'Restlessness' and 'Impatient'). That is, for these symptoms, only nicotinized cigarettes were effective in suppressing withdrawal and scores were elevated similarly when participants did not smoke or when they smoked denicotinized cigarettes. Interestingly, difficulty concentrating (and decreased vigor) has been identified previously as a nicotine-specific withdrawal symptom when former smokers, dependent on nicotine gum, received placebo gum in a double-blind study [41].

Taken together, these results may highlight withdrawal symptoms that can be treated most effectively with NRT alone, versus symptoms that might be treated more effectively when NRT is supplemented with other strategies. NRT may be especially helpful when abstaining smokers report difficulty concentrating, restlessness and impatience. When they complain of urge to smoke or increased hunger, behavioral techniques may be more helpful in symptom suppression than higher NRT doses (e.g. [42]). Because most smokers experience a variety of withdrawal symptoms, augmenting NRT with interventions that address specific symptoms may help to maximize withdrawal suppression. Counseling, antidepressants (i.e. bupropion, nortriptyline) and NRT can all aid in smoking cessation [22,43], and combining behavioral and pharmacotherapy enhances treatment efficacy [44]. However, 11% long-term abstinence rates, even with combination therapy [45], suggest the need for further improvement. The addition of specific behavioral strategies to target smoking-related stimuli may address this need.

The observation that denicotinized cigarettes suppress withdrawal (see also [26,28,29,34,46]) seems to contradict reports that cigarette-related stimuli increase urge to smoke and other withdrawal symptoms (e.g. [47–49]). This apparent contradiction can be explained using an influential model of drug urges and drug use behavior (e.g. [50]). According to this model, long-term cigarette smokers complete complex action plans during drug self-administration and, for most, these action plans have become highly automatized [50]. That is, these action plans are 'readily enabled by particular stimulus configurations (i.e. stimulus bound), initiated and completed without intention, difficult to impede in the presence of triggering stimuli, effortless, and enacted in the absence of awareness' [50, p. 154]. Because these automatized action plans are stimulus bound, they can become activated by cues, such as the sight or smell of a cigarette. Failure to complete an activated automatized action plan (e.g. seeing and smelling a cigarette, but not smoking it) invokes non-automatic cognitive processes that are manifested as drug urges (e.g. in a smoker, the urge to smoke a cigarette [50]) and other withdrawal symptoms. In contrast, completing an activated automatized action plan (e.g. seeing and smelling and smoking a cigarette, even a denicotinized cigarette), might be expected to elicit no ratings of urge and other withdrawal symptoms. Of course, other non-nicotine components of tobacco smoke may also contribute to the ability of denicotinized tobacco cigarettes to suppress withdrawal (i.e. tobacco-induced monoamine oxidase B inhibition [51]).

Results reported here should be interpreted within the context of study limitations. First, the denicotinized cigarettes had inferior taste and sensory qualities, and participants smoked fewer of them. This difference may explain why the denicotinized cigarettes were not as effective at suppressing withdrawal symptoms such as 'Hunger' and 'Desire for sweets' toward the end of the 5-day study conditions. They also highlight the need for a better placebo cigarette in order to deliver smoking-related stimuli effectively. Secondly, although this study's 5 days of denicotinized cigarette exposure was longer than others [25–29], it may still have been too brief to characterize fully the duration of placebo-induced withdrawal suppression. Longer-term studies examining this phenomenon are needed, as the goal of treatment is long-term abstinence and therefore requires long-term withdrawal suppression. Finally, larger samples would help to detect potential gender differences in tobacco abstinence, nicotine withdrawal and symptom suppression with smoking-related stimuli and/or NRT (e.g. [52–54]).

The current study suggests that some abstinence symptoms may be related more closely to nicotine, while others may be more related to smoking-related stimuli. As the discrimination of tobacco abstinence symptoms becomes clearer, more targeted interventions may be provided and may help to improve current cessation treatments.

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References

1. Centers for Disease Control and Prevention (2002) Annual smoking-attributable mortality, years of potential life lost, and economic costs—United States, 1995–99. *Morbidity and Mortality Weekly Report*, **51**, 300–303.
2. Stratton, K., Shetty, P., Wallace, R. & Bondurant, S., eds (2001) *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Academy Press.
3. US Department of Health and Human Services (1989) *Reducing the Health Consequences of Smoking: 25 Years of Progress*. A report of the Surgeon General. Rockville, MD: Public Health Service, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
4. Denissenko, M. F., Pao, A., Tang, M. & Pfeifer, G. P. (1996) Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. *Science*, **274**, 430–432.
5. Hecht, S. S. & Hoffmann, D. (1988) Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis*, **9**, 875–884.
6. Cummings, K. M., Jaen, C. R. & Giovino, G. (1985) Circumstances surrounding relapse in a group of recent exsmokers. *Preventive Medicine*, **14**, 195–202.
7. Droungas, A., Ehrman, R. N., Childress, A. R. & O'Brien, C. P. (1995) Effect of smoking cues and cigarette availability on craving and smoking behavior. *Addictive Behaviors*, **20**, 657–673.
8. Piasecki, T. M., Jorenby, D. E., Smith, S. S., Fiore, M. C. & Baker, T. B. (2003) Smoking withdrawal dynamics. I. Abstinence distress in lapsers and abstainers. *Journal of Abnormal Psychology*, **112**, 3–13.
9. Hughes, J. R. & Hatsukami, D. K. (1986) Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*, **43**, 289–294.
10. Shiffman, S. M. & Jarvik, M. E. (1976) Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology*, **50**, 35–39.
11. Tiffany, S. T. & Drobes, D. J. (1991) The development and initial validation of a questionnaire on smoking urges. *British Journal of Addiction*, **86**, 1467–1476.
12. Heishman, S. J., Taylor, R. C. & Henningfield, J. E. (1994) Nicotine and smoking: a review of effects on human performance. *Experimental and Clinical Psychopharmacology*, **2**, 345–395.
13. Hatsukami, D. K., Hughes, J. R., Pickens, R. W. & Svikis, D. (1984) Tobacco withdrawal symptoms: an experimental analysis. *Psychopharmacology*, **84**, 231–236.
14. Pickworth, W. B., Fant, R. V., Nelson, R. A., Rohrer, M. S. & Henningfield, J. E. (1999) Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine and Tobacco Research*, **1**, 357–364.
15. Shiffman, S. M. (1979) The tobacco withdrawal syndrome. *NIDA Research Monograph*, **23**, 158–184.
16. Hughes, J. R., Hatsukami, D. K., Pickens, R. W., Krahn, D., Malin, S. & Luknic, A. (1984) Effect of nicotine on the tobacco withdrawal syndrome. *Psychopharmacology*, **83**, 82–87.
17. Gross, J. & Stitzer, M. L. (1989) Nicotine replacement: ten-week effects on tobacco withdrawal symptoms. *Psychopharmacology*, **98**, 334–341.
18. Martin, W. R. & Sloan, J. W. (1977) Neuropharmacology and neurochemistry of subjective effects, analgesia, tolerance, and dependence produced by narcotic analgesics. In: Martin, W. R., eds. *Handbook of Experimental Pharmacology*, vol. 45. *Drug Addiction I*, pp. 43–158. Heidelberg: Springer-Verlag.
19. US Department of Health and Human Services (1988) *The Health Consequences of Smoking: Nicotine Addiction*. A report of the Surgeon General. Rockville, MD: Public Health Service, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
20. Eissenberg, T., Stitzer, M. L. & Henningfield, J. E. (1999) Current issues in nicotine replacement. In: Seidman, D. F. & Covey, L. S., eds. *Helping the Hard-Core Smoker: a Clinician's Guide*, pp. 137–158. Mahwah, NJ: Lawrence Erlbaum Associates.
21. Henningfield, J. E. (1995) Nicotine medications for smoking cessation. *New England Journal of Medicine*, **333**, 1196–1203.
22. Hughes, J. R., Shiffman, S., Callas, P. & Zhang, J. (2003) A meta-analysis of the efficacy of over-the-counter nicotine replacement. *Tobacco Control*, **12**, 21–27.
23. Hughes, J. R., Hatsukami, D. K. & Skoog, K. P. (1986) Physical dependence on nicotine in gum. A placebo substitution trial. *JAMA*, **255**, 3277–3279.
24. Hatsukami, D. K., Skoog, K., Huber, M. & Hughes, J. (1991) Signs and symptoms from nicotine gum abstinence. *Psychopharmacology*, **104**, 496–504.
25. Baldinger, B., Hasenfratz, M. & Battig, K. (1995) Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field condition. *Human Psychopharmacology*, **10**, 127–136.
26. Buchhalter, A. R., Schrinel, L. & Eissenberg, T. (2001) Withdrawal suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine and Tobacco Research*, **3**, 111–118.
27. Pickworth, W. B., Fant, R. V., Butschky, M. F. & Henningfield, J. E. (1996) Effects of transdermal nicotine delivery on measures of acute nicotine withdrawal. *Journal of Pharmacology and Experimental Therapeutics*, **279**, 450–456.
28. Brauer, L. H., Behm, F. M., Lane, J. D., Westman, E. C., Perkins, C. & Rose, J. E. (2001) Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine and Tobacco Research*, **3**, 101–109.
29. Rose, J. E., Behm, F. M., Westman, E. C. & Johnson, M. (2000) Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacology, Biochemistry and Behavior*, **67**, 71–81.
30. Gire, J. T. & Eissenberg, T. (2000) Placebo control study of acute smokeless tobacco abstinence in young adult men. *Psychology of Addictive Behaviors*, **14**, 356–366.
31. Levin, E. D., Behm, F., Carnahan, E., LeClair, R., Shipley, R. & Rose, J. E. (1993) Clinical trials using ascorbic acid aerosol to aid smoking cessation. *Drug and Alcohol Dependence*, **33**, 211–223.
32. Fagerström, K. O. (1978) Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors*, **3**, 235–241.
33. Federal Trade Commission (2000) *'Tar', Nicotine, and Carbon Monoxide of the Smoke of 1294 Varieties of Domestic Cigarettes for the Year 1998*. Washington, DC: Federal Trade Commission.
34. Breland, A. B., Buchhalter, A. R., Evans, S. E. & Eissenberg, T. (2002) Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine and Tobacco Research Supplement*, **2**, S131–S140.

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35. Gariti, P., Alterman, A. I., Ehrman, R., Mulvaney, F. D. & O'Brien, C. P. (2002) Detecting smoking following smoking cessation treatment. *Drug and Alcohol Dependence*, **65**, 191–196.
36. Murray, R. P., Connett, J. E., Istvan, J. A., Nides, M. A. & Rempel-Rossum, S. (2002) Relations of cotinine and carbon monoxide to self-reported smoking in a cohort of smokers and ex-smokers followed over 5 years. *Nicotine and Tobacco Research*, **4**, 287–294.
37. Pickworth, W. B., Bunker, E. B. & Henningfield, J. E. (1994) Transdermal nicotine: reduction of smoking with minimal abuse liability. *Psychopharmacology*, **115**, 9–14.
38. McLeod, D., Griffiths, R. R., Bigelow, G. E. & Yingling, J. (1982) An automated version of the digit symbol substitution test (DSST). *Behavior Research Methods and Instrumentation*, **14**, 463–466.
39. Eissenberg, T., Griffiths, R. R. & Stitzer, M. L. (1996) Mecamylamine does not precipitate withdrawal in cigarette smokers. *Psychopharmacology*, **127**, 328–336.
40. Behm, F. M., Schur, C., Levin, E. D., Tashkin, D. P. & Rose, J. E. (1993) Clinical evaluation of a citric acid inhaler for smoking cessation. *Drug and Alcohol Dependence*, **31**, 131–138.
41. Hatsukami, D. K., Huber, M., Callies, A. & Skoog, K. (1993) Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology*, **111**, 449–456.
42. Benowitz, N. L., Zevin, S. & Jacob, P. III (1998) Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *Journal of Pharmacology and Experimental Therapeutics*, **287**, 958–962.
43. Covey, L. S., Sullivan, M. A., Johnston, J. A., Glassman, A. H., Robinson, M. D. & Adams, D. P. (2000) Advances in non-nicotine pharmacotherapy for smoking cessation. *Drugs*, **59**, 17–31.
44. Stitzer, M. L. & Walsh, S. L. (1997) Psychostimulant abuse: the case for combined behavioral and pharmacological treatments. *Pharmacology, Biochemistry and Behavior*, **57**, 457–470.
45. Molyneux, A., Lewis, S., Leivers, U., Anderton, A., Antoniak, M., Brackenridge, A., Nilsson, F., McNeill, A., West, R., Moxham, J. & Britton, J. (2003) Clinical trial comparing nicotine replacement therapy (NRT) plus brief counseling, brief counseling alone, and minimal intervention on smoking cessation in hospital inpatients. *Thorax*, **58**, 484–488.
46. Butschky, M. F., Bailey, D., Henningfield, J. E. & Pickworth, W. B. (1995) Smoking without nicotine delivery decreases withdrawal in 12-hr abstinent smokers. *Pharmacology, Biochemistry and Behavior*, **50**, 91–96.
47. Carter, B. L. & Tiffany, S. T. (1999) Meta-analysis of cue-reactivity in addiction research. *Addiction*, **94**, 327–340.
48. Dols, M., van den Hout, M., Kindt, M. & Willems, B. (2002) The urge to smoke depends on the expectation of smoking. *Addiction*, **97**, 87–93.
49. Sayette, M. A., Martin, C. A., Wertz, J. M., Shiffman, S. & Perrott, M. A. (2001) A multi-dimensional analysis of cue-elicited craving in heavy smokers and tobacco chippers. *Addiction*, **96**, 1419–1432.
50. Tiffany, S. T. (1990) A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychological Review*, **97**, 147–168.
51. Fowler, J. S., Volkow, N. D., Wang, G. J., Pappas, N., Logan, J., MacGregor, R., Alexoff, D., Wolf, A. P., Warner, D., Cilento, R. & Zezulkova, I. (1998) Neuropharmacological actions of cigarette smoke: Brain monoamine oxidase b (mao b) inhibition. *Journal of Addictive Diseases*, **17**, 23–35.
52. Bohadana, A., Nilsson, F., Rasmussen, T. & Martinet, Y. (2003) Gender differences in quit rates following smoking cessation with combination nicotine therapy: influence of baseline smoking behavior. *Nicotine and Tobacco Research*, **5**, 111–116.
53. Wetter, D. W., Kenford, S. L., Smith, S. S., Fiore, M. C., Jorenby, D. E. & Baker, T. B. (1999) Gender differences in smoking cessation. *Journal of Consulting and Clinical Psychology*, **67**, 555–562.
54. Wetter, D. W., Fiore, M. C., Young, T. B., McClure, J. B. & deMoor, C. A. (1999) Gender differences in response to nicotine replacement therapy: objective and subjective indexes of tobacco withdrawal. *Experimental and Clinical Psychopharmacology*, **7**, 135–144.

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Global Perspectives

Nicotine and Carcinogen Exposure with Smoking of Progressively Reduced Nicotine Content Cigarette

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Abstract

Background: **Reducing the nicotine content of cigarettes to make them non-addictive has been widely discussed as a potential strategy for tobacco regulation. A major concern with nicotine reduction is that smokers will compensate for reduced nicotine by smoking more cigarettes and/or smoking more intensively, thereby increasing their exposure to tobacco smoke toxins. This study examined whether gradual reduction in nicotine exposure increases exposure to tobacco smoke toxins.**
Methods: **This 10-week longitudinal study of 20 healthy smokers involved smoking their usual brand followed by different types of research cigarettes with progressively lower nicotine content, each smoked for 1 week. Subjects were followed for 4 weeks after returning to smoking their usual brand (or quitting). Smoking behaviors, chemical biomarkers of tobacco smoke exposure, and cardiovascular effect biomarkers were measured.**
Findings: **Intake of nicotine declined progressively as the nicotine content of cigarettes was reduced, with little evidence of compensation. Cigarette consumption and markers of exposure to carbon monoxide and polycyclic aromatic hydrocarbons, as well as cardiovascular biomarkers remained stable, whereas urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol excretion decreased. Twenty-five percent of participants had spontaneously quit smoking 4 weeks after completing the research cigarette taper.**
Implications: **Our findings with reduced nicotine content cigarettes differ from those of commercial low yields for which compensatory smoking for lower nicotine delivery is substantial. Our data suggest that the degree of nicotine dependence of smokers can be lowered without increasing their exposure to tobacco smoke toxins. Gradual reduction of nicotine content of cigarettes seems to be feasible and should be further evaluated as a national tobacco regulatory strategy.** (Cancer Epidemiol Biomarkers Prev 2007; 16(11):2479–85)

Introduction

That nicotine addiction sustains tobacco use for most smokers is well established (1). Once a person is addicted to nicotine, quitting smoking is difficult, and more than 90% of smokers who try to quit each year fail. Young people do not start to smoke because they are addicted. Rather, they start smoking because of psychosocial and environmental influences, particularly peer influences, psychological factors, and advertising, and to some extent genetic factors (2). Young people generally underestimate the addictiveness of nicotine, and most of them at first intend to smoke for only a few years (3). However, once they begin to smoke, many become addicted to nicotine, and this addiction sustains the self-injurious behavior into adulthood.

It is difficult to prevent the young from experimenting with cigarettes. However, federal regulation of the availability of nicotine in tobacco products might make it possible to avoid the transition from experimental or occasional smoking to addiction. A strategy for tobacco regulation that has been widely discussed is the Benowitz-Henningfield 1994 proposal to reduce the nicotine content of cigarettes to make cigarettes non-addictive (4-6). This proposal argued that if the nicotine content of cigarettes were lowered gradually, smokers would decrease their intake of nicotine (essentially weaning them from the nicotine addiction). This would reduce the level of addiction in smokers, making it easier for them to quit, and would prevent adolescents from becoming addicted. Tengs et al. (7) did a computer simulation of a nationally mandated nicotine reduction policy. This simulation predicted that a progressive decrease in the nicotine content of cigarettes over 6 years would result in a decline in smoking prevalence from 23% to

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5% of the U.S. population, with a cumulative gain of 157 million quality adjusted life-years.

A major concern with a nicotine reduction strategy has been that smokers would compensate for reduced nicotine levels by smoking more cigarettes and/or smoking cigarettes more intensely, therefore increasing their exposure to tobacco smoke toxins. Reduction of nicotine exposure might also result in undesirable withdrawal symptoms and/or mood disturbances; but might, if nicotine intake was to decline, result in a lower degree of dependence and more confidence in the ability to quit smoking. The present research examines these questions among adult, generally heavy smokers.

It is important to understand how reduced nicotine content (RNC) cigarettes studied in this research differ from commercial low-yield cigarettes. The research cigarettes used in the present study contain different amounts of nicotine, although they have similar tar yields (by machine testing) compared with popular normal yield cigarettes. In contrast, commercial low-yield cigarettes contain just as much nicotine per cigarette as do higher yield cigarettes (8, 9). Commercial low-yield cigarettes are low yield as a consequence of engineering characteristics, such as faster rate of burn, more porous paper, the use of reconstituted or expanded tobacco, and the placement of ventilation holes in or above the filter. Because there is plenty of nicotine available in the tobacco of commercial low-yield cigarettes, it is easy for the smoker to alter puff rate and/or smoking intensity and/or to block ventilation holes to increase nicotine intake per cigarette to the desired level (10).

Materials and Methods

Overview of Study Design. This was a 10-week, unblinded study in which smokers smoked their usual brand of cigarette and then five types of research cigarettes. Progressively lower nicotine content cigarettes were smoked, each for 1 week. Smokers were then followed for an additional 4 weeks after returning to smoking cigarettes of their choosing (or quitting). The study was not blinded because we wanted to simulate a real-world regulatory situation in which the nicotine content of cigarettes is progressively decreased with the knowledge of the smoker.

Subjects. Twenty-one healthy smokers were recruited by newspaper advertisements and were paid for participation in the study. Subjects were determined not to be interested in quitting smoking in the next 6 months. One subject withdrew before completion of the study due to an unanticipated need to travel. Subjects who completed the study included 11 men and 9 women with average age of 29 (range, 18-57). Before the study, subjects smoked an average of 20.1 cigarettes per day [range, 8-40; 95% confidence interval (95% CI), 16.4-23.8]; had smoked for an average of 12.4 years (95% CI, 7.9-16.8); had a Fagerstrom Test for Nicotine Dependence (FTND) score averaging 4.3 (95% CI, 3.3-5.2); and had an average baseline plasma cotinine concentration of 198 ng/mL (95% CI, 157-238). Written informed consent was obtained from each subject. The study was approved by the Institutional Review Board at the University of California, San Francisco.

Study Protocol. Subjects were studied in a community clinic. Subjects were asked to come to the clinic weekly, at which time cigarettes were dispensed, blood and urine samples were collected, and a battery of questionnaires was administered. Subjects were instructed to smoke their cigarettes as desired, but not to smoke any other type of cigarette and not to use other forms of tobacco or nicotine medications. Subjects were provided with two more packs per week than they usually smoked and were asked to contact the research staff for additional cigarettes if they thought they would not have enough to last the week. Subjects typically attended the clinic in the late afternoon and early evening. In addition, the plasma nicotine concentration boost from smoking one cigarette was measured. This cigarette was smoked under observation, and plasma nicotine concentrations were measured before and 2 min after smoking the cigarette.

Plasma samples were assayed for concentrations of nicotine and cotinine (the proximate metabolite of nicotine), and blood was assayed for carboxyhemoglobin and for selected cardiovascular biomarkers. The following biomarkers were selected as predictors of coronary heart disease risk and/or markers of inflammation, endothelial function, and platelet activation: white blood cell count, C-reactive protein, fibrinogen, interleukin-6, sICAM, and P-selectin. Urine samples were assayed for concentrations of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a carcinogen itself and metabolite of the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),as well as metabolites of four polycyclic aromatic hydrocarbons (PAH) found in tobacco smoke. NNAL and the PAH metabolites are biomarkers of exposure to common tobacco smoke carcinogens (11).

Questionnaires included smoking behavior over the previous week, Profile of Mood Scale (12), Minnesota Nicotine Withdrawal Scale (13), CESD Depression Scale (14), and a cigarette acceptance questionnaire (15). The cigarette acceptance questionnaire uses items with 7-point ratings that cluster into seven scales: satisfaction, similarity to usual brand, psychological reward, aversion, respiratory sensations, craving, and perceived strength. On entry into the study, at the end of the nicotine reduction phase and at the end of the study, subjects were also administered the FTND (16) and a self-efficacy questionnaire (17). The self-efficacy questionnaire is a 14-item instrument that asks about the confidence of smokers in their ability to resist smoking in various high-risk situations (17). Higher self-efficacy is associated with a higher probability of quitting smoking and lower risk of relapse after quitting.

Cigarettes. The RNC cigarettes were manufactured by Philip Morris Tobacco Company by blending nicotine-free tobacco with tobacco containing the usual amounts of nicotine. The paper and filters and weight of tobacco in the research cigarettes were similar to that of a Marlboro cigarette. The target nicotine content per cigarette were 12, 8, 4, 2 and 1 mg to allow for a 50% reduction in nicotine dose at each step between 8 and 1 mg. These five levels were selected so that at the end of tapering (week 6), the maximum nicotine intake could be expected to be 0.2 mg per cigarette or less, based on bioavailability calculations that have been described

previously (4). This level of nicotine availability represents an estimate of the threshold level of nicotine to maintain nicotine addiction. The characteristics of the research nicotine cigarettes, as well as the subjects' usual brand of cigarettes, are presented in Table 1. Machine testing of cigarettes using standard U.S. Federal Trade Commission procedures were done by the U.S. Centers for Disease Control and Prevention.

Analytical Chemistry. Plasma nicotine and cotinine were measured by gas chromatography with nitrogen-phosphorous detection modified for simultaneous determination of nicotine and cotinine using a capillary column (18, 19). Urine concentrations of NNAL (free plus conjugated) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described previously (20), with the following modifications. A liquid-liquid extraction procedure was used instead of solid-phase extraction, and the HPLC separation was carried on a Phenomenex Synergi Polar-RP column, 2 mm ID × 250 mm length. Polycyclic aromatic hydrocarbon metabolites were measured in urine by LC-MS/MS (21). Cardiovascular biomarkers were assayed by enzyme immunoassay using commercial kits.

Statistical Analysis. Because measurements for each individual were correlated over time, a repeated measures model was constructed for each of the major variables. A mixed model regression analysis was done using PROC MIXED in SAS (version 9.1). The primary outcomes were changes from baseline to the end of tapering and to the end of follow-up, so data from weeks 1, 6, and 10 were included in the analyses. Means and 95% CIs were computed at each of the three time points. Percent differences in mean values were computed for each pair of time points, with P values and 95% CIs for the differences constructed using the Tukey-Kramer adjustment for multiple comparisons. Variable values for total NNAL, polycyclic aromatic hydrocarbon metabolites, and several of the cardiovascular biomarkers were log-transformed to achieve approximate normality, and the analyses were done on the natural logarithm of the values. Geometric means and corresponding percent differences are reported for log-transformed variables. All data for the 20 participants who completed the study were included in the primary analysis. Because several subjects had stopped smoking at week 6 (n = 4) and week 10 (n = 5), the analyses were repeated omitting those subjects. Having stopped smoking was defined biochemically as having a plasma cotinine concentration of <10 ng/mL.

Results

Cigarette Consumption. Average cigarette consumption increased slightly in weeks 2 to 5 and decreased slightly in week 6 compared with baseline smoking of the usual brand, but at the end of tapering, the change was not statistically significant (Fig. 1, Table 2). In a model that included all 10 weeks of data with the Tukey-Kramer adjustment for multiple comparisons, there were no significant differences in weeks 1 to 5, but cigarette consumption was significantly higher on week 5 compared with week 6. Cigarettes smoked per day were significantly lower at the end of the 4 weeks follow-up period compared with baseline or the end of tapering.

Biochemical Exposures. Plasma cotinine concentrations were similar while smoking usual brand and 12 mg RNC cigarettes, and then cotinine levels progressively decreased with progressive nicotine content reduction (Fig. 2, Table 2). During follow-up, cotinine levels increased significantly compared with week 6, but still remained significantly below baseline at week 10. Plasma nicotine followed similar trajectories over time. The boost in plasma nicotine after smoking a single cigarette decreased over the weeks of tapering (not measured at week 10). Blood carboxyhemoglobin did not significantly change when smoking RNCs, but decreased significantly between weeks 6 and 10 (Fig. 3). Urine NNAL was significantly reduced at week 6 compared with baseline and reduced at week 10 compared with both baseline and week 6. No significant temporal changes between baseline and the end of tapering were observed in urinary excretion of various polycyclic aromatic hydrocarbon metabolites. However, at week 10, urinary excretion of 2-naphthol and 2-hydroxyfluorene were significantly lower compared with week 6.

Cardiovascular Measurements and Biomarkers. Body weight increased significantly by an average of 0.9 kg comparing baseline and week 6, but these changes lessened and became nonsignificant by week 10 (Table 3).

Table 1. Characteristics of research cigarettes

	Usual brand	Research cigarettes nominal nicotine content				
		12 mg	8 mg	4 mg	2 mg	1 mg
Measured nicotine content (mg)	NM	10.1	7.4	3.5	1.5	0.6
Tobacco weight (mg)	NM	624	619	620	618	614
FTC method						
Nicotine (mg)	1.0 (0.9-1.2)*	0.8	0.6	0.3	0.2	0.1
Tar (mg)	12.2 (10.8-13.7)*	10.9	10.9	7.8	9.2	10.2
Carbon monoxide (mg)	12.6 (11.7-13.5)	11.3	12.0	10.8	12.0	10.7
NNK (ng)	NM	63	67	64	57	56
Pyrene (ng)	NM	41	38	51	43	34
Naphthalene (ng)	NM	662	560	470	466	553
Phenanthrene (ng)	NM	120	120	106	113	132
Fluorene (ng)	NM	145	143	149	153	129

Abbreviation: NM, not measured.
*Mean (95% CI).

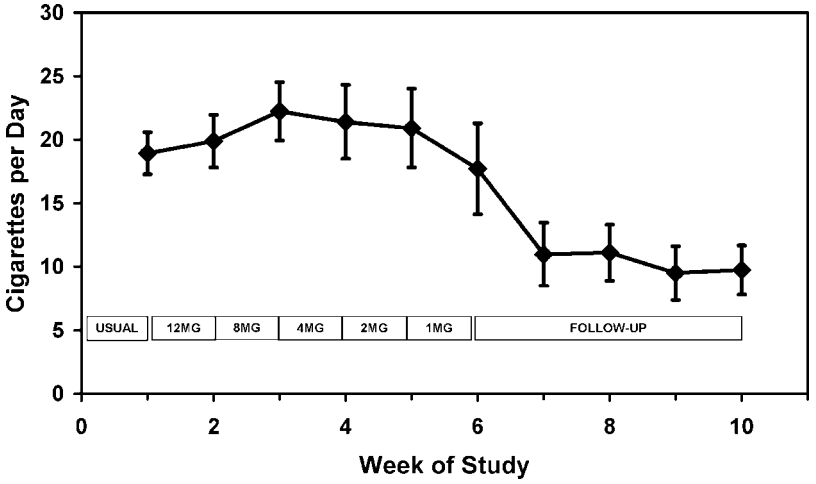


Figure 1. Cigarette consumption over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10). *Points,* mean values for 20 subjects; *bars,* SE.

No significant changes between baseline and week 6 were observed in blood pressure, heart rate, white blood cell count, hemoglobin, HDL cholesterol, C-reactive protein, fibrinogen, sICAM, IL-6, or P-selectin.

Subjective Responses. No significant changes were observed in the Profile of Mood Scale scores or the CESD depression rating. The withdrawal scores for irritability and increased eating were significantly higher at week 6 compared with baseline [week 6 to week 1, 1.7 (95% CI, 0.4-3.0) and 2.3 (95% CI, 0.6-4.0)]. Self-reported eating remained higher at week 10 [2.2 (0.7-3.7)] compared with baseline. The cigarette acceptance questionnaire indicated that subjects found the reduced nicotine cigarettes to be less strong, less flavorful, of generally lower quality and less satisfying compared with the usual brand. There was, however, no significant increase in cigarette craving while smoking RNC cigarettes.

Quitting/Self-Efficacy during Follow-up. Although subjects did not intend to quit smoking on entry into the study, five subjects did quit smoking (confirmed by plasma cotinine levels of <10 ng/mL) after completing the RNC taper. The self-efficacy rating (inquiring as to how confident one is that he or she can quit) was significantly higher at weeks 6 and 10 compared with baseline [week 6 to week 1, 1.3 (95% CI, 0.3-2.3); week 10 to week 1, 2.3 (95% CI, 0.8-3.8)]. The FTND decreased from 4.3 (3.3-5.2) at baseline to 3.6 (2.4-4.7) at week 6 ($P = 0.09$) and 2.5 (1.3-3.6) at week 10 ($P < 0.001$). Analysis of the cigarette consumption, biochemical exposure, and cardiovascular data in only those subjects who continued to smoke at weeks 6 and 10 (that is, excluding data from subjects with cotinine levels <10 ng/mL) resulted in small effects on mean values and had effects on statistical significance of a few of the various comparisons. These included the comparison of cigarette consumption between weeks 6 and 10; weight gain between weeks 1 and 6; decrease in NNAL between weeks 1 and 6; and decreases in PAH metabolite excretion, all of which were no longer significant.

Table 2. Smoking behavior and chemical exposures while smoking reduced nicotine cigarettes

	Week 1, mean (95% CI)	Week 6, mean (95% CI)	Week 10, mean (95% CI)	% difference week 6 versus week 1, mean (95% CI)	% difference week 10 versus week 1, mean (95% CI)	% difference week 10 versus week 6, mean (95% CI)
Cigarettes per day	18.9 (15.5-22.3)	17.7 (10.4-25.0)	10.1 (6.2-14.0)	−6 (−37-24)	**−47 (−63 to −30)**	**−43 (−80 to −6)**
Pre-smoking plasma nicotine (ng/mL)	13.0 (10.2-15.7)	3.8 (1.6-6.1)	8.3 (4.1-12.4)	**−70 (−101 to −40)**	−36 (−76-4)	**115 (28-202)**
Nicotine boost (ng/mL)	8.2 (5.4-11.1)	1.0 (0.6-1.4)	NM	**−88 (−122 to −54)**	NM	NM
Blood COHB (%)	3.2 (2.6-3.9)	3.6 (2.3-4.9)	2.1 (1.2-3.0)	11 (−22-45)	**−35 (−64 to −7)**	**−42 (−66 to −18)**
Plasma cotinine (ng/mL)	194 (152-235)	62 (28-96)	109 (64-153)	**−68 (−93 to −43)**	**−44 (−63 to −25)**	75 (9-142)
Total NNAL* (pmol/mg creat)	1.17 (0.79-1.73)	0.92 (0.58-1.44)	0.53 (0.29-0.95)	**−22 (−38-0)**	**−55 (−71 to −32)**	**−43 (−60 to −17)**
1-OH-pyrene* (pmol/mg creat)	0.97 (0.62-1.33)	1.06 (0.80-1.50)	0.89 (0.62-1.33)	18 (−12-57)	−6 (−44-56)	−20 (−46-16)
2-Naphthol* (pmol/mg creat)	77.9 (62.0-97.4)	80.5 (62.0-104.4)	57.5 (43.4-77.0)	3 (−23-37)	**−26 (−43 to −5)**	**−28 (−48 to −1)**
Sum of hydroxyphenanthrene isomers* (pmol/mg creat)	2.4 (1.8-3.4)	2.6 (1.9-3.4)	2.6 (1.7-3.8)	6 (−23-45)	5 (−25-47)	−1 (−24-30)
2-Hydroxyfluorene* (pmol/mg creat)	6.9 (5.1-9.3)	7.8 (5.8-10.6)	4.7 (2.9-7.7)	13 (−15-50)	−32 (−58-11)	**−39 (−60 to −9)**

NOTE: Week 1 is while smoking usual brand. Week 6 is while smoking the lowest RNC cigarette (1 mg). Week 10 is 4 weeks after the end of RNC smoking. Values in bold indicate significant differences ($P < 0.05$).
*Geometric means; NM = not measured; creat = creatinine.

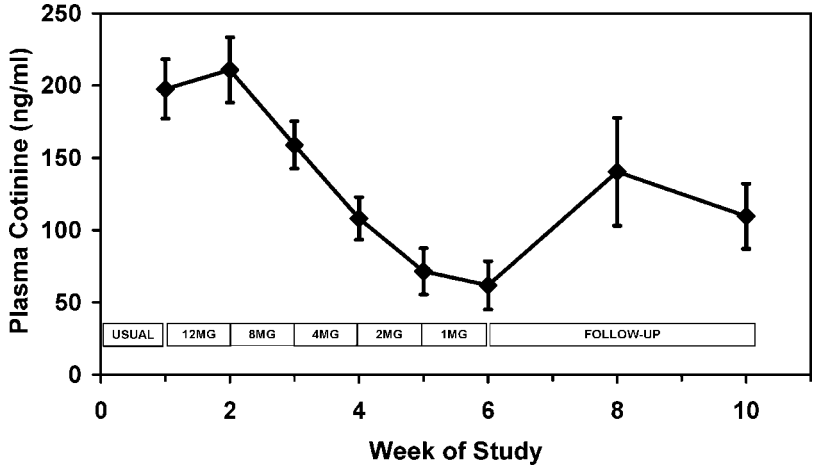


Figure 2. Plasma cotinine concentration over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10).

Excluding quitters, the FTND decreased from 4.9 (4.1-5.7) at baseline to 4.4 (3.1-5.6) at week 6 (not significant) and 3.4 (2.1-4.6) at week 10 ($P < 0.01$).

Discussion

We present novel findings on the smoking behavioral response, biochemical exposures, cardiovascular risk biomarkers and acceptability during a progressive reduction of the nicotine content of cigarettes. We found that progressive reduction of the nicotine content of cigarettes resulted in a progressive reduction in nicotine intake as measured by nicotine and cotinine levels. We found little evidence of compensation, as shown by stable levels of cigarette consumption and stable levels of the tobacco smoke biomarkers carbon monoxide and PAH metabolites.

Urine NNAL excretion was significantly decreased (about 20%) after nicotine reduction. NNAL is a metabolite of the tobacco-specific nitrosamine NNK, which is formed from nicotine in the presence of nitrates in tobacco, primarily during the curing process (22). As the nicotine content of cigarettes declines, one would expect that levels of NNK would decline as well. Comparing the 12- and 1-mg RNC machine deliveries, there was an 11% decrease in NNK yield. We did not have data on NNK yields for the usual brands of cigarettes, so we could not compare the machine yields of NNK for cigarettes smoked at weeks 1 and 6 to see if the change in yield corresponded to the actual change in NNAL excretion over the same period of time. However, it is most likely that lower NNK yields explain the observed decrease in NNAL excretion in our subjects while smoking RNC cigarettes.

Cardiovascular biomarkers showed no evidence of a more adverse risk profile when subjects smoked RNC. After stopping smoking of low nicotine content cigarettes, consumption of the subject's usual brand of cigarette dropped below baseline levels, and plasma cotinine remained lower than baseline for at least 4 weeks, suggesting that the level of nicotine dependence had been reduced. Nicotine withdrawal scores for irritability and eating increased over the course of tapering, consistent with the reduction in nicotine intake. The relatively mild intensity of these symptoms is consistent with the gradual reduction in nicotine intake. Also supporting a reduced level of nicotine dependence was the significant decline in the FTND score, observed both in the analysis of all subjects and after excluding subjects who had quit smoking.

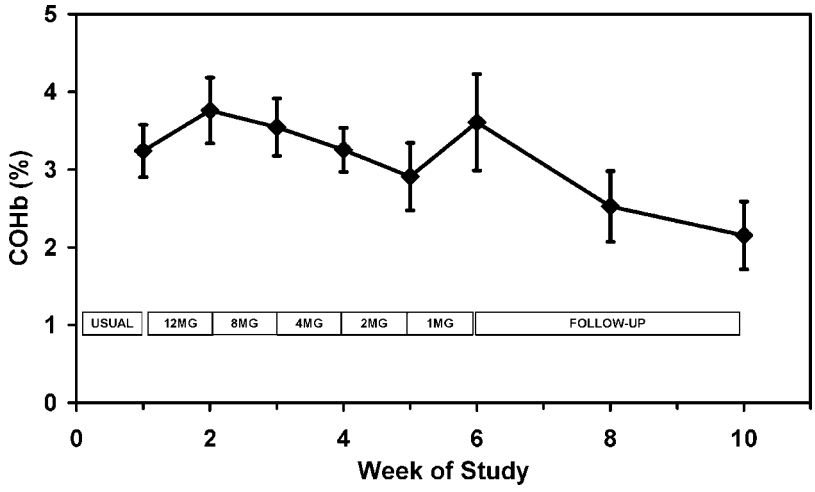


Figure 3. Blood carboxyhemoglobin (COHB) concentration over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10).

Table 3. Cardiovascular biomarkers while smoking reduced nicotine cigarettes

	Week 1, mean (95% CI)	Week 6, mean (95% CI)	Week 10, mean (95% CI)	% difference week 6 versus week 1, mean (95% CI)	% difference week 10 versus week 1, mean (95% CI)	% difference week 10 versus week 6, mean (95% CI)
Body weight (kg)	71.4 (65.8-77.1)	72.3 (66.7-78.0)	72.0 (66.4-77.7)	**1 (0-2)**	1 (0-2)	0 (−1-1)
Systolic blood pressure (mm Hg)	122 (116-129)	124 (116-132)	123 (117-130)	1 (−4-7)	1 (−5-7)	−1 (−8-7)
Diastolic blood pressure (mm Hg)	79.0 (73.4-84.6)	76.6 (71.9-81.2)	78.8 (74.9-82.8)	−3 (−10-4)	0 (−9-8)	3 (−3-9)
Heart rate	76.0 (71.2-80.7)	72.9 (67.2-78.5)	79.8 (73.7-86.0)	−4 (−12-3)	5 (−6-16)	10 (−3-22)
WBC count (1,000)	7.3 (6.5-8.2)	7.7 (6.9-8.4)	7.6 (6.5-8.8)	4 (−6-15)	4 (−11-20)	0 (−15-15)
Hemoglobin (%)	14.7 (14.1-15.2)	14.4 (13.8-14.9)	14.4 (13.9-14.9)	−2 (−4-0)	−2 (−4-0)	0 (−2-2)
HDL cholesterol (ng/dL)	49.9 (40.9-58.8)	51.2 (43.3-59.0)	51.5 (42.3-60.7)	3 (−7-12)	3 (−6-13)	1 (−9-10)
C-reactive protein* (mcg/mL)	1.00 (0.59-1.68)	1.32 (0.72-2.42)	1.25 (0.67-2.35)	33 (−26-136)	26 (−36-148)	−5 (−57-107)
sICAM* (ng/mL)	241 (219-265)	253 (219-293)	229 (207-253)	5 (−6-18)	−5 (−12-2)	−10 (−18-0)
Fibrinogen *,† (mg/dL)	247 (223−273)	263 (232-298)	259 (243-275)	7 (−4-18)	5 (−9-21)	−2 (−16-16)
IL-6* (pg/mL)	1.02 (0.76-1.37)	0.97 (0.71-1.31)	1.16 (0.77-1.74)	−5 (−26-22)	14 (−28-80)	20 (−19-77)
P-selectin* (ng/mL)	40 (35-45)	41 (35-48)	40 (35-46)	3 (−6-13)	1 (−5-7)	−3 (−14-10)

NOTE: Week 1 is while smoking usual brand. Week 6 is while smoking the lowest RNC cigarette (1 mg). Week 10 is 4 weeks after the end of RNC smoking. Values in bold indicate significant differences ($P < 0.05$).

*Geometric means.

†$n = 11$.

The results of our study are quite different from those reported for commercial low-yield cigarette-switching studies. Smokers who switch from higher to lower yield commercial cigarettes exhibit a high degree of compensation, with relatively little or no reduction in nicotine intake or exposure to other tobacco smoke toxins (10, 20). The key difference between commercial low-yield cigarettes and the RNC cigarettes described in our study is that in the RNC cigarettes, the absolute content of nicotine in the tobacco is reduced. In contrast, commercial low-yield cigarette tobacco contains just as much nicotine as does higher yield cigarette tobacco, and compensation can easily be achieved by taking bigger and faster puffs and/or by blocking ventilation holes (8-10). These behaviors markedly reduce the extent of ventilation so that nicotine can easily be extracted from the cigarettes. In contrast, it is virtually impossible to fully compensate for RNC in cigarettes because nicotine is just not present in the tobacco in adequate amounts.

That most smokers compensate little or not at all when the nicotine content of cigarette tobacco is reduced in the absence of changes in tar and other characteristics of the cigarette was observed in another study of smoking single cigarettes with variable nicotine content conducted in our laboratory (23), as well in a study by Rose et al. (24). If the smoker finds it is very difficult to extract nicotine from a cigarette, he or she may give up trying and accept lower doses of nicotine, gradually reducing their level of dependence. Tar and other combustion products in cigarette smoke also contribute to the sensory characteristics of inhaled smoke. Tar-related sensory characteristics of the cigarette smoke do provide some reinforcement and may lessen withdrawal symptoms compared with the combined reduction of tar and nicotine deliveries (25). Regardless of the mechanism, our study suggests that smokers can be safely switched to RNC cigarettes without increasing their exposure to toxic tobacco smoke chemicals and without any apparent adverse cardiovascular effects.

A reduction in nicotine intake while smoking reduced content cigarettes might be expected to be associated with the emergence of nicotine withdrawal symptoms, including related mood disturbances. Our subjects did report significantly more irritability and increased eating at week 6 compared with baseline, consistent with nicotine withdrawal. Body weight increased an average of 0.9 kg at week 6, which is also a feature of nicotine withdrawal. There was no increase in cigarette craving, and no significant changes in mood or depression scores were recorded. The relatively mild nicotine withdrawal symptoms reported most likely are due to the gradual reduction of nicotine exposure over several weeks. Although subjects did not find the research cigarettes to be as strong, flavorful, or as satisfying as the usual brand, in general subjects found the cigarettes to be acceptable. Although compliance with smoking only the research cigarette and not other brands during the tapering phase could not be verified, the observed decline in nicotine exposure indicated that compliance was substantial.

Our study had some limitations. The number of subjects was relatively small, and there was a relatively rapid lowering of the nicotine content of their cigarettes. It is possible that a longer period of smoking at each nicotine reduction stage would have resulted in a different degree of compensation for lower nicotine availability. The study was not blinded, although this would also be the case if low nicotine content cigarettes were mandated as part of a national strategy to reduce the addictiveness of cigarettes. Compliance with smoking only the research nicotine cigarettes could not be tested, but the observation of a steady reduction of nicotine exposure, as evidenced by the decline in blood cotinine levels, argues for compliance—a lack of compliance would be expected to have diminished such a treatment effect. Finally, our subjects were relatively young, generally middle class and well educated and may not be typical of highly addicted smokers in developed countries.

The implications of our findings are twofold. First, our data suggest that gradual nicotine reduction of cigarettes is safe and is a potentially feasible regulatory strategy. As the number of participants in our study is small and the

tapering rapid, further research on more gradual reduction and longer term exposure to reduce nicotine cigarettes is certainly warranted. Teng et al. who modeled the effects of a reduced nicotine policy on public health as mentioned previously, concluded that ''Policy makers would be hard-pressed to identify another domestic public health intervention short of historical sanitation efforts, that has offered this magnitude of benefit to the population''(7).

Although not a primary purpose of this research, our study provides evidence that reduction of the nicotine content of cigarettes reduces the level of nicotine dependence and makes it easier for smokers to quit smoking. We observed that after gradual reduction of nicotine intake and upon returning to smoking their usual brands, smokers smoked fewer cigarettes per day and took in less nicotine per day compared with their usual level before the reduced nicotine cigarette intervention. Furthermore, their FTND score decreased significantly from baseline to when subjects had returned to smoking their usual brand. In support of this trend, both at the end of tapering and also at week 10 after resuming their usual cigarettes, self-efficacy (measured by a questionnaire assessing confidence in being able to quit smoking) was significantly greater compared with baseline. Several of our subjects quit smoking spontaneously, although they had not intended to do so when entering the study. It is likely that this occurred because the level of physical dependence was reduced. We view this as an intriguing finding, but because the number of subjects in the study was small and the study was not controlled, no definitive conclusion about quitting can be made. However, if the level of dependence can be reduced as suggested, one might expect that smoking cessation would be easier. Thus, gradual reduction of nicotine intake as a regulatory strategy might make it easier for smokers to quit smoking. Our study did not address the question of whether reduced nicotine cigarettes results in reduced addiction potential among adolescent experimental smokers, an issue that must be addressed in future research.

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References

1. Benowitz NL. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. N Engl J Med 1988;319:1318–30.
2. Turner L, Mermelstein R, Flay B. Individual and contextual influences on adolescent smoking. Ann N Y Acad Sci 2004;1021:175–97.
3. Preventing tobacco use among young people. A report of the Surgeon General. Executive summary. MMWR Recomm Rep 1994; 43:1–10.
4. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. N Engl J Med 1994;331:123–5.
5. Henningfield JE, Benowitz NL, Slade J, Houston TP, Davis RM, Deitchman SD. Reducing the addictiveness of cigarettes. Tob Control 1998;7:281–93.
6. Gray N, Henningfield JE, Benowitz NL, et al. Toward a comprehensive long term nicotine policy. Tob Control 2005;14:161–5.
7. Tengs TO, Ahmad S, Savage JM, Moore R, Gage E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts. Prev Med 2005;40:170–80.
8. Benowitz NL, Hall SM, Herning RI, Jacob P III, Jones RT, Osman AL. Smokers of low yield cigarettes do not consume less nicotine. N Engl J Med 1983;309:139–42.
9. Kozlowski LT, Mehta NY, Sweeney CT, et al. Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United States. Tob Control 1998;7:369–75.
10. Benowitz NL. Compensatory smoking of low yield cigarettes. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. National Cancer Institute Smoking and Tobacco Control Monograph No. 13. Bethesda (MD): NIH, National Cancer Institute; NIH Publication No. 02–5074, October, 2001:39–64.
11. Hecht SS. Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. Carcinogenesis 2002;23:907–22.
12. McNair DM, Lorr M, Doppleman LF. Profile of mood states. San Diego: Educational and Industrial Testing Service; 1971.
13. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986;43:289–94.
14. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1: 385–401.
15. Rose JE, Westman EC, Behm FM, Johnson MP, Goldberg JS. Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. Pharmacol Biochem Behav 1999;62:165–72.
16. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991;86:1119–27.
17. Baer JS, Lichtenstein E. Classification and prediction of smoking relapse episodes: an exploration of individual differences. J Consult Clin Psychol 1988;56:104–10.
18. Jacob P III, Wilson M, Benowitz NL. Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. J Chromatogr 1981;222:61–70.
19. Jacob P III, Yu L, Wilson M, Benowitz NL. Selected ion monitoring method for determination of nicotine, cotinine and deuterium-labeled analogs: absence of an isotope effect in the clearance of (*S*)-nicotine-3′,3′-d2 in humans. Biol Mass Spectrom 1991;20:247–52.
20. Benowitz NL, Jacob P III, Bernert JT, et al. Carcinogen exposure during short-term switching from regular to ''light'' cigarettes. Cancer Epidemiol Biomarkers Prev 2005;14:1376–83.
21. Jacob P III, Wilson M, Benowitz NL. Determination of phenolic metabolites of polycyclic aromatic hydrocarbons in human urine as their pentafluorobenzyl ether derivatives using liquid chromatography-tandem mass spectrometry. Anal Chem 2007;79:587–98.
22. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. Chem Res Toxicol 1998;11:559–603.
23. Benowitz NL, Jacob P III, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther 2006;80:703–14.
24. Rose J, Behm F. Effects of low nicotine content cigarettes on smoke intake. Nicotine Tob Res 2004;6:309–19.
25. Rose JE. Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology (Berl) 2006;184:274–85.