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

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

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.

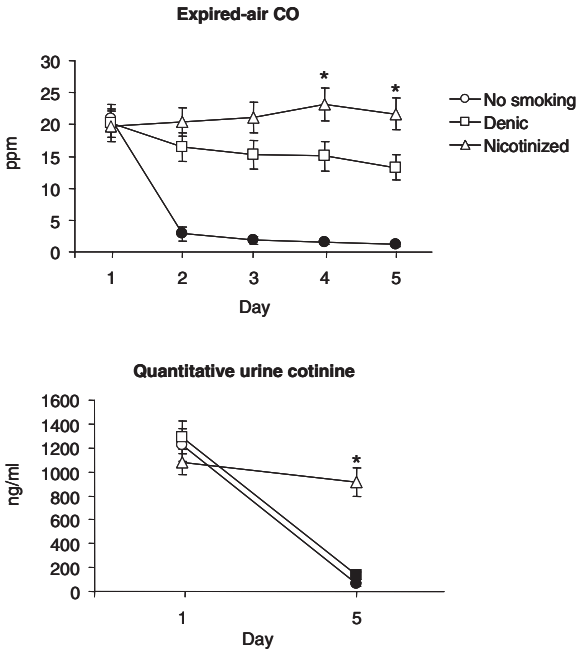

Figure 1 Averaged data (± 1 SEM) from 31 subjects for expired air carbon monoxide (top) and quantitative urine cotinine (bottom) during three 5-day conditions in which they smoked nicotinized (triangles), denicotinized (squares) or no cigarettes (circles). Filled symbols represent significant differences 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

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

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.

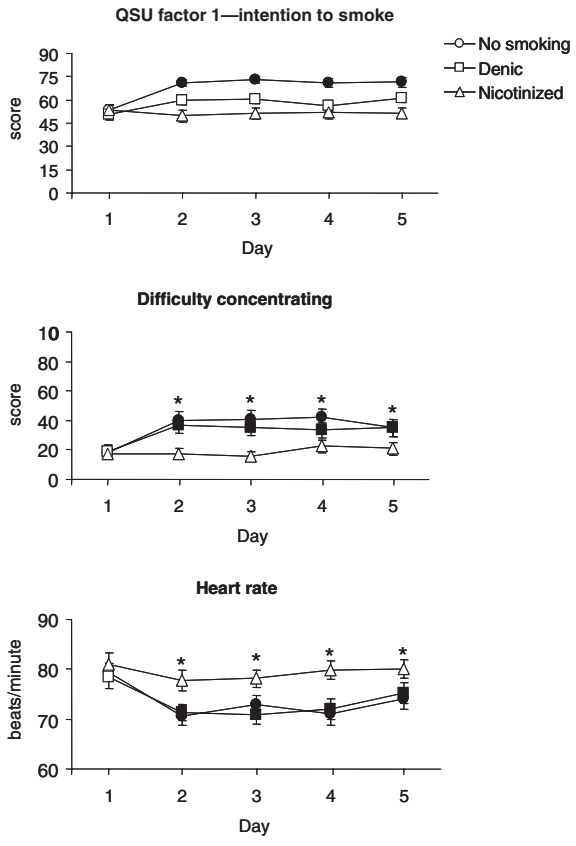

Figure 2 Averaged data (± 1 SEM) from 31 subjects on factor 1 of the Tiffany–Drobes Questionnaire of Smoking Urges [11] (top), the visual analog scale item assessing difficulty concentrating (middle) and heart rate (bottom). In all other respects, the figure is identical to Fig. 1

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

(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,

'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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