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Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers

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Abstract

Background—Non-combustible potential reduced exposure products (PREPs; eg, Star Scientific's Ariva; a variety of other smokeless tobacco products) are marketed to reduce the harm associated with smoking. This marketing occurs despite an absence of objective data concerning the toxicant exposure and effects of these PREPs. Methods used to examine combustible PREPs were adapted to assess the acute effects of non-combustible PREPs for smokers.

Methods—28 overnight abstinent cigarette smokers (17 men, 14 non-white) each completed seven, Latin-squared ordered, approximately 2.5 h laboratory sessions that differed by product administered: Ariva, Marlboro Snus (Philip Morris, USA), Camel Snus (RJ Reynolds, Winston-Salem, North Carolina, USA), Commit nicotine lozenge (GlaxoSmithKline; 2 mg), own brand cigarettes, Quest cigarettes (Vector Tobacco; delivers very low levels of nicotine) and sham smoking (ie, puffing on an unlit cigarette). In each session, the product was administered twice (separated by 60 min), and plasma nicotine levels, expired air CO and subjective effects were assessed regularly.

Results—Non-combustible products delivered less nicotine than own brand cigarettes, did not expose smokers to CO and failed to suppress tobacco abstinence symptoms as effectively as combustible products.

Conclusions—While decreased toxicant exposure is a potential indicator of harm reduction potential, a failure to suppress abstinence symptoms suggests that currently marketed non-combustible PREPs may not be a viable harm reduction strategy for US smokers. This study demonstrates how clinical laboratory methods can be used to evaluate the short-term effects of non-combustible PREPs for smokers.

Chronic inhalation of tobacco cigarette smoke toxicants such as carbon monoxide (CO) and carcinogens causes disease and death.¹² Quitting smoking is the most effective way to avoid smoking-related diseases³⁴; however, this is challenging because many smokers are nicotine dependent.⁵ When these dependent smokers abstain, aversive abstinence symptoms (eg, anxiety, restlessness⁶) increase the likelihood of relapse.⁷⁸ Because relapse rates are high,⁹¹⁰ there is a growing interest in harm reduction approaches to preventing smoking-related diseases and death (eg, Stratton *et al*¹¹).

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For cigarette smokers, tobacco harm reduction may involve reducing exposure to cigarette smoke toxicants, perhaps with potential reduced exposure products (PREPs¹²). Currently marketed PREPs for smokers include cigarette-like combustible tobacco products, non-combustible tobacco products (ie, smokeless tobacco) and non-combustible, non-tobacco products that deliver pharmaceutically pure nicotine (eg, nicotine patch or gum). While PREPs are often marketed to reduce toxicant exposure, decades of experience with the so-called low-yield cigarettes, which decrease neither toxicant exposure nor smoking-related diseases, highlights the importance of measuring smokers' PREP-associated toxicant exposure.¹¹¹³ Abstinence symptom suppression is also relevant: if a PREP cannot suppress aversive abstinence symptoms, smokers who try the PREP may relapse to cigarette use as they often do during a quit attempt.¹⁴¹⁵ Thus, tobacco toxicant exposure and abstinence symptom suppression are key PREP evaluation outcomes.

A growing body of literature demonstrates, at least for combustible PREPs, that the clinical laboratory methods are valuable for PREP evaluation. Clinical laboratory outcomes include nicotine and CO exposure, cardiovascular response and tobacco abstinence symptom suppression (eg, Breland and colleagues^{16–18}). However, there have been no published clinical laboratory evaluations of the toxicant exposure and abstinence symptom suppressing effects of non-combustible PREPs in cigarette smokers. The present study was designed to explore the extent to which controlled clinical laboratory methods can be used to investigate the acute effects of non-combustible PREPs. We hypothesised that, relative to own brand cigarettes, non-combustible PREPs would expose users to lower levels of nicotine and CO, and suppress tobacco abstinence symptoms less effectively.

METHOD

Participants

Forty-eight participants provided informed consent and attended at least one session in this institutional review board-approved study. Seven of these participants were discontinued because venous access could not be maintained (n=4), a previously undisclosed chronic health condition was revealed during the first session (n=1), non-compliance with protocol occurred during session (n=1) or study recruitment goals had been reached (n=1). In addition, eight participants withdrew (ie, did not attend scheduled sessions; failed to respond to subsequent contact attempts): inspection of demographic characteristics and other information did not suggest a factor predictive of withdrawal from the protocol. Thirty-three individuals completed the study, and, through administrative error, five duplicated already-completed Latin square condition orders. Data from these five individuals were excluded from further analyses.

The 28 study participants (17 men, 14 non-white) were included if they were healthy, aged 18–55 years (mean 32.2 years (SD 10.1)), provided an afternoon screening expired air CO level of at least 15 ppm (mean 25.7 ppm (SD 10.7)), had a urine cotinine analysis result of at least 4 on a seven-point (0–6; NicAlert, Nymox Corp., Maywood, New Jersey, USA¹⁹;) scale (mean 6 (SD 0)), and reported smoking at least 15 cigarettes/ day (mean 22.4 (SD 7.5)) for at least 1 year (mean 10.8 years (SD 9.9)). Exclusion criteria consisted of history of chronic health problems; current pregnancy or breastfeeding; active menopause; current use of smokeless tobacco; currently attempting to quit smoking; or self-reported use of Marlboro Snus, Camel Snus or Ariva (ie, >1 pack).

Materials

Non-combustible products—Star Scientific Inc.'s Ariva (ARIVA) is a compressed tobacco tablet purported to be low in tobacco-specific nitrosamines (approximate weight 0.2

g). “Mint” was chosen arbitrarily as the flavour for this study. One tablet produces a maximal plasma nicotine concentration of approximately 2.7 ng/ml nicotine.^{20,21}

R.J. Reynolds’s Camel Snus (CS) is a pouch of pasteurised tobacco (approximate weight 0.3 g). “Original” was chosen arbitrarily for this study. CS was first marketed in select US cities in summer 2006, and R.J. Reynolds Tobacco Company provided product at that time (stored at -4°C). In spring 2008, a new version of CS was marketed. Relative to the 2006 version, the 2008 version is packaged differently and weighs more (approximate weight 0.4 g). Because the two CS versions may differ in other ways, this study compared them: 14 participants used the 2006 version and 14 used the 2008 version (obtained through retail outlets). The 2006 CS contains 28.2 mg/g dry weight total nicotine and 6.1 mg/g unprotonated nicotine (nicotine data for the 2008 CS are not yet available).²²

Philip Morris Inc.’s Marlboro Snus (MS) is also a pouch of pasteurised tobacco (approximate weight 0.2 g). “Mild” was chosen arbitrarily for this study. MS contains 12.8 mg/g dry weight total nicotine and 0.35 mg/g unprotonated nicotine.²² MS was obtained through retail outlets.

GlaxoSmithKline’s Commit lozenge (COMMIT) is a pharmaceutical product marketed as a smoking cessation aid. The 2 mg (original flavour) lozenge was chosen for this study (maximal plasma nicotine concentration approximately 4.4 ng/ml²³).

Combustible products—Participants’ self-reported own brand of cigarettes were used in the own brand (OWN) and sham (SHAM; puffing on an unlit cigarette) conditions. According to the Federal Trade Commission method, on average, OWN yielded 1.1 mg nicotine (SD 0.3), 15.5 mg tar (SD 3.3) and 15.2 mg CO (SD 2.8). Vector Tobacco Inc.’s Quest (QUEST) is made from genetically modified low nicotine tobacco (Quest 3, nicotine=0.05 mg, menthol flavour if own brand was menthol).

Procedure

Participants completed seven, approximately 2.5 h sessions that differed by product used: ARIVA, CS, MS, COMMIT, OWN, SHAM, QUEST. Before a session could begin, overnight cigarette abstinence was verified (ie, expired air CO ≤ 10 ppm; see Breland *et al*¹⁶). Then, a catheter was inserted into a forearm vein and the session began (at time 0) with continuous physiological recording. Thirty minutes after session onset (time +30), participants responded to all subjective effect measures, 7 ml of blood was sampled and session-specific product was administered. Participants then responded to subjective measures, and 7 ml blood was sampled at 5, 15, 30 and 45 min post administration. CO was measured 15, 30 and 45 min post administration (reliable CO measurement occurs at least 5 min post smoking²⁴). Sixty minutes after the first product administration (time +90), participants responded to the subjective measures, blood was sampled, product was administered again and the postadministration measurement/sampling schedule was repeated. The catheter was removed, participants were paid for their time and, if necessary, another session scheduled. Payment for completing the study was US\$450.

Administration instructions

Opaque paper was used to mask brand identifiers on OWN, QUEST and SHAM. OWN and QUEST were smoked ad libitum. For SHAM, participants were asked to take 10 puffs approximately 20 s apart (similar to Breland *et al*¹⁶). For the non-combustible products, no brand information was revealed to participants; products were administered in unmarked containers. For CS and MS, participants were asked to place the pouch between their lip and

gum for 15 min. For ARIVA and COMMIT, participants allowed the product to dissolve in their mouth without chewing or swallowing it.

Outcome measures

Physiological measures—Blood samples were centrifuged, plasma stored at -70°C and analysed for nicotine level (as in Breland *et al*¹⁸; limit of quantitation (LOQ)=2.0 ng/ml). Heart rate was measured every 20 s (Model 506, Criticare Systems, Waukesha, Wisconsin, USA). Expired air CO was assessed with a BreathCO monitor (Vitalograph, Lenexa, Kansas, USA).

Subjective measures—The Tiffany–Drobes Questionnaire of Smoking Urges Brief (QSU Brief) consists of 10 smoking-related items and has been empirically validated.²⁵ Participants rated each item on a seven-point scale ranging from 0 (strongly disagree) to 6 (strongly agree). The items form two factors: factor 1 (intention to smoke) and factor 2 (anticipation of relief from withdrawal). In addition, 35 items used a computerised visual analogue scale (VAS) to assess various subjective effects. A word or phrase was centred above a horizontal line anchored on the left with “Not at all” and on the right with “Extremely”. Participants responded by moving a cursor to any point on the line and clicking, producing a vertical mark that could be adjusted if necessary. The score for each scale was the distance of the vertical mark from the left anchor, expressed as a percentage of total line length (see Breland *et al*¹⁶). Tobacco abstinence symptoms⁶ were used to form 11 VAS items, which are presented verbatim in table 1. The 10 VAS items of the Direct Effects of Nicotine Scale are also presented in table 1 (see Evans *et al*²⁶). The 14 VAS items of the Direct Effects of Tobacco scale were adapted from items reported in studies of smoking’s subjective effects (eg, Foulds, Pickworth and colleagues^{27,28}) by substituting the word “product” for “cigarette”. The 14 items were “Was the product satisfying?”, “Was the product pleasant?”, “Did the product taste good?”, “Did the product make you dizzy?”, “Did the product calm you down?”, “Did the product help you concentrate?”, “Did the product make you feel more awake?”, “Did the product reduce your hunger for food?”, “Did the product make you sick?”, “Did the product taste like your own brand of cigarette?”, “Did the product feel like your own brand of cigarette?”, “Did the product feel as harsh as your own brand of cigarette?”, “Did the product feel as mild as your own brand of cigarette?” and “Would you like more of the product RIGHT NOW?” (see Breland *et al*¹⁸).

Data analyses

Heart rate values were averaged for 5 min periods before each product administration or any blood sampling procedures. For plasma nicotine, results below the LOQ were replaced with the LOQ. In the event of missing data, an average of the value before and after the missing value was used (less than 0.07% of data were missing).

Plasma nicotine, subjective and physiological data were analysed initially using a mixed repeated measures analysis of variance where CS version (2006 or 2008) was entered as a between-subjects factor, and the three within-subjects factors were condition (seven levels; ARIVA, CS, MS, COMMIT, OWN, SHAM, QUEST) by use episode (two levels; first, second) by time (number of levels depended upon outcome measure). Of 320 main effects and interactions involving the between-subjects factor (CS version), only 6 were significant ($p<0.05$). Because these few significant results may reflect chance rather than real differences, the between-subjects factor was dropped and analyses were repeated using the within-subject factors only. Huynh–Feldt corrections were used to account for violations of sphericity,²⁹ and Tukey’s Honestly Significant Difference³⁰ was used to explore differences between means ($p<0.05$).

RESULTS

Statistical analyses (main effects and interactions) for all measures are displayed in table 1. Interactions that involve the condition factor are most relevant as they indicate that the results observed differed across products and at least one other factor.

Physiological measures

As table 1 shows, significant condition by use episode and condition by time interactions were observed for plasma nicotine ($F>3.5$; $p<0.05$). As seen in figure 1A, relative to baseline (collapsed across all conditions, 2.4 ng/ml (SEM 0.2)), OWN was associated with significant increases in plasma nicotine level at nearly every time point. The greatest mean increase was observed 5 min after the first (mean 20.7 ng/ml (SEM 2.8)) and second (mean 20.6 ng/ml (SEM 2.0)) product administration. Neither QUEST nor SHAM increased plasma nicotine level reliably. Relative to baseline, mean CS plasma nicotine level was significantly greater 15 min after the second product administration (7.6 ng/ml (SEM 1.1)). At that same time point, mean plasma nicotine level for MS was 2.9 ng/ml (SEM 0.3), for ARIVA was 3.4 ng/ml (SEM 0.3) and for COMMIT was 4.6 ng/ml (SEM 0.5; all NS). Relative to mean plasma nicotine levels in the OWN condition, levels observed in all other conditions were significantly lower 5 and 15 min after the first, and 5, 15 and 30 min after the second product administration.

For heart rate, a significant condition by use episode by time interaction was observed ($p<0.001$). For OWN, mean baseline heart rate was 67.8 bpm (SEM 1.9), which increased significantly to 82.3 bpm (SEM 2.3) 5 min after the first product administration; it remained significantly elevated 15 and 30 min post administration. Significant increases relative to baseline also were observed 5, 15 and 30 min after the second administration. For QUEST, mean baseline heart rate was 68.7 bpm (SEM 2.1), which increased significantly to 73.1 bpm (SEM 2.1) 5 min 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 CS condition; heart rate at baseline was 67.8 bpm (SEM 2.3), which increased significantly to 72.0 bpm (SEM 2.4) 15 min after the first product administration. No significant increases were observed for ARIVA, COMMIT or MS.

For CO, a significant condition by use episode interaction was observed ($p<0.001$). Relative to baseline (collapsed across all conditions, mean 6.5 ppm (SEM 0.5)), expired air CO increased in the OWN and QUEST conditions after the first (OWN, mean 12.8 ppm (SEM 0.7); QUEST, 11.0 ppm (SEM 0.6)) and second product administration (OWN, mean 17.5 ppm (SEM 1.0); QUEST, 14.4 ppm (SEM 0.8)). There were no significant changes in any other condition.

Abstinence symptom suppression and direct effects of nicotine

A significant condition by time interaction was observed for both factors of the QSU Brief ($F>4.4$, $p<0.001$). Figure 1B displays data for factor 1 (intention to smoke), which had the higher condition by time F value. Relative to baseline, OWN was associated with significant decreases at nearly every time point. A similar pattern was observed for QUEST. For SHAM, scores remained relatively high and stable. Factor 1 scores during non-combustible conditions tended to decrease after the second product administration only. Relative to baseline, scores in the CS condition were significantly decreased 15 min (mean decrease 6.3 (SEM 2.3)) and 30 min (mean decrease 5.4 (SEM 2.2)) after the second product administration. Similarly, for COMMIT, scores were decreased significantly relative to baseline at 15 min (mean decrease 5.9 (SEM 1.9)) and 30 min (mean decrease 6.3 (SEM 2.2)).

1.9)) after the second product administration ($p < 0.05$). No significant differences were observed after ARIVA or MS. During all non-combustible conditions, factor 1 scores were significantly higher relative to OWN at 5 and 15 min after the first product administration and at 5, 15, 30 and 45 min after the second product administration.

Significant condition by time interactions were observed for “Urges to smoke” and “Craving a cigarette/nicotine” (see table 1; $F > 6.7$, $p < 0.001$). Figure 1C shows the results for “Craving a cigarette/nicotine”, the item with the larger F value. For this item, OWN was associated with significant decreases in craving scores relative to baseline at nearly every time point. QUEST was associated with a similar pattern, while mean craving scores during SHAM were relatively high and stable over both administrations. For the non-combustible products, relative to baseline, scores in the CS condition were significantly decreased 15 min (mean decrease 20.9 (SEM 6.5)) and 30 min (mean decrease 20.0 (SEM 5.5)) after the first product administration and 5 min (mean decrease 19.0 (SEM 6.0)), 15 min (mean decrease 23.9 (SEM 6.1)) and 30 min (mean decrease 22.1 (SEM 6.0)) after the second product administration. For COMMIT, mean craving score decreased significantly at every time point after the second product administration. For MS, craving decreased significantly only once, 30 min after the first product administration, while ratings in the ARIVA condition never decreased significantly. During all non-combustible conditions, craving scores were significantly higher relative to OWN at 5 and 15 min after the first product administration and at 5, 15, 30 and 45 min after the second product administration.

A significant condition by use episode by time interaction was observed for the Direct Effects of Nicotine item assessing “Dizzy”, while significant condition by time interactions were observed on items assessing salivation, nausea, headache and heart pounding ($F > 2.1$, $p < 0.05$). The three-way interaction for the “Dizzy” item is explained by an increase from baseline in the OWN condition at the 5 min time point after the first administration (mean increase 12.3 (SEM 5.5); NS) that was not observed after the second administration and was also not observed in any other condition. For salivation, all non-combustible products (but no combustible products) produced a significant increase relative to baseline. For nausea, no products produced significant increases relative to baseline; however, after the first administration of ARIVA or CS, there was a trend towards increased ratings 5 min after product administration (ARIVA mean increase 11.9 (SEM 5.5); CS mean increase 14.5 (SEM 5.2); NS).

Direct effects of tobacco

Significant condition by use episode by time interactions were observed for most Direct Effects of Tobacco items (table 1; $F > 2.1$, $p < 0.05$). Four of these items related to own brand cigarette smoking (eg, “Did the cigarette taste like your own brand of cigarette?”). Across these items, scores during the OWN condition were consistently higher than other conditions. For example, for the item “Does the product taste like your own brand?” in the OWN condition, the mean score at baseline was 0.3 (SEM 0.3), which increased significantly to 67.0 (SEM 6.9) 5 min after the first product administration. For QUEST, the mean baseline score was 0.1 (SEM 0.1), which increased to 11.1 (SEM 3.4) 5 min after the first product administration (NS). Among non-combustible products, no significant increases were observed for this item at any time point after the first product administration.

The other items on this scale concerned perceptions on a variety of dimensions (eg, taste, satisfaction). Figure 1D presents the responses to one such item, “Was the product pleasant?”. Relative to baseline, scores on this item increased significantly for all time points after the first product administration in the OWN, QUEST, ARIVA and MS conditions, with significant increases in the CS condition at 5 and 15 min after the first product administration and no significant increases observed in SHAM or COMMIT. Relative to

OWN, mean scores on this item were significantly lower for all other conditions across all postadministration time points. This general pattern of results was also observed on items assessing “Was the product satisfying?” and “Did the product taste good?”. For items assessing product effects on ratings of “calm you down”, “help you concentrate”, “reduce hunger”, “more awake” and “more product right now”, significant increases were observed for OWN, with fewer or no significant increases relative to baseline observed in any other non-combustible conditions.

DISCUSSION

The clinical laboratory methods used to evaluate the toxicant exposure and subjective effects associated with acute exposure to combustible PREPs (eg, Breland, Strasser and colleagues¹⁶¹⁷³¹) were adapted in this study to evaluate non-combustible PREPs for smokers. This study demonstrated the importance of controlled laboratory evaluation. For example, including an own brand condition demonstrated the dose of nicotine to which smokers are accustomed as well as the rapidity of its delivery: on average, 5 min after beginning to smoke a single own brand cigarette, participants’ mean plasma nicotine level increased by approximately 18 ng/ml. Non-combustible PREPs included in this study delivered a nicotine dose an order of magnitude less, and significant increases were observed later, if at all (ie, 15 min after the second product administration; see figure 1A). The own brand condition also revealed the usual level of CO exposure (about 6 ppm on average) and, as might be expected, no non-combustible PREP increased CO.

This study also highlighted the importance of assessing the PREP subjective effects and compared them to positive (OWN) and negative (SHAM) controls. For example, on measures of tobacco abstinence effects, OWN demonstrated the magnitude of suppression a smoker might expect a PREP to deliver, while SHAM demonstrated a failure to suppress abstinence (see figure 1B and C). Several non-combustible PREPs produced reliable suppression at some time points among several measures of abstinence symptomology (eg, QSU Brief factor 1, “Craving a cigarette/nicotine”, “Urges to smoke”), although OWN always produced suppression of greater magnitude. PREPs that fail to suppress abstinence effectively are unlikely to substitute for normally marketed cigarettes completely, and thus may have limited harm reduction potential.¹⁵¹⁸

Another factor that may limit the likelihood that a PREP will substitute completely for normally marketed cigarettes involves acceptability—the extent to which the product provides sensory characteristics that are pleasant and/or match those provided by a smoker’s usual brand of cigarettes. In this study, in virtually every measure of acceptability, non-combustible PREPs were closer to the lower limit (ie, SHAM) than the upper limit (ie, OWN). When PREPs are unable to deliver nicotine, suppress abstinence symptoms and satisfy sensory demands as effectively as a smoker’s usual brand of cigarettes, their potential as instruments of harm reduction for tobacco users is very uncertain.

In addition to offering experimental control and a variety of relevant outcome measures, clinical laboratory methods for PREP evaluation are reliable and adaptable. The reliability of these methods has been noted elsewhere¹⁷ and is evidenced here by the similarity of results across studies that used the same outcome measures and control conditions.¹⁴¹⁶¹⁷ The adaptability of these methods is evidenced by the fact that they are demonstrably useful for evaluating combustible PREPs for smokers,^{1416–18} and non-combustible PREPs for smokeless tobacco users³² and smokers (the present study). In addition, our ability to test two versions of CS in this study demonstrates how the methods might be used to respond to changes in PREP design, although a within-subjects manipulation would likely have greater power than the relatively insensitive between-subjects factor reported here.

An acute study limits assessment of how a longer PREP experience influences study outcomes as well as PREP-induced changes in carcinogen exposure. However, evaluating the short-term effects of PREP exposure remains relevant because, after trying a particular PREP a few times, smokers must choose to purchase that PREP or their usual brand of cigarettes. That choice may be guided by the knowledge that, in the short-term, the PREP failed to suppress abstinence symptoms and satisfy sensory factors.

In conclusion, this study demonstrates how clinical laboratory methods can be used to evaluate the short-term effects of non-combustible PREPs for smokers. Results suggest that while these non-combustible products do not expose smokers to CO, they also deliver less nicotine than own brand cigarettes and fail to suppress tobacco abstinence symptoms effectively. Indeed, the subjective effects observed in this study do not support the notion that, as presently formulated, non-combustible PREPs for smokers will be a viable harm reduction strategy for the population from which this sample was drawn (ie, US tobacco cigarette smokers). Comprehensive premarket PREP evaluation using established methods and representative samples in the context of a regulated and iterative process designed to minimise toxicant exposure and maximise abstinence symptom suppression may be the most productive method for realising the public health potential of PREPs for tobacco users.

What this paper adds

- The tobacco industry has begun marketing to smokers orally administered, non-combustible potential reduced exposure products (PREPs; eg, compressed tobacco tablets; small pouches of tobacco). Few studies describe the effects of these PREPs in smokers. Careful evaluation of these and other PREPs is essential, given that previous industry-sponsored PREPs (ie, low-yield cigarettes) reduced neither smokers' exposure to tobacco-delivered toxicants nor tobacco-associated mortality.
- This study adapted methods used to examine combustible PREPs to assess the acute effects of these non-combustible PREPs for smokers. The non-combustible products delivered less nicotine than own brand cigarettes, did not expose smokers to CO and failed to suppress tobacco abstinence symptoms as effectively as combustible products. While decreased toxicant exposure is a potential indicator of harm reduction potential, a failure to suppress abstinence symptoms suggests that currently marketed non-combustible PREPs may not be a viable harm reduction strategy. This study demonstrates how clinical laboratory methods can be used to evaluate the short-term effects of non-combustible PREPs for smokers.

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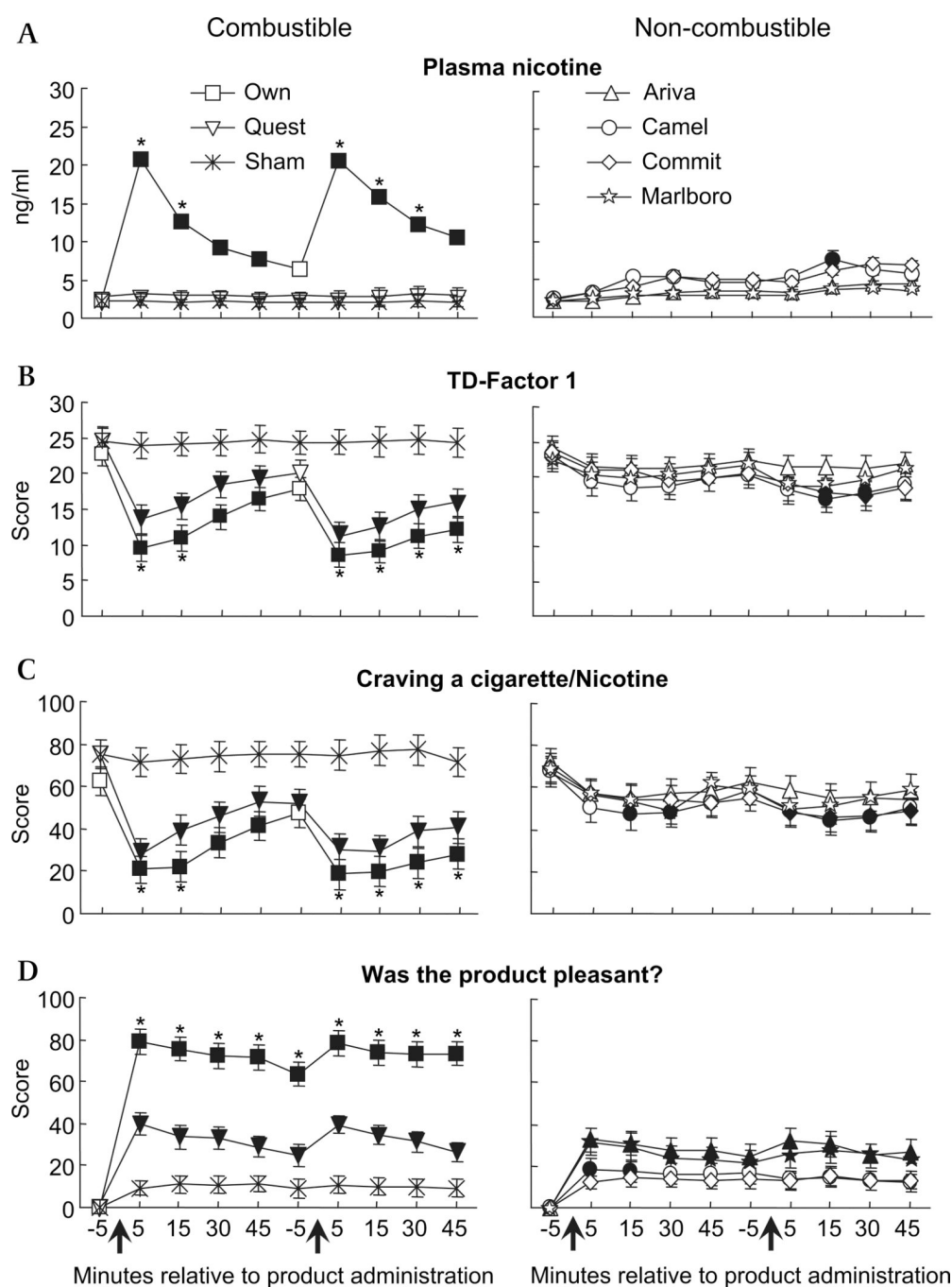


Figure 1. Mean data (±1 SEM) for plasma nicotine (A), factor 1 from the Tiffany Drobes QSU Brief (B), “Craving a cigarette/nicotine” from the Hughes–Hatsukami Withdrawal Scale (C) and “Was the product pleasant?” from the Direct Effects of Tobacco Scale (D) across conditions (n=28). Arrows indicate product administration, filled symbols indicate a significant difference relative to baseline, and asterisks (*) indicate a significant difference of OWN mean relative to all non-combustible product means at that time point ($p < 0.05$, Tukey's Honestly Significant Difference).

Table 1

Statistical analyses results for all measures

	Condition (C)		Use (U)		Time (T)		C×U		C×T		U×T		C×U×T	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p
Physiological effects														
Plasma nicotine *	48.5	<0.001	44.6	<0.001	56.6	<0.001	10.3	<0.001	47.6	<0.001	3.5	<0.05	1.7	NS
Heart rate *	7.0	<0.001	35.8	<0.001	62.9	<0.001	2.3	<0.05	24.3	<0.001	18.0	<0.001	2.9	<0.001
Expired air CO [†]	59.7	<0.001	38.8	<0.001	116.4	<0.001	147.8	<0.001	156.4	<0.001	2.1	NS	1.9	NS
Subjective effects QSU brief*														
Factor 1	11.4	<0.001	11.8	<0.01	31.3	<0.001	3.1	<0.05	10.7	<0.001	2.1	NS	1.0	NS
Factor 2	4.9	<0.01	1.1	NS	8.7	<0.01	2.2	NS	4.4	<0.001	2.0	NS	1.4	NS
Hughes–Hatsukami*														
Urges to smoke	10.4	<0.001	6.1	<0.05	37.2	<0.001	1.2	NS	6.7	<0.001	4.3	<0.05	1.0	NS
Irritability/frustration/anger	2.6	<0.05	1.9	NS	7.2	<0.001	1.9	NS	1.6	NS	3.2	<0.05	1.5	NS
Anxious	2.5	<0.05	0.1	NS	7.4	<0.001	0.5	NS	0.8	NS	6.8	<0.01	0.7	NS
Difficulty concentrating	1.6	NS	0.0	NS	3.7	<0.05	1.5	NS	0.9	NS	1.4	NS	1.3	NS
Restlessness	1.4	NS	1.2	NS	6.6	<0.01	2.2	NS	1.1	NS	3.9	<0.05	0.9	NS
Hunger	1.3	NS	7.9	<0.01	5.8	<0.01	1.8	NS	1.5	NS	0.8	NS	1.2	NS
Impatient	3.2	<0.05	0.2	NS	6.2	<0.01	1.4	NS	1.5	NS	4.1	<0.01	1.2	NS
Craving a cigarette/nicotine	11.3	<0.001	9.6	<0.01	29.2	<0.001	2.9	<0.05	6.9	<0.001	5.8	<0.01	1.4	NS
Drowsiness	0.4	NS	0.1	NS	4.9	<0.01	1.5	NS	1.0	NS	3.6	<0.05	1.5	NS
Depression/feeling blue	0.8	NS	0.4	NS	0.8	NS	1.1	NS	1.1	NS	0.6	NS	1.2	NS
Desire for sweets	1.8	NS	0.5	NS	2.7	NS	2.0	NS	1.3	NS	2.8	<0.05	0.8	NS
Direct effects of nicotine *														
Nauseous	2.9	<0.05	0.0	NS	4.7	<0.05	1.8	NS	2.5	<0.05	1.9	NS	1.4	NS
Dizzy	2.1	NS	0.1	NS	4.4	<0.01	1.1	NS	1.6	NS	1.5	NS	2.3	<0.05
Lightheaded	1.7	NS	0.1	NS	5.0	<0.01	1.0	NS	2.3	<0.05	0.5	NS	1.2	NS
Nervous	0.7	NS	0.4	NS	1.1	NS	1.9	NS	1.5	NS	1.3	NS	1.1	NS
Sweaty	0.7	NS	1.9	NS	1.7	NS	1.1	NS	2.0	NS	1.1	NS	1.0	NS
Headache	1.6	NS	4.1	NS	2.2	NS	1.3	NS	2.1	<0.05	1.9	NS	1.0	NS

	Condition (C)		Use (U)		Time (T)		C×U		C×T		U×T		C×U×T	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p
Excessive salivation	5.9	<0.001	0.8	NS	17.0	<0.001	1.5	NS	4.8	<0.001	2.8	<0.05	1.6	NS
Heart pounding	3.2	<0.05	0.9	NS	1.2	NS	0.5	NS	0.9	NS	1.1	NS	1.2	NS
Confused	2.4	NS	2.0	NS	0.7	NS	1.0	NS	0.9	NS	1.1	NS	0.6	NS
Weak	1.3	NS	2.9	NS	0.9	NS	0.7	NS	1.0	NS	1.0	NS	0.8	NS
Direct effects of tobacco*														
Satisfy	35.9	<0.001	31.1	<0.001	54.5	<0.001	4.4	<0.01	15.5	<0.001	30.7	<0.001	7.7	<0.001
Pleasant	30.9	<0.001	16.6	<0.001	59.2	<0.001	3.7	<0.01	13.5	<0.001	34.4	<0.001	8.7	<0.001
Taste good	24.9	<0.001	16.4	<0.001	50.6	<0.001	6.6	<0.001	9.5	<0.001	38.4	<0.001	6.6	<0.001
Dizzy	6.3	<0.001	0.5	NS	8.2	<0.001	2.5	<0.05	1.8	NS	11.0	<0.001	3.6	<0.01
Calm	11.3	<0.001	1.3	NS	26.0	<0.001	2.5	<0.05	5.1	<0.001	27.7	<0.001	3.7	<0.001
Help concentrate	9.5	<0.001	5.6	<0.05	13.8	<0.001	1.3	NS	3.2	<0.01	10.4	<0.001	2.4	<0.01
Feel awake	11.5	<0.001	1.8	NS	21.3	<0.001	0.6	NS	3.4	<0.001	17.5	<0.001	3.2	<0.01
Reduce hunger	3.3	<0.01	9.0	<0.01	14.6	<0.001	0.2	NS	1.7	NS	17.9	<0.001	2.1	<0.05
Feel sick	5.2	<0.01	1.3	NS	11.4	<0.001	0.6	NS	2.7	<0.05	6.8	<0.01	1.8	NS
Taste like own brand	55.8	<0.001	24.1	<0.001	32.1	<0.001	12.8	<0.001	22.9	<0.001	19.5	<0.001	16.3	<0.001
Feel like own brand	48.4	<0.001	22.3	<0.001	36.9	<0.001	8.3	<0.001	22.2	<0.001	23.3	<0.001	13.7	<0.001
Harsh as own brand	13.9	<0.001	11.9	<0.01	22.9	<0.001	4.1	<0.01	5.3	<0.001	17.5	<0.001	4.0	<0.001
Mild as own brand	34.6	<0.001	8.8	<0.01	33.6	<0.001	4.7	<0.01	11.1	<0.001	21.7	<0.001	9.8	<0.001
More of product right now	17.4	<0.001	0.7	NS	12.6	<0.001	0.8	NS	3.4	<0.001	40.1	<0.001	10.9	<0.001

* $df_C=(61\ 62)$; $df_U=(1\ 27)$; $df_T=(41\ 08)$; $df_{C \times U}=(61\ 62)$; $df_{C \times T}=(24\ 648)$; $df_{U \times T}=(41\ 08)$; $df_{C \times U \times T}=(24\ 648)$.

† $df_C=(61\ 62)$; $df_U=(1\ 27)$; $df_T=(2\ 54)$; $df_{C \times U}=(61\ 62)$; $df_{C \times T}=(12\ 324)$; $df_{U \times T}=(2\ 54)$; $df_{C \times U \times T}=(12\ 324)$.