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Response to reduced nicotine content cigarettes among smokers differing in tobacco dependence severity

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Abstract

This study examines whether tobacco dependence severity moderates the acute effects of reducing nicotine content in cigarettes on the addiction potential of smoking, craving/withdrawal, or smoking topography. Participants (N = 169) were daily smokers with mild, moderate, or high tobacco-dependence severity using the Heaviness of Smoking Index. Following brief abstinence, participants smoked research cigarettes varying in nicotine content (0.4, 2.4, 5.2, 15.8 mg nicotine/g tobacco) in a within-subject design. Results were analyzed using repeated measures analysis of co-variance. No main effects of dependence severity or interactions with nicotine dose were noted in relative reinforcing effects in concurrent choice testing or subjective effects on the modified Cigarette Evaluation Questionnaire. Demand for smoking in the Cigarette Purchase Task was greater among more dependent smokers, but reducing nicotine content decreased demand independent of dependence severity. Dependence severity did not significantly alter response to reduced nicotine content cigarettes on the Minnesota Tobacco Withdrawal Scale nor Questionnaire of Smoking Urges-brief (QSU) Factor-2 scale; dependence severity and dose interacted significantly on the QSU-brief Factor-1 scale, with reductions dependent on dose among highly but not mildly or moderately dependent smokers. Dependence severity and dose interacted significantly on only one of six measures of smoking topography (i.e., maximum flow rate), which increased as dose increased among mildly and moderately but not highly dependent smokers. These results suggest that dependence severity has no moderating influence on the ability of

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reduced nicotine content cigarettes to lower the addiction potential of smoking, and minimal effects on relief from craving/withdrawal or smoking topography.

Keywords

Tobacco dependence; Dependence severity; Heaviness of Smoking Index; Cigarette smoking; Reduced nicotine content cigarettes; Addiction; Reinforcement; Withdrawal; Craving; Smoking topography; Vulnerable populations

1. Introduction

Tobacco dependence severity is a robust predictor of success in quitting cigarette smoking (Baker et al., 2017; Borland et al., 2010; Kurti et al., 2016; Mercincavage et al., 2013; Vangeli et al., 2011). Indeed, two specific measures of dependence severity, the number of cigarettes smoked per day (CPD) and time to first cigarette upon waking, have broad generality in predicting initiation and maintenance of smoking cessation and have been validated in clinical samples and self-quitters (Baker et al., 2017; Borland et al., 2010; Kurti et al., 2016; Mercincavage et al., 2013; Vangeli et al., 2011). The Heaviness of Smoking Index (HSI, Heatherton et al., 1989) combines these two markers with comparable or greater predictive validity than either individual item alone (e.g., Borland et al., 2010; Kurti et al., 2016; Schnoll et al., 2013). The brevity and associated lower participant burden of the HSI is another notable practical advantage of that instrument (Schnoll et al., 2013).

The primary purpose of the present study is to examine whether individual differences in dependence severity as measured by the HSI moderate response to reduced nicotine content cigarettes. On July 28, 2017, Scott Gottlieb, MD, Commissioner of the U.S. Food and Drug Administration (FDA), announced a new regulatory plan to reduce the adverse impact of cigarette smoking on U.S. public health. That plan includes consideration of a policy to reduce the maximal nicotine content in cigarettes in order to lower their addiction potential (U.S. Food and Drug Administration, 2017). There is overwhelming scientific evidence that nicotine is the constituent in cigarette smoke that promotes dependence or addiction (U.S. Department of Health and Human Services (US DHHS), 1988; U.S. DHHS, 2014). The rationale behind reducing the nicotine content of cigarettes is to (a) lower the dependence severity of current smokers thereby making it easier for them to quit should they choose to do so and (b) reduce the likelihood that those who experiment with smoking will develop dependence (Benowitz and Henningfield, 1994).

The 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA) granted the FDA regulatory authority over cigarettes and other tobacco products (Family Smoking Prevention and Tobacco Control Act (H.R. 1256) (2009)). That legislation includes authority to establish a standard to reduce the maximal nicotine content of cigarettes if doing so benefits public health. Knowing whether reducing the nicotine content of cigarettes reduces the addiction potential of smoking even among more dependent smokers is important in assessing the potential impact that such a policy may have on existing smokers. Other important questions to examine are whether reduced nicotine content cigarettes adequately

reduce withdrawal and craving and whether they may prompt compensatory smoking in more severely dependent smokers (Keith et al., 2017; US DHHS, 2001, 2010).

Results from controlled studies of reduced nicotine content cigarettes among psychiatrically and socioeconomically stable, healthy smokers have been promising, with extended exposure to these cigarettes producing significant reductions in CPD and nicotine dependence, and increases in quit attempts with little evidence of compensatory smoking (Benowitz et al., 2012; Donny et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2013a, 2013b). More recently, studies of reduced nicotine content cigarettes have been initiated in populations especially vulnerable to smoking and dependence, including individuals with psychiatric conditions or socioeconomic disadvantage (AhnAllen et al., 2015; Faulkner et al., 2017; Higgins et al., 2016, 2017; Tidey et al., 2013, 2016, 2017). These studies have mostly although not exclusively (Tidey et al., 2017) examined acute exposure. Again results are encouraging, with reduced nicotine content cigarettes producing weaker relative reinforcing and positive subjective effects, key markers of addiction potential, while also providing significant relief from withdrawal and craving, and no evidence of compensatory smoking.

To our knowledge, there is only a single report in this emerging literature examining whether tobacco dependence severity moderates response to reduced nicotine content cigarettes. That study examined acute response to varying doses of reduced nicotine content cigarettes following brief smoking abstinence among young adults, a population especially vulnerable to cigarette smoking and eventual dependence (Faulkner et al., 2017). Withdrawal and craving ratings were significantly greater among more dependent smokers prior to but not after smoking indicating that reduced nicotine content cigarettes reduced craving and withdrawal equally across doses. Dependence severity was not associated with subjective ratings of cigarette quality or sustained attention. More direct measures of addiction potential (e.g., reinforcing effects) were not assessed. The present study is a secondary analysis of a study that examined acute exposure to reduced nicotine content cigarettes in participants from three populations also especially vulnerable to cigarette smoking and dependence: individuals with affective disorders, individuals with opioid dependence, and socioeconomically disadvantaged women of reproductive age (Higgins et al., 2017). The study explicitly focused on assessing addiction potential, noting that reducing nicotine content dose-dependently decreased the addiction potential of smoking in these vulnerable populations (relative reinforcing and positive subjective effects) while reducing craving and withdrawal, with minimal differences between populations and no evidence of compensatory smoking. Higgins et al. (2017) did not examine any potential moderating influence of dependence severity. Considering that one-quarter or more of U.S. adult smokers are severely dependent on cigarette smoking (e.g., Schnoll et al., 2013), the present study is focused on that topic.

2. Methods

2.1. Study sample

Participants in this multisite study (University of Vermont, Brown University, Johns Hopkins University School of Medicine) included 169 adult daily smokers (56 with affective

disorders, 60 with opioid dependence, 53 socioeconomically disadvantaged women of reproductive age), who provided written informed consent. Participants from each population were studied at the University of Vermont; Brown University studied only those with affective disorders; Johns Hopkins University studied those with opioid dependence and disadvantaged women. Study inclusion and exclusion criteria have been reported previously (Higgins et al., 2017).

Instead of categorizing study participants by psychiatric condition or socioeconomic status in the present study, they were categorized by dependence severity. All study participants completed the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) as well as a tobacco history questionnaire at study intake assessment. HSI scores were calculated by summing scores from items 1 and 4 of the FTND. Possible HSI scores range from 0 to 6. Using HSI cut-points previously established in a U.S. nationally representative sample of current smokers (Schnoll et al., 2013), participants with scores of 0–2, 3, and 4–6 were categorized as mildly, moderately, and highly dependent, respectively. These dependence severity categories are associated with different sociodemographics, health outcomes, quality of life, productivity, and health care utilization characteristics (Schnoll et al., 2013). Prior research comparing HSI scores treated as a categorical variable show them to be comparable in predictive utility to treating scores as a continuous variable (Borland et al., 2010).

2.2. Research cigarettes

This study used Spectrum research cigarettes manufactured by 22nd Century Group (Clarence, NY) and obtained from the National Institute on Drug Abuse. Four nicotine doses were investigated with nicotine content averaged across menthol and non-menthol products (assignment of a menthol or non-menthol product was based on a participant's usual brand): 15.8, 5.2, 2.4, and 0.4 mg of nicotine per gram of tobacco (mg/g). The 15.8 mg/g dose served as a control for nicotine levels typical of commercial cigarettes. All sessions were conducted under double-blind conditions.

2.3. Procedure

These procedures have been described previously (Higgins et al., 2017). Briefly, participants completed fourteen 2–4 h sessions in a within-subjects design. Participants abstained from smoking for 6–8 h prior to sessions. Sessions were organized into three phases. In Phase 1 (Sessions 1–5), participants sampled the research cigarettes under double-blind conditions with cigarettes identified by arbitrary letter codes. Participants were oriented to the research protocol in Session 1 using their usual-brand cigarette. In Sessions 2–5 participants smoked one research cigarette per session. Participants smoked the research cigarettes ad lib using a plastic cigarette holder connected to a device that recorded smoking topography (Clinical Research Support System, CReSS; Lee et al., 2003). After smoking the assigned cigarette each session, participants completed the Cigarette Purchase Task (CPT), a behavioral economic simulation task that has participants estimate the number of cigarettes they would anticipate smoking in a 24-hour period across a wide range of cigarette prices; those estimates are used to model (1) participant cigarette smoking rate when unconstrained by cost (Intensity), (2) maximal amount of money one is willing to spend on daily smoking

(Omax), (3) the price at which smoking rate begins decreasing proportionate to increasing price (Pmax), (4) the price at which one would quit smoking rather than incur the cost (Breakpoint), and (5) overall sensitivity of demand to price (Alpha) (Jacobs and Bickel, 1999; MacKillop et al., 2008). Participants also completed the modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007) once prior to and immediately after smoking, and the Minnesota Tobacco Withdrawal Scale (MTWS) (Hughes and Hatsukami, 1986) and Questionnaire of Smoking Urges-brief scale (QSU-brief) (Cox et al., 2001) administered prior to and every 15 min for 60 min after smoking. Phase 2 (Sessions 6–11) directly tested the relative reinforcing effects of the different dose cigarettes by allowing participants to choose which cigarette they preferred to smoke in two-choice concurrent test sessions (Lussier et al., 2005; Johnson et al., 2004). Each of the six possible cigarette dose-pair combinations was tested once in separate sessions. In these 3-hour sessions, a participant sat alone in a comfortable, ventilated room. When they wished to smoke, they used a computer mouse to click on one of two icons on a screen representing the two cigarettes available that session. After ten clicks on the icon they could take two puffs of the associated cigarette (Lussier et al., 2005). Participants were free to choose either option as often as they wished or abstain. Lastly, Phase 3 (Sessions 12–14) used the same arrangement as Phase 2, but compared only the 0.4 and 15.8 g/mg doses. This phase assessed whether preference could be reliably shifted away from the high dose. Puffs from the low dose remained available by clicking that option 10 times while the number of clicks necessary to earn puffs from the highest dose started at 10 and increased each time it was chosen to 160, 320, 640, 1280, 2400, 3600, 4800, 6000, 7200, and 8400 clicks (Sigmon et al., 2003).

2.4. Statistical methods

Analyses of Phase 1 results examined whether tobacco dependence severity (HSI) moderates the effect of dose on CPT, mCEQ and smoking topography by using repeated-measures analysis of covariance, with nicotine dose as the within-participant factor and HSI as a fixed effect with three levels. The comparison of HSI levels on demographic characteristics using Fisher's Exact Test and the Wilcoxon Rank Sum Test found significant differences on age and level of education; therefore, they were included as covariates. Sex was also included as a covariate based on prior reports on male-female differences in response to reduced nicotine content cigarettes (Faulkner et al., 2018; Perkins and Karelitz, 2015). The MTWS, QSU-Brief, and breath CO levels were examined similarly with time as another within-participant factor. To measure CO boost, pre-smoking CO values were subtracted from post-smoking CO values. Analyses also included fixed effects for (1) session and (2) the three primary study vulnerable populations who were studied in independent experiments using parallel research protocols and combined for analysis in the original and this secondary study. Time-by-dose and HSI-by-dose interactions were included to test whether CO boost or subjective effects before and after smoking differed by dose and to test for differential effects of HSI by dose; when not significant, interaction effects were dropped from models. Because the research cigarettes were presented in random order using a Latin square design, sequence was included in the model as a random effect. An additional random effect was included to account for the three study sites. Significant main or interaction effects were followed by post hoc testing using Bonferroni corrections, dividing the critical value ($p < .05$) by the number of comparisons to derive a more conservative Type I error rate.

Differences in preference among all possible dose pairs (Phase 2) were similarly examined using repeated-measures analysis of variance, with each pairwise combination as the within-participant factor, HSI as a fixed effect, and education, age, and sex as covariates. Differences among participants in preference for the highest- vs lowest-dose cigarettes (Phase 3) were examined using a repeated-measures analysis of covariance, with session as the repeating factor, population and HSI as the between-subjects factors and education, age, and sex as covariates.

To describe aggregate-level cigarette demand on the CPT, demand curves were fit to mean reported consumption at each price across participants, doses, and HSI. To quantify participant-level CPT demand elasticity, a demand curve was fit to individual consumption at each price for each dose. When fitting demand curves, we constrained demand intensity to the participants' reported consumption at $0.00 to leave elasticity as the only fitted parameter. Elasticity values > 1.00 were winsorized to 1.00 prior to statistical analysis (22 of 845 cases). All other demand indices were empirically quantified from observed values. Omax, Pmax, Breakpoint, and Alpha were log10 transformed to correct for skewness. We reviewed CPT results and found systematic patterns in 92.7% of demand curves; no data were excluded from analyses. In cases where participants reported zero consumption across all prices (54 of 845 cases), curve fitting was not possible, so elasticity was not analyzed and other demand indices were quantified as 0.

Across all tests, statistical significance was defined as $p < .05$ (2-tailed). Significant main or interaction effects were followed by post hoc testing using Bonferroni corrections, dividing the critical value ($p < .05$) by the number of comparisons to derive a more conservative Type I error rate. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and [CPT tool].

3. Results

3.1. Participant characteristics

Approximately one third of participants fell into each dependence severity category (Table 1). Distribution of participants from among the three populations initially recruited for this study did not differ significantly across dependence severity categories. Only two socio-demographic characteristics differed significantly by dependence severity, with those with high dependence severity being older and less educated. As expected, more severely dependent participants smoked more cigarettes per day, had higher baseline breath CO levels, higher mean FTND total scores, and started smoking at a younger age.

3.2. Relative reinforcing effects of smoking

3.2.1. Direct testing—No significant differences by dependence severity were noted in how participants chose between the different dose cigarettes in concurrent choice testing. Participants chose the higher nicotine dose at significantly greater than chance levels across each of the 6 dose pairs independent of dependence severity ($F[5835] = 6.12$, $p < .001$) (Table 2). There were no significant interactions of dependence severity and nicotine dose.

When the 0.4 and 15.8 mg doses were retested in Phase 3 with the former still available at 10 mouse clicks but the latter on a progressive ratio schedule, participants chose the 0.4 mg/g dose significantly more than the 15.8 mg/g dose independent of dependence severity level (t (158) = 3.41, $p < .001$) (Table 3).

3.2.2. Simulation modeling—CPT demand varied by dependence severity and cigarette nicotine dose (Fig. 1, upper and lower panels, respectively). Regarding dependence severity, demand Intensity (F[2154] = 20.43, $p < .001$) and Omax (F[2157] = 3.96, $p = .02$) were greater among more dependent smokers (Table 4, upper panel); no significant differences by dependence severity were noted on Pmax, Breakpoint, or Alpha. Regarding dose effects, significant dose differences were discerned across each CPT index (Fs[3489] ≥ 5.19, $ps \leq 0.002$) except Alpha, with a general pattern of more intense and persistent demand at higher nicotine doses (Table 4, lower panel). No significant interactions of dependence severity and nicotine dose were noted.

3.3. Participant ratings

3.3.1. Modified Cigarette Evaluation Questionnaire—No significant differences by dependence severity were noted on any mCEQ subscale (Table 5, upper panel). Significant effects of nicotine dose were noted across mCEQ measures (Fs[3501] ≥ 7.08, $ps < 0.001$) (Table 5, lower panel), with mean scores increasing as a function of increasing nicotine dose. No significant interactions of dependence severity and nicotine dose were noted.

3.3.2. Minnesota Tobacco Withdrawal Scale—No significant differences by dependence severity were noted in MTWS total scores (Table 6, upper panel) nor any interactions involving dependence severity. There was a significant interaction of dose and time (F[12, 2014] = 2.64, $p = .002$) (Table 6, lower panel); each of the varying dose cigarettes decreased pre-smoking ratings with duration of effects greatest at the 15.8 mg/g dose.

There was a significant main effect of dependence severity (F [2156] = 5.60, $p = .005$) and an interaction of dose and time (F[12, 2014] = 5.86, $p < .001$) on the MTWS Desire-to-Smoke item (Fig. 2). More severely dependent smokers reported a stronger desire to smoke. Each of the doses reduced ratings post-smoking, but the duration of effects was greater at the 15.8 mg/g dose. There was no significant interaction of dependence severity and dose on this item.

3.3.3. Brief Questionnaire of Smoking Urges (QSU-brief)—There were significant interactions of dose and time (F[12, 2014] = 8.92, $p < .0001$) and dependence severity and dose (F [6495] = 2.32, $p = .03$) on Factor-1 ratings (i.e., urges associated with positive reinforcing effects) (Fig. 3, upper panel). More dependent smokers reported greater mean urges than less dependent smokers. The interaction of dose and time on this measure corresponds to the 15.8 mg/g dose having the longest duration of action. Lastly, the significant interaction of dependence severity and dose corresponds to each of the cigarettes producing comparable craving reductions among the mild and moderately but not the highly

dependent smokers with whom the 15.8 mg dose produced greater reductions than the lower doses.

Factor-2 ratings (i.e., urges associated with negative reinforcing effects) showed a similar pattern of significant effects of dependence severity (F[2153] = 3.45, $p = .03$) and interaction of dose and time (F [12, 2014] = 5.22, $p < .001$), but no significant interaction of dependence severity and dose (Fig. 3, bottom panel).

3.4. Smoking topography

There were no significant main effects of dependence severity noted in smoking topography. There were significant main effects of dose on three of the six measures (total puff volume, mean maximum flow rate, and puff number) (Fs[3488] ≥ 3.54, $ps \leq 0.01$) (Table 7). The effects of dose were in the direction of larger, more intense, and greater number of puffs as a function of increasing nicotine dose, opposite of what is expected with compensatory smoking. There was a significant interaction of dependence severity and dose on mean maximum flow rate (F [6482] = 2.39, $p = .03$), where rates increased by dose among mildly and moderately but not highly dependent smokers (Fig. 4). Again, this effect was not suggestive of compensatory smoking.

There were no significant main effects of dependence severity or nicotine dose on breath CO levels across the 60 min of post-smoking monitoring (not shown). There was a significant effect of time (F [3504] = 104.46, $p < .0001$), with levels increasing from pre- to post-smoking and then dissipating over time. No significant interactions between dependence severity, dose, or time were observed.

4. Discussion

The present results offer no evidence that the ability of reduced nicotine content cigarettes to lower the addiction potential of smoking is moderated by tobacco dependence severity. Reducing the nicotine content of cigarettes decreased the relative reinforcing effects of smoking independent of dependence severity, with convergent support for that conclusion across two measures (concurrent choice testing, CPT). Importantly, preference for higher over lower dose cigarettes could also be reversed by increasing response effort to obtain the former independent of dependence severity. Reducing nicotine content also decreased the positive subjective effects of smoking on the mCEQ independent of dependence severity consistent with lower addiction potential.

We saw minimal evidence that reducing the nicotine content of cigarettes would leave more severely dependent smokers with untoward levels of withdrawal or craving (Donny et al., 2014; Hatsukami et al., 2013a, 2013b). Each of the cigarette doses investigated reduced MTWS total scores from pre-smoking levels. Those effects were larger in magnitude and of longer duration at the highest dose, but did not interact with dependence severity. Indeed, no differences by dependence severity were noted on MTWS total scores. That differs from results reported by Faulkner et al. (2017) who noted significant differences in withdrawal symptomology by dependence severity. Accounting for this between-study discrepancy is difficult as different instruments were used to assess withdrawal in the two studies and the

populations differed. The MNWS was used in the present study while the Shiffman-Jarvik Withdrawal scale (Shiffman and Jarvik, 1976) was used in the Faulkner et al. (2017, 2018) study, and they studied younger (mean age 22.3 + 2.2) smokers without comorbid psychiatric conditions while the present study examined older smokers (35.6 ± 11.4) and presence of a comorbid psychiatric condition was an inclusion criterion in two-thirds of the sample and not an exclusion criterion in the other third. The three measures used to assess craving in the present study all showed differences by dependence severity consistent with what Faulkner et al. reported. For two of those measures (MTWS Desire-to-Smoke item and QSU-brief Factor 2) there were no significant dose differences in the ability of smoking to decrease craving across the different levels of dependence severity consistent with the pattern reported by Faulkner et al. The exception to that pattern was observed on the QSU-brief Factor 1 scale, where each of the doses decreased craving comparably among those with mild and moderate dependence severity while effects were dose-dependent among highly dependent smokers. That observation suggests that reducing the nicotine content of cigarettes below current commercial levels could impact highly dependent smokers more than moderately or mildly dependent smokers in terms of experiencing greater craving. This interaction of dependence severity and nicotine content was not reported by Faulkner et al. perhaps suggesting that this may be an effect specific to older, more dependent smokers. This interaction of dependence severity and dose in the present study was only observed on the QSU Factor 1 subscale that focuses specifically on craving for the positive reinforcing effects of smoking suggesting that dimension is more sensitive to differences by dependence severity.

Regarding the potential of reduced content cigarettes engendering compensatory smoking in more severely dependent smokers, we saw no evidence supporting that concern in the present study. Indeed, in the only interaction of dependence severity and dose observed on a measure of smoking topography, mildly and moderately dependent smokers responded in a manner opposite of what occurs with compensatory smoking (i.e., they smoked the lower content cigarettes less intensively) while highly dependent smokers showed no differences in smoking intensity by nicotine content level.

A secondary aim of this study was to advance knowledge about potential differences in how nicotine influences smoking across dependence severity levels. Considered together, these results indicate that smokers across dependence severity levels share a preference for higher over lower nicotine doses and experience a common profile of subjective effects from smoking. Where differences by dependence severity appear to come into play is in how those shared effects translate into demand intensity and associated urges. Whether this is attributable to individual differences in self-regulatory capabilities or some other system that governs demand intensity and associated smoking desire/urges was not examined in the present study but is a topic that merits further investigation (Bickel et al., 2007, 2016). At a practical level, the present results suggest that targeting interventions to more effectively reduce intensity of demand and associated urges will be important to improving cessation outcomes among more severely dependent smokers (MacKillop et al., 2016; O'Connor et al., 2016).

Potential limitations of the present study are that (a) this is a secondary analysis of data collected to test other hypotheses and thus did not include dependent measures potentially relevant to elucidating processes underpinning differences between smokers of different dependence severity levels, (b) the population consisted exclusively of smokers with other co-morbid conditions potentially limiting generalizability to the general population of smokers, (c) only acute exposure to the cigarettes was examined leaving unanswered whether results will generalize to extended exposure, and (d) the study was conducted under double blind conditions leaving unanswered how these same populations would respond under un-blinded conditions more representative of naturalistic settings. These limitations notwithstanding, the present study helps address the important regulatory question of whether dependence severity will moderate response to a policy reducing the nicotine content of cigarettes, and provides new knowledge on potential differences in how nicotine influences smoking among more versus less dependent smokers.

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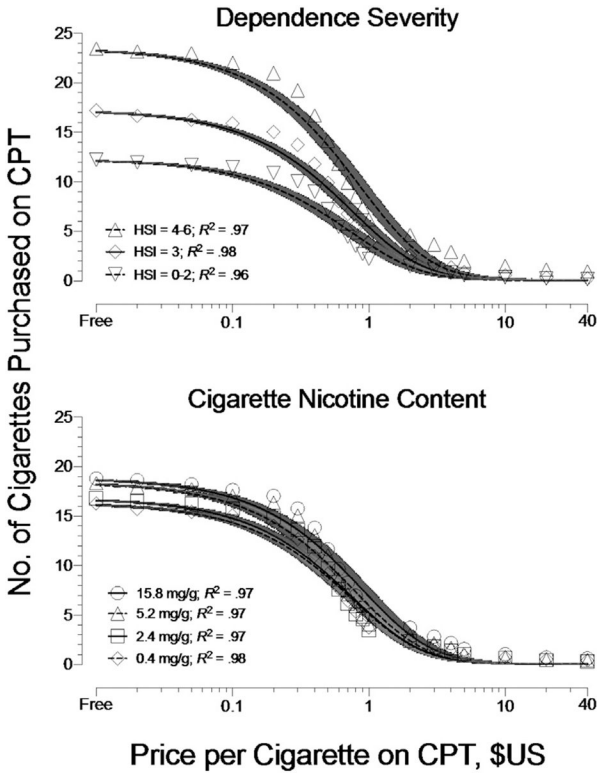

Fig. 1.

Results from the Cigarette Purchase Task simulating demand for cigarette smoking at escalating prices. The upper panel shows results from smokers categorized as mildly (scores = 0–2), moderately (score = 3), and highly (score = 4–6) dependent on the Heaviness of Smoking Index (HSI). Data points represent means for the three dependence severity levels at escalating prices averaging across participants and cigarette nicotine content doses (0.4, 2.4, 5.2, 15.8 mg/g). The lower panel shows results by cigarette nicotine content dose; data points represent means at escalating prices for each dose averaging across participants and dependence-severity levels. Shaded areas represent 95% CIs in the best-fit lines. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

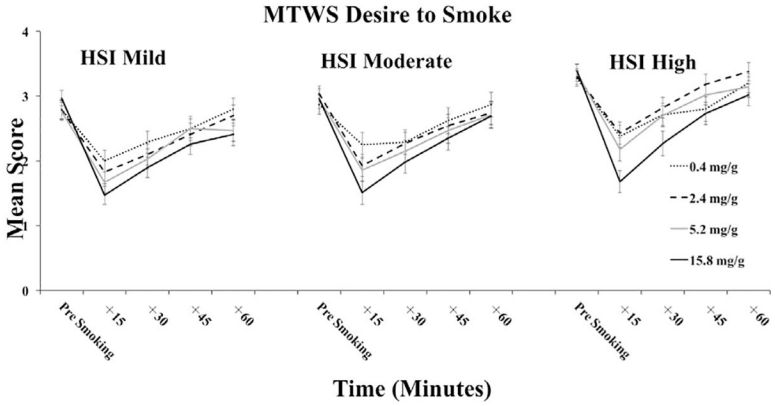

Fig. 2.

Time-course of mean ratings on the Minnesota Tobacco Withdrawal Scale (MTWS) Desire-to-Smoke item by Heaviness of Smoking Index (HSI) severity category with results from mildly, moderately, and highly dependent smokers shown in the left, center, and right-most panels. Error bars represent ± 1 SEM. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

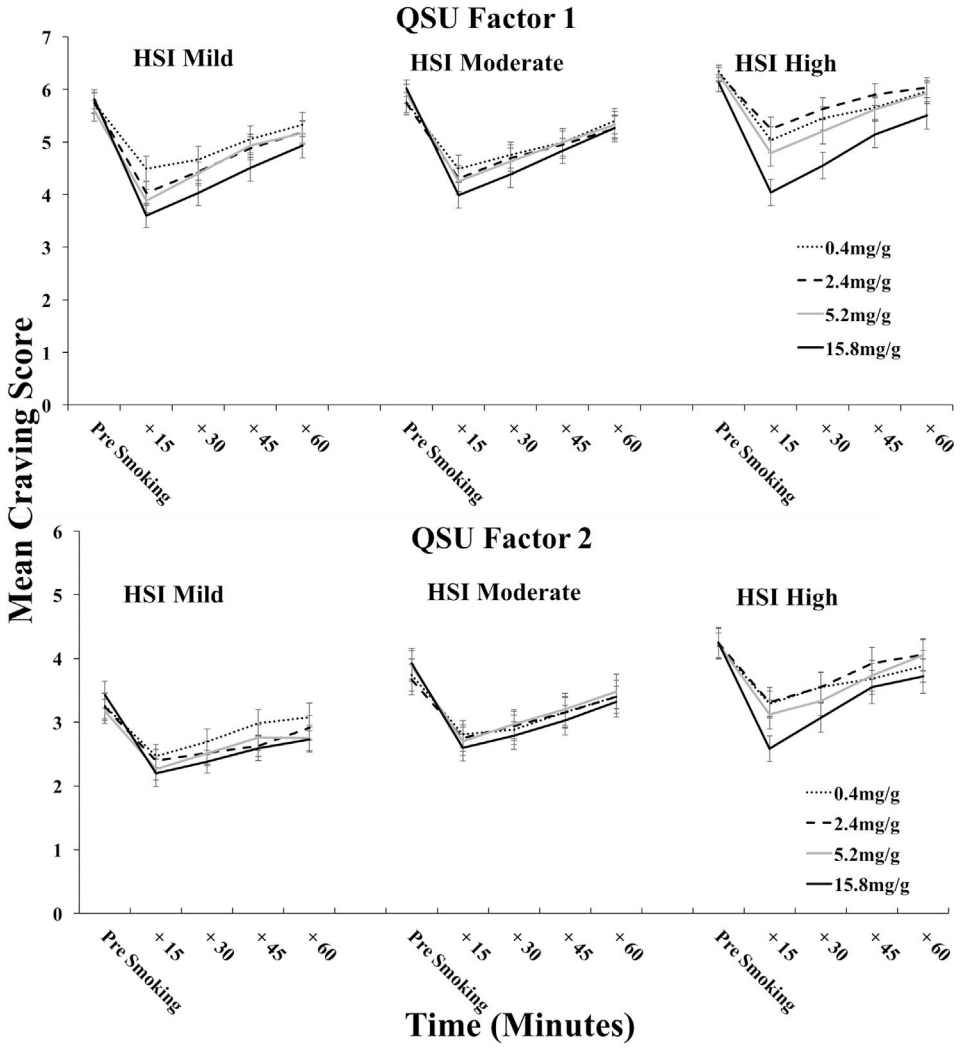

Fig. 3.

Upper panel: time-course of mean ratings on the brief Questionnaire of Smoking Urges (QSU) Factor 1 Scale with results from mildly, moderately, and highly dependent smokers shown in the left, center, and right-most panels. Error bars represent ± 1 SEM. Lower panel: time-course of mean ratings on the brief Questionnaire of Smoking Urges (QSU) Factor 2 Scale with results from mildly, moderately, and highly dependent smokers shown in the left, center, and right-most panels. Error bars represent ± 1 SEM. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

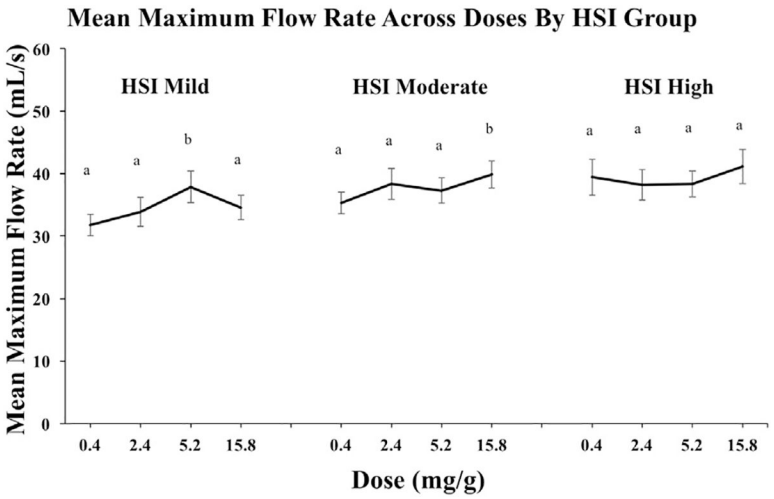

Fig. 4.

Effects of varying nicotine content level on mean maximum flow rate (mL/s) by Heaviness of Smoking Index (HSI) severity category with results from mildly, moderately, and highly dependent smokers shown in the left, center, and right-most panels. Maximum flow rate was measured using the Clinical Research Support System (CReSS, Lee et al., 2003). Error bars represent ± 1 SEM. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

Table 1

Participant characteristics for all participants and by three levels of Heaviness of Smoking Index (HSI) dependence severity. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

		HSI score			
	All (n=169)	**HSI mild (n = 58)**	**HSI moderate (n = 55)**	**HSI high (n=56)**	***p* value**
Age (M ± SD)	35.56 ± 11.38	32.14 ± 11.57	36.51 ± 11.56	38.18 ± 10.28	< .01
Gender (% female)	120 (71.0)	43(74.14)	41 (74.5)	36 (64.3)	.42
Population					.12
Affective disorders	56	26 (44.83)	12 (21.82)	18 (32.14)	
Opioid dependent	60	15 (25.86)	24 (43.64)	21(37.50)	
Low SES women	53	17 (29.31)	19 (34.55)	17 (30.36)	
Race/ethnicity					.43
White	123 (72.78)	37 (63.79)	42 (76.36)	44 (78.57)	
Native American/Alaskan native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian	1 (0.59)	0 (0.0)	0 (0.0)	1 (1.79)	
Black/African-American	23 (13.61)	10 (17.24)	6 (10.91)	7 (12.50)	
Native Hawaiian/Pacific-islander	1 (0.59)	1 (1.72)	0 (0)	0 (0)	
Other or > 1 race	15 (8.88)	6 (10.34)	5 (9.09)	4 (7.14)	
Latino	6 (3.55)	4 (6.90)	2 (3.64)	0 (0)	
Education					.02
8th grade or less	4 (2.37)	1 (1.72)	2 (3.64)	1 (1.79)	
Some high school	23 (13.61)	5 (8.62)	5 (9.09)	12 (23.21)	
High school graduate/equivalent	58 (34.32)	14 (24.14)	21 (38.18)	23 (41.07)	
Some college	64 (37.87)	27 (46.55)	23 (41.82)	13 (25.00)	
2-year associate's degree	10 (5.92)	3 (5.17)	3 (5.45)	4 (7.14)	
College graduate/4-year degree	6 (3.55)	5 (8.62)	0 (0.0)	1 (1.79)	
Graduate or professional degree	4 (2.37)	3 (5.17)	1 (1.82)	0 (0.0)	
Marital status					.39
Married	27 (15.98)	7 (12.07)	11 (20.00)	9 (16.07)	
Never married	103 (60.95)	42 (72.41)	30 (54.55)	31 (55.36)	
Divorced/separated	35 (20.71)	8 (13.79)	12 (21.82)	15 (26.79)	

		HSI score			
	All (n=169)	**HSI mild (n = 58)**	**HSI moderate (n = 55)**	**HSI high (n=56)**	***p* value**
Widowed	4 (2.37)	1 (1.72)	2 (3.64)	1 (1.79)	
Cigarettes per day (M ± SD)	15.79 ± 7.46	10.38 ± 3.82	15.16 ± 4.90	22.02 ± 7.79	< .01
Primary menthol smoker	61 (36.09)	24 (41.38)	20 (36.36)	17 (30.4)	.48
Breath CO (ppm) (M ± SD)	22.37 ± 11.96	16.84 ± 5.80	23.36 ± 13.37	27.13 ± 13.05	< .01
Age started smoking regularly (M years ± SD)	16.26 ± 4.27	17.05 ± 4.09	16.11 ± 4.50	15.59 ± 4.15	.03
Heaviness of Smoking Index (M ± SD)	2.9 ± 1.3	1.6 ± 0.6	3.0 ± 0.0	4.4 ± 0.7	

Table 2

Percent of choices for the higher dose in phase 2 concurrent choice test sessions of all possible dose pairs.

	Percent of choices for higher dose in a given dose pair (mean ± SEM)					
	2.4 v. 0.4 mg/g	**5.2 v. 2.4 mg/g**	**5.2 v. 0.4 mg/g**	**15.8 v. 5.2 mg/g**	**15.8 v. 2.4 mg/g**	**15.8 v. 0.4 mg/g**
Overall	59.83 ± 3.34 *	59.09 ± 3.34 *	64.09 ± 3.34 *	65.32 ± 3.34 *	69.76 ± 3.34 *	73.11 ± 3.34 *
HSI mild	62.67 ± 4.76	53.25 ± 4.76	60.29 ± 4.76	65.91 ± 4.77	69.65 ± 4.77	71.72 ± 4.77
HSI moderate	53.26 ± 4.97	58.40 ± 4.98	61.31 ± 4.97	63.23 ± 4.97	67.20 ± 4.97	71.35 ± 4.97
HSI high	63.55 ± 4.97	65.64 ± 4.97	70.66 ± 4.97	66.83 ± 4.97	72.45 ± 4.97	76.27 ± 4.97

Tabled values represent least square means (± SEM). Shown in the top row show is mean percent choice for the higher nicotine dose adjusted by all covariates. The bottom three rows show mean percent choice for the higher dose separately for mildly (scores = 0–2), moderately (scores = 3), and highly (scores = 4–6) dependent participants. The higher dose was chosen significantly more than the lower dose across all dose pairs with no significant main effects of dependence severity or interactions of dependence severity and dose. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

*Significant effect of dose, $p < .05$.

Table 3

Percent of choices for the lower dose in concurrent testing of the 0.4 versus 15.8 mg/g nicotine doses available at different response costs.

	Percent of choices (mean ± SEM)	
	0.4 mg/g	**15.8 mg/g**
Overall	60.17 ± 2.98	39.83 ± 2.98
HSI mild	61.86 ± 4.29	38.14 ± 4.29
HSI moderate	60.72 ± 4.39	39.28 ± 4.39
HSI high	57.93 ± 4.42	42.07 ± 4.42

Tabled values represent least square means (± SEM). The 0.4 and 15.8 mg/g nicotine doses were concurrently available with the lower dose always available at 10 mouse clicks and higher dose available on a progressive ratio schedule (10, 160, 320, 640, 1280, 2400, 3600, 4800, 6000, 7200, and 8400). Means in the upper row are collapsed across all participants, while those in all other rows are collapsed across only participants within the level of dependence severity indicated. There was a significant preference for the lower over the higher dose. There was no significant effect of dependence severity as preference for the lower dose was discernible across mildly (scores = 0–2), moderately (scores = 3), and highly (scores = 4–6) dependent participants. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

Table 4

Cigarette purchase task indices.

	Intensity of demand	Omax*	Pmax*	Breakpoint*	Alpha (α)*
Dependence severity, mean ± SEM					
HSI mild	11.92 ± 1.59[a]	3.55 ± 0.50[ab]	0.72 ± 0.14	1.62 ± 0.31	0.05 ± 0.006
HSI moderate	16.61 ± 1.67[b]	2.51 ± 0.38[b]	0.48 ± 0.10	1.29 ± 0.26	0.04 ± 0.004
HSI high	22.89 ± 1.71[c]	7.94 ± 1.19[a]	1.12 ± 0.22	2.95 ± 0.59	0.02 ± 0.002
Nicotine dose, mean ± SEM					
0.4 mg/g	15.89 ± 1.42[a]	2.19 ± 0.24[a]	0.45 ± 0.08[a]	1.05 ± 0.18[a]	0.04 ± 0.004
2.4 mg/g	16.37 ± 1.43[ab]	3.72 ± 0.41[ab]	0.69 ± 0.12[b]	1.66 ± 0.28[b]	0.04 ± 0.004
5.2 mg/g	17.92 ± 1.42[bc]	4.90 ± 0.54[bc]	0.78 ± 0.14[b]	2.09 ± 0.36[bc]	0.03 ± 0.002
15.8 mg/g	18.38 ± 1.42[c]	7.24 ± 0.80[c]	1.20 ± 0.22[c]	3.09 ± 0.52[c]	0.03 ± 0.002

Tabled values represent least square means (± SEM). Upper panel shows mean ratings for each Cigarette Purchase Task index averaged across cigarette nicotine dose for smokers categorized as mildly (scores = 0–2), moderately (score = 3), and highly (scores = 4–6) dependent on the Heaviness of Smoking Index (HSI). Lower panel shows mean ratings by dose averaged across participants. There were significant main effects of dependence severity on Intensity of Demand and Omax, but not Pmax, Breakpoint, or Alpha, (upper panel) and significant effects of dose on all indices except Alpha (lower panel). There were no significant interactions. Post hoc testing was conducted on indices where there were main effects; data points not sharing a superscript letter differed significantly within each index in post hoc testing. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

* Least square means and SEMs for log-transformed indices were back calculated to the original scale.

Table 5

Modified cigarette evaluation questionnaire subscale scores by dependence severity and cigarette nicotine dose.

	Smoking satisfaction	Psychological reward	Aversion	Enjoyment of respiratory tract sensations	Craving reduction	Taste
Dependence severity, mean ± SEM						
HSI mild	3.84 ± 0.22	2.92 ± 0.21	1.43 ± 0.13	3.36 ± 0.23	4.03 ± 0.25	3.35 ± 0.21
HSI moderate	3.70 ± 0.23	3.12 ± 0.22	1.54 ± 0.14	3.19 ± 0.25	4.12 ± 0.27	3.30 ± 0.22
HSI high	3.87 ± 0.23	3.02 ± 0.22	1.52 ± 0.14	3.37 ± 0.25	4.33 ± 0.27	3.25 ± 0.23
Nicotine dose, mean ± SEM						
0.4 mg/g	3.16 ± 0.19^{a}	2.69 ± 0.18^{a}	1.41 ± 0.11^{a}	2.77 ± 0.21^{a}	3.65 ± 0.23^{a}	2.67 ± 0.19^{a}
2.4 mg/g	3.59 ± 0.19^{b}	2.85 ± 0.18^{ab}	1.45 ± 0.11^{a}	3.02 ± 0.21^{a}	3.95 ± 0.23^{ab}	3.07 ± 0.19^{b}
5.2 mg/g	3.84 ± 0.19^{b}	3.08 ± 0.18^{b}	1.45 ± 0.11^{a}	3.42 ± 0.21^{b}	4.24 ± 0.23^{b}	3.31 ± 0.19^{b}
15.8 mg/g	4.61 ± 0.19^{c}	3.46 ± 0.18^{c}	1.69 ± 0.11^{b}	4.00 ± 0.21^{c}	4.82 ± 0.23^{c}	4.16 ± 0.19^{c}

Tabled values represent least square means (± SEM). Upper panel shows mean ratings for each modified Cigarette Evaluation Questionnaire subscale/item averaged across participants and nicotine dose for smokers categorized as mildly (scores = 0–2), moderately (score = 3), and highly (score = 4–6) dependent on the Heaviness of Smoking Index (HSI). Lower panel shows mean ratings by nicotine dose averaged across participants and HSI dependence severity. There were no significant main effects of dependence severity or interactions of dependence severity and dose. There were significant main effects of dose across all subscales/item. Data points not sharing a superscript letter differ significantly within each subscale/item or dose in post hoc testing. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

Table 6

Minnesota Tobacco Withdrawal Scale (MTWS) total scores by dependence severity, cigarette nicotine dose and time.

MTWS total scores, mean ± SEM				
Dependence severity				
HSI mild				0.71 ± 0.15
HSI moderate				0.76 ± 0.16
HSI high				1.00 ± 0.16
	Nicotine dose			
	0.4 mg/g	**2.4mg/g**	**5.2mg/g**	**15.8 mg/g**
MTWS total score, mean ± SEM				
Pre-smoking baseline	1.00 ± 0.14*[1]	0.97 ± 0.14*[1]	1.02 ± 0.14*[1]	1.02 ± 0.14*[1]
+15 minutes	0.65 ± 0.14*[2]	0.60 ± 0.14*†[2]	0.61 ± 0.14*†[2]	0.53 ± 0.14†[2]
+30 minutes	0.75 ± 0.14*[3]	0.74 ± 0.14*[3]	0.77 ± 0.14*[3]	0.63 ± 0.14†[3]
+45 minutes	0.89 ± 0.14*[4]	0.87 ± 0.14*[4]	0.89 ± 0.14*[4]	0.77 ± 0.14†[4]
+60 minutes	0.97 ± 0.14*[1,5]	0.92 ± 0.14*†[1,4]	1.01 ± 0.14*[1]	0.86 ± 0.14†[5]

Upper panel shows least square mean (± SEM) ratings for MTWS total scores by dependence severity categorized as mildly (scores = 0–2), moderately (score = 3), and highly (score = 4–6) dependent on the Heaviness of Smoking Index (HSI), collapsing across nicotine dose and time. There was no significant main effect of dependence severity or interaction of dependence severity and dose. Shown in the lower panel are least square mean (± SEM) ratings by dose and time averaging across dependence severity levels. There was a significant interaction of dose and time; within each assessment time (rows) data points not sharing a symbol differ significantly after Bonferroni corrections and within each dose (columns) data points not sharing a number differ significantly after Bonferroni corrections. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.

Table 7

Smoking topography parameters by dependence severity and nicotine dose.

	Total puff volume	Mean puff volume	Mean puff duration	Mean inter-puff interval	Mean maximum flow rate	Puff number
Dependence severity, mean ± SEM						
HSI mild	653.85 ± 65.43	53.24 ± 3.08	1.58 ± 0.09	23.44 ± 1.77	38.62 ± 6.55	12.33 ± 0.90
HSI moderate	593.99 ± 67.38	49.75 ± 3.26	1.56 ± 0.10	23.33 ± 1.84	37.78 ± 6.57	12.06 ± 0.94
HSI high	649.24 ± 68.72	52.59 ± 3.29	1.53 ± 0.10	23.45 ± 1.90	42.38 ± 6.56	12.20 ± 0.96
Nicotine dose, mean ± SEM						
0.4 mg/g	591.79 ± 61.33[a]	50.33 ± 2.75	1.56 ± 0.09	23.21 ± 1.63	37.86 ± 6.44[a]	11.51 ± 0.82[a]
2.4 mg/g	613.03 ± 61.40[a]	51.60 ± 2.76	1.54 ± 0.09	22.99 ± 1.63	39.29 ± 6.44[ab]	11.87 ± 0.82[a]
5.2 mg/g	616.33 ± 61.41[a]	52.89 ± 2.76	1.58 ± 0.09	23.49 ± 1.63	40.35 ± 6.44[ab]	11.79 ± 0.82[a]
15.8 mg/g	708.29 ± 61.43[b]	52.62 ± 2.76	1.54 ± 0.09	23.94 ± 1.63	40.89 ± 6.44[b]	13.62 ± 0.82[b]

Tabled values represent least square means (± SEM). Upper panel shows mean values for six smoking topography measures for participants categorized as mildly (scores = 0–2), moderately (score = 3), and highly (score = 4–6) dependent on the Heaviness of Smoking Index (HSI), adjusted by nicotine doses. There were no significant main effects of dependence severity or interactions of dependence severity and dose. Lower panel denotes smoking topography parameters at different nicotine doses, adjusted by dependence severity levels. There were significant main effects of dose on only three of the six measures (total puff volume, maximum flow rate, and puff number); data points for those measure that do not share a letter differ significantly in post hoc testing. Data were collected from March 23, 2015, through April 25, 2016 at University of Vermont, Brown University, and Johns Hopkins University School of Medicine.