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Evaluating the utility of the modified cigarette evaluation questionnaire and cigarette purchase task for predicting acute relative reinforcing efficacy of cigarettes varying in nicotine content

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ABSTRACT

Background: Nicotine is the addictive component in cigarettes that maintain cigarette smoking that subsequently leads to morbidity and mortality. Methods for assessing the abuse liability of cigarettes are essential to inform new tobacco product standards. This secondary analysis evaluated the utility of one subjective effects measure, the modified Cigarette Evaluation Questionnaire (mCEQ), and one behavioral economic task, the Cigarette Purchase Task (CPT), for predicting acute relative reinforcing efficacy measured by concurrent choice Self-Administration (SA).

Methods: Smokers ($N = 169$) belonging to one of three vulnerable populations participated in a multi-site, double-blind study evaluating research cigarettes with varying levels of nicotine (0.4, 2.4, 5.2, 15.8 mg/g). Participants sampled cigarettes and completed the mCEQ and CPT. In subsequent sessions, cigarette preference was assessed using a concurrent choice SA procedure. Mixed-model repeated measures analysis of variance tests were used to evaluate the utility of the mCEQ subscales and CPT indices for predicting preference for the higher compared to lower nicotine content cigarettes. In addition, stepwise regressions were used to determine which subscales and indices independently predicted concurrent choice SA.

Results: Greater increases on the Satisfaction and Enjoyment of Respiratory Tract Sensations mCEQ subscales independently predicted higher dose preference in concurrent choice testing. Elasticity was the only CPT index that predicted choice. However, its predictive utility differed by dose among opioid-maintained individuals.

Conclusion: The mCEQ and CPT predict behavioral measures of relative reinforcing efficacy as assessed in concurrent choice SA, with the mCEQ Satisfaction and Enjoyment of Respiratory Tract Sensations subscales being the strongest independent predictors.

1. Introduction

Cigarette smoking is a public health crisis responsible for nearly half a million U.S. deaths each year (National Center for Chronic Disease, 2014). The morbidity and mortality associated with cigarette smoking can be conceptualized as a side effect of nicotine addiction (Henningfield, 2014). Laboratory methods for assessing the addiction potential of cigarettes are essential for understanding how cigarettes may be used within various populations of interest, with different levels of nicotine, in contexts when alternative sources of nicotine are available or when these products are used in conjunction with other compounds or drugs. Such laboratory methods include behavioral indices, self-report measures of subjective effects, and hypothetical purchase tasks.

Concurrent choice SA is a behavioral task for directly observing rates of voluntary drug use that has long been used to assess the addiction potential of various drugs (Fischman and Foltin, 1991; Johnson and Bickel, 2006; Schuster and Thompson, 1969). This method directly

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assesses the relative reinforcing effects of cigarettes which translates to rates of use outside the laboratory (Haney and Spealman, 2008). A reinforcer is defined by the extent to which it increases future rates of the behavior it follows (Catania, 2012). Therefore, drugs or doses of drugs that are chosen at relatively higher rates are considered to have greater relative reinforcing effects and greater addiction potential. In a concurrent choice SA procedure, two doses of a drug or a drug and a non-drug reinforcer are available at the same time and can be voluntarily administered after a participant performs a given behavior (e.g., clicking on a mouse, pulling a plunger). There are a number of reports using this arrangement under double-blind conditions that show that smokers prefer nicotine content closest to what is found in commercially available cigarettes compared to lower-nicotine content cigarettes, and that as the dose decreases, preference for the product also decreases (Boren et al., 1990; Higgins et al., 2017a, b; Perkins et al., 1996, 2017; Perkins et al., 2018; Shahan et al., 1999).

Subjective effect measures provide another method by which relative reinforcing effects may be evaluated (Fischman and Foltin, 1991). These are not direct measures of preference but are designed to evaluate states, moods or sensations that typically dose-dependently accompany the drug being studied. This method has been used frequently to describe cigarettes with different levels of nicotine (Benowitz et al., 2006; Boren et al., 1990; Butschky et al., 1995; Gross et al., 1997; Hatsukami et al., 2013a; Higgins et al., 2017a,b), with findings indicating that increases in nicotine dose correspond to increases in both positive and negative subjective effects. There is evidence that subjective effects like Satisfaction and Aversion may be, respectively, positively and negatively predictive of SA and therefore may capture acute relative reinforcing effects (Arger et al., 2017 and Perkins et al., 2018).

A third approach to assessing relative reinforcing efficacy is use of the Cigarette Purchase Task (CPT). The CPT is an easily administered self-report method that queries how many cigarettes a participant would smoke in a 24-hour period at various hypothetical price conditions (Jacobs and Bickel, 1999). More recently, the CPT has been used to characterize the addiction potential of cigarettes varying in nicotine content (Higgins et al., 2017a,b; Smith et al., 2017). Five indices are derived from the task which captures how consumption changes under environmental constraint. Intensity measures consumption when there are no or minimal costs, capturing unconstrained consumption of cigarettes. P_{max} is the price per cigarette when consumption becomes sensitive to price. Breakpoint is the price point at which participants will no longer purchase cigarettes because cost is too high. O_{max} is the largest cost a participant is willing to incur to obtain cigarettes. Finally, Elasticity provides an overall index of the sensitivity of cigarette consumption to escalating price. There is some evidence that CPT indices correspond to usual brand cigarette preference relative to nondrug reinforcers in a concurrent choice setting (Chase et al., 2013).

This secondary analysis will determine how a subjective effect measure, the modified Cigarette Evaluation Questionnaire (mCEQ), and a hypothetical purchase task, the CPT, correspond to a direct behavioral measure of the relative reinforcing effects of cigarettes varying in nicotine content as measured in a concurrent choice SA procedure. There have been relatively few reports assessing correspondence between subjective effects and the relative reinforcing effects of cigarettes with varying levels of nicotine. To our knowledge, the relationship between the hypothetical Cigarette Purchase Task (CPT) and concurrent choice SA of cigarettes varying in nicotine content has not been reported. These analyses will demonstrate the utility of the mCEQ and CPT for measuring relative reinforcing effects. Additional analyses further explore the relative utility of these measures by examining the relationship between the mCEQ and CPT with concurrent choice SA across unique smoker populations.

2. Method

This is a secondary analysis of a multisite, double-blind, 3-phase laboratory study testing the acute effects of cigarettes with varying levels of nicotine among three vulnerable populations (socioeconomically disadvantaged women of childbearing age, opioid-maintained individuals and individuals with affective disorders; Higgins et al., 2017a) who are especially at risk to the effects of cigarette smoking (Higgins et al., 2016; Higgins and Chilcoat, 2009; Goodwin et al., 2014; Schroeder, 2016; Weinberger et al., 2018). Groups were not mutually exclusive (e.g., women who were socioeconomically disadvantaged could also be diagnosed with an affective disorder). Methodological details relevant to this secondary analysis are outlined below.

2.1. Participants

Participants are 169 smokers (53 socioeconomically disadvantaged women of childbearing age, 60 opioid-maintained individuals, and 56 individuals with affective disorders) who completed all study sessions. Socioeconomically disadvantaged women were between the ages of 18 and 44 and their highest level of educational achievement was a high school degree. Opioid-maintained individuals were between the ages of 18 and 70 and their prescribing physician confirmed they had > 70% drug-free urines in the past month. Participants with affective disorders were between the ages of 18 and 70 and met criteria on the Mini-International Neuropsychiatric Interview for major depression or anxiety disorders. Participants were deemed ineligible if they endorsed (1) using other tobacco/nicotine products on 9 or more days in the last 30, (2) using any smoking cessation product in the last 30 days, or (3) current serious psychiatric disorders (e.g., psychosis, dementia), substance use, or suicidal ideation. Substance use was evaluated with urinalysis and past 30-day use questionnaire.

2.2. Procedures

Participants completed all visits under acute abstinence which was biochemically verified with at least a 50% reduction in their screening CO value (Johnson et al., 2004; Tidey et al., 1999). In addition, before each session, researchers equated the time since last cigarette puff across all participants by having participants take two ad-lib puffs of their usual brand cigarette and allowing 30 min to elapse prior to beginning session specific tasks. This secondary analysis used data from Phases 1 and 2, which are described in more detail below.

Phase 1 consisted of four sessions where participants sampled the research cigarettes. After the 30-minute waiting period, participants smoked one assigned research cigarette ad-lib through the desktop smoking topography device. Cigarettes were labeled with an arbitrary letter code (e.g., A, B, C and D) which corresponded to different cigarette doses depending on the sequence to which a participant was randomized. Cigarette labeling was kept consistent throughout all subsequent phases. Immediately after smoking the cigarette, participants completed the mCEQ and CPT.

Phase 2 consisted of six sessions where participants chose between two cigarettes both available on a fixed-ratio schedule of reinforcement (FR-10) for three hours. When participants wanted to smoke a certain cigarette, they clicked with a computer mouse 10 times on a computer icon which had the letter code of the corresponding cigarette (Fig. 1). Participants then lit the selected cigarette without inhaling, placed it in the mouth-piece of the desktop smoking topography device and took two standardized puffs (˜60 mL) with feedback displayed on a separate computer monitor. Participants were given 2 min to take the two puffs. During each session in Phase 2, participants could make as many or as few choices for either cigarette as they wanted. The presentation sequence for the six dose comparisons was randomized across participants.

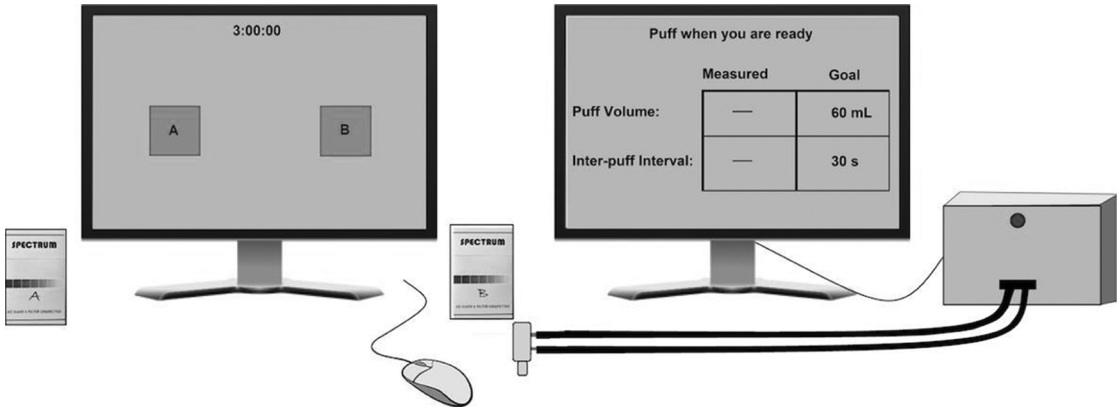

Fig. 1. Laboratory Concurrent Choice Computer and Smoking Topography Machine Arrangement.
This schematic depicts the arrangements of computers, cigarettes and smoking topography machine during Phase 2. The computer on the left ran the concurrent choice program which displayed two icons with letter codes corresponding to the two cigarettes available. The computer on the right provided real-time feedback of puffing behavior with corresponding puff volume and inter-puff interval goals.

2.3. Materials

2.3.1. Research cigarettes

Spectrum research cigarettes manufactured by 22nd Century Group (Clarence, NY) were obtained from the National Institute on Drug Abuse. The study used four nicotine doses, 0.4, 2.4, 5.2, 15.8 mg of nicotine per gram of tobacco (mg/g), and cigarettes were available in menthol or non-menthol flavors based on participant's usual brand cigarette type. The 15.8 mg/g dose is similar to the nicotine content of commercially available cigarettes and functioned as a control condition.

2.3.2. Modified cigarette evaluation questionnaire

Participants rated each of 12 questions (Table 1, left column) on a Likert scale which ranges from 1 (not at all) to 7 (extremely). Responses formed five unique subscales (Table 1, right column). The subscales that make up the questionnaire demonstrate satisfactory convergent validity and have demonstrated good test-retest reliability (Cappelleri et al., 2007). While the Satisfaction and Psychological Reward subscales demonstrated good internal consistency, the Aversion subscale has demonstrated poor internal consistency.

2.3.3. Cigarette purchase task

The same methods used in the parent study (Higgins et al., 2017a,b) were used to analyze the CPT in the present study.

Participants indicated how many cigarettes they would purchase at 20 different price points per cigarette (free, 2¢, 5¢, 10¢, 20¢, 30¢, 40¢, 50¢, 60¢, 70¢, 80¢, 90¢, $1, $2, $3, $4, $5, $10, $20, $40). Participants were instructed to assume that (1) the only available nicotine/tobacco product for use is the assigned study cigarette and (2) all cigarettes purchased must be used in the next 24 h and cannot be stockpiled for a later date.

Table 1
mCEQ Questions and Corresponding Subscales.

Questions	Subscale
Was smoking satisfying?	Satisfaction
Did the cigarette taste good?	
Did you enjoy smoking?	
Did smoking calm you down?	Psychological Reward
Did smoking make you feel more awake?	
Did smoking make you feel less irritable?	
Did smoking help you concentrate?	
Did smoking reduce your hunger for food?	
Did you enjoy the sensations in your throat and chest?	Enjoyment of Respiratory Tract Sensation
Did smoking immediately reduce your craving for a cigarette	Craving Reductions
Did smoking make you dizzy?	Aversion
Did smoking make you nauseous?	

Four of the five indices of the CPT (Intensity, O_{max}, P_{max}, and Breakpoint) were calculated from observed values. Intensity is the quantity of cigarettes 'purchased' when cigarettes were free. O_{max} is the largest expenditure incurred at a single price point. P_{max} is the price point at which O_{max} occurs and represents the point at which the demand curve becomes elastic. Breakpoint is the point at which a participant first indicates they would not purchase any cigarettes, presumably because the costs are too high. Greater Intensity, O_{max}, P_{max}, and Breakpoint and lower Elasticity are associated with greater demand for cigarettes.

Regarding Elasticity, participant-level data were fit to a demand curve ($\ln Q = \ln Q_0 + k(e_0^{-\alpha(QC)} - 1)$) where Q is the quantity consumed, Q_0 (i.e., Intensity) is the quantity consumed when the cigarettes are free (y-intercept), k is the range of the cigarettes consumed in logarithmic units and was kept constant across all individual curve fits and C equals the unit price (Hursch and Silberberg, 2008). α corresponds to Elasticity and was derived for each participant from the demand curve based upon their responses. To log transform the data and model the demand curve, price points where participants reported smoking zero cigarettes were replaced with 0.001.

Elasticity values greater than 1.00 (22 of 845 cases) were winsorized to 1.00 prior to statistical analysis. Analyzing the data with winsorized values produced similar results to setting extreme values to 'missing data'. For the purposes of this study, we only report analyses with winsorized values. We reviewed CPT results and found systematic patterns in 92.7% of demand curves; including unsystematic data did not meaningfully change the results, so 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. Demand curves for the four doses had R^2s which ranged from 0.97 - 0.98, indicating that the demand curves sufficiently described the pattern of data collected. Standard deviation of the residuals indicated that the demand curve well-described purchase task data for the 0.4 mg/g, (Sy.x: $M = 2.34$, *95% CI:* 2.10–2.59), 2.4 mg/g, (Sy.x: $M = 2.30$, *95% CI:* 2.05–2.55), 5.2 mg/g, (Sy.x: $M = 2.46$, *95% CI:* 2.22–2.69), and 15.8 mg/g, (Sy.x: $M = 2.38$, *95% CI:* 2.16–2.60), cigarettes (all R^2s = 0.88 ranges between 0.86 and 0.90).

2.4. Statistical method

Alpha levels for significant findings were set at $p <$ .05.

Diagnostics of multicollinearity determined that multiple regression tests met all necessary assumptions (Ernst and Albers, 2017).

2.4.1. Preparing data to characterize dose comparisons

To characterize the six dose comparisons, difference scores were calculated for each mCEQ subscale and CPT index by subtracting scores/values for the lower dose from scores/values of the higher dose.

To quantify relative reinforcing effects of the cigarettes using data from the concurrent choice assessment, a proportion was calculated for each of the six dose comparisons. Each proportion was computed by dividing the total puffs earned for the higher of the two doses available by the total puffs earned in the choice session. Higher percentages indicated more choices for the higher dose cigarette.

2.4.2. Assessing the predictive utility of individual subscales and indices

Mixed effects repeated measures analysis of variance (ANOVAs) were used to predict proportion of choices for the higher dose with dose comparison as the repeated fixed effect and mCEQ and CPT difference scores, the main independent variables of interest, as fixed effects.

To account for any variability introduced by the design of the parent study, all models included a fixed effect for session and a random effect for the sequence of dose comparison presentations. Vulnerable population group was entered as an additional fixed effect and site (i.e., University of Vermont, Johns Hopkins University, Brown University) was included as a random effect. Finally, because participants could take as many or as few puffs as that they wanted in the choice session, total puffs earned were entered as an additional fixed effect.

Interaction terms were initially included in the model to evaluate whether any prediction of choice by mCEQ or CPT depended on Dose Comparison or Vulnerable Population group. If interaction terms were not significant, they were removed from the model.

2.4.3. Assessing independent predictors of choice

Two separate regression models evaluated which mCEQ subscales and CPT indices were independent predictors of choice. The models included all of the subscale or CPT index difference scores as fixed effects. Non-significant subscales or indices were removed from the model starting with the scale or index with the highest p-value. The model was rerun until the only subscales or indices significantly predictive of choice remained. Finally, this method was repeated including both mCEQ subscales and CPT indices in a single model.

3. Results

3.1. Participant characteristics

As reported in Higgins et al. (2017b), the majority of the 169 participants were female, Caucasian, had a high school education or less and were never married (Table 2). The three populations did not differ on smoking characteristics, smoking an average of 16 CPD and 35% of participants were menthol cigarette smokers. Participants started smoking regularly at 16 years old and had moderate levels of dependence according to the Fagerstrom Test for Cigarette Dependence.

3.2. Descriptive statistics for predictor and outcome variables

The means and standard errors for mCEQ subscale and CPT index difference scores and proportion of choices for the higher dose cigarette are presented for each dose comparison in Table 3. As reported in Higgins et al. (2017a,b), participants showed dose-dependent increases in all five mCEQ subscales and four of the five CPT indices (Intensity, P_{max}, Breakpoint, O_{max}). With regards to the concurrent choice task, participants preferred the higher over the lower dose across all dose pairs with greater preference shown when the dose contrast was larger.

3.3. mCEQ subscales as predictors of choice

3.3.1. Subscales analyzed individually

When analyzed separately, all five mCEQ subscales predicted choice. Greater difference scores for mCEQ subscales were associated with greater preference for the higher dose cigarette (Fig. 2; Satisfaction: $\beta = .07$, $F(1, 1002) = 192.85$, $p < .0001$; Psychological Reward: $\beta = .07$, $F(1, 1003) = 95.01$, $p < .0001$; Enjoyment of Respiratory Tract Sensations: $\beta = 0.06$, $F(1, 1004) = 141.17$, $p < .0001$; Craving Reduction: $\beta = .03$, $F(1, 1002) = 45.35$, $p < .0001$; and Aversion: $\beta = .03$, $F(1, 1003) = 4.66$, $p = .03$).

There was a significant Satisfaction–by-Vulnerable Population interaction where increases in Satisfaction subscale difference scores corresponded to larger increases in preference for the higher dose among socioeconomically disadvantaged women compared to the other two populations, $F(2, 998) = 10.06$, $p < .0001$. In all populations, however, there was a positive and significant relationship between Satisfaction difference scores and choice. No other mCEQ subscale difference scores significantly interacted with Vulnerable Population or Dose Comparison when predicting choice.

Because Aversion subscale difference scores predicted choice in the opposite direction of Arger et al. (2017), post-hoc analyses examined how the two items comprising the Aversion subscale (Nausea and Dizziness) predicted choice. Both Nausea and Dizziness difference scores were significantly predictive of choice across dose comparisons and vulnerable population. However, Nausea difference scores were *negatively* predictive of choice, $\beta = -0.02$, $F(1, 1003) = 4.23$, $p = .04$, while Dizziness difference scores were *positively* predictive of choice, $\beta = .04$, $F(1, 1003) = 22.61$, $p < .001$. These analyses are consistent with poor internal consistency previously reported by Cappelleri et al. (2007).

3.3.2. mCEQ subscales as independent predictors

When all five subscales were included in a final model to test which subscales were independent predictors of cigarette preference, only Satisfaction and Enjoyment of Respiratory Tract Sensations difference scores remained significant, $\beta = .06$, $F(1, 1001) = 52.32$, $p < .0001$, $\beta = .02$, $F(1, 1001) = 7.03$, $p < .01$, respectively. Higher Satisfaction and Enjoyment of Respiratory Tract Sensations difference scores corresponded to a higher proportion of choices for the high dose cigarette.

3.4. CPT indices as predictors of choice

When analyzed separately, Intensity and Elasticity index difference scores were predictive of choice and O_{max}, P_{max} and Breakpoint difference scores were not.

3.4.1. Intensity

Higher Intensity difference scores weakly but significantly corresponded to greater preference for the higher dose cigarettes, $\beta = 0.002$, $F(1, 944) = 19.44$, $p < .001$. However, there was a significant 3-way interaction among Intensity, Population and Dose Comparison, indicating that the predictive utility of Intensity varied depending on Vulnerable Population and Dose Comparison, $F(10, 882) = 2.70$, $p < .01$ (Fig. 3). More specifically, Intensity difference scores predicted choice among socioeconomically disadvantaged women of childbearing age ($\beta = .02$, $F(1, 288) = 18.35$, $p < .001$) and individuals with affective disorders ($\beta = .004$, $F(1, 312) = 5.49$, $p < .05$) but not among opioid-maintained individuals ($\beta = -0.007$, $F(1, 336) = 0.00$, $p = .99$; Fig. 3). In addition, there was a significant Intensity–by-Dose Comparison interaction among socioeconomically disadvantaged women of childbearing age ($F(5, 276) = 3.03$, $p = .01$), where the Intensity index difference scores were only significantly predictive of choice in the 0.4 v. 2.4, 5.2 v. 15.8 and 2.4 v 15.8 mg/g dose comparisons.

Table 2
Participant Characteristics.

	All (n = 169)	Disadvantaged Women (n = 53)	Opioid-Maintained (n = 60)	Affective Disorders (n = 56)
Age (years, M ± SD)	35.6 ± 11.4	30.0 ± 7.0	41.0 ± 11.2	35.0 ± 12.4
Gender (% Female)	71	100	60	55
Race (%)				
White	73	77	70	71
American Indian/Alaskan Native	0	0	0	0
Asian	0.6	0	0	2
Black/African-American	14	15	20	5
Native Hawaiian/Pacific Islander	0.6	0	2	0
Other/More than 1 race	9	4	9	14
Latino/a	3	4	0	6
Education (%)				
8th Grade or less	2	2	3	2
Some High School	14	17	17	7
High School Graduate/Equivalent	34	38	37	28
Some college	38	43	35	36
2- Year Associate's Degree	6	0	8	9
College Graduate/4-Year Degree	3	0	0	11
Graduate or Professional Degree	2	0	0	7
Marital Status (%)				
Married	15	27	7	14
Never married	61	64	53	66
Divorced/Separated	21	8	35	17
Widowed	2	2	3	2
Cigarettes Per Day (M ± SD)	15.8 ± 7.5	14.5 ± 6.3	16.5 ± 6.1	16.3 ± 9.5
Primary Menthol Smoker (%)	35	30	38	36
Age Started Smoking Regularly (years, M ± SD)	16.3 ± 4.3	16.4 ± 3.7	16.2 ± 5.5	16.2 ± 3.1
Fagerstrom Test for Cigarette Dependence (M ± SD)	5.0 ± 2.2	4.6 ± 2.3	5.3 ± 1.8	5.0 ± 2.3

3.4.2. Elasticity

Lower Elasticity difference scores were associated with greater preference for the higher dose cigarettes, β = -0.22, $F(1, 849) = 22.55$, $p < .001$. There was a significant 3-way interaction among Elasticity, Population and Dose Comparison, indicating that the predictive utility of Elasticity differed by vulnerable population and dose comparison, $F(10, 791) = 2.25$, $p = .01$. In all three vulnerable populations of interest, difference scores on the Elasticity index were negatively associated with choice (Fig. 4). However, among opioid-maintained individuals, difference scores on the Elasticity index were differentially predictive of choice across different dose comparisons (Elasticity–by-Dose: $F(5, 298) = 3.96$, $p < .01$), with scores positively predicting choice for the 2.4 v. 5.2 dose comparison and negatively predicting choice across all other dose comparisons.

3.4.3. CPT indices as independent predictors

When all five indices were included in a model to test which were independent predictors of cigarette preference, only Elasticity difference scores remained significant, β = -0.22, $F(1, 849) = 22.55$, $p < .001$. Lower Elasticity difference scores for the high dose cigarette corresponded to a higher proportion of choices for the high dose cigarette.

3.5. Unique predictors of choice

When all mCEQ subscales and CPT indices were included as potential predictors in a final model, only Satisfaction and Enjoyment of Respiratory Tract Sensations subscales difference scores predicted preference for the higher dose cigarette. Thus, the CPT indices do not add any information to the model presented above for the mCEQ subscales.

Table 3
Descriptive Statistics [Mean (Standard Error)] for Predictor Differences and Outcome Variables across Dose Comparisons.

	Dose Comparison					
	0.4 vs. 2.4	2.4 vs. 5.2	0.4 vs. 5.2	5.2 vs. 15.8	2.4 vs. 15.8	0.4 vs. 15.8
mCEQ Subscale						
Satisfaction	0.41 (0.14)	0.26 (0.13)	0.67 (0.13)	0.77 (0.14)	1.04 (0.14)	1.45 (0.14)
Psychological Reward	0.16 (0.10)	0.23 (0.10)	0.39 (0.11)	0.37 (0.11)	0.60 (0.11)	0.76 (0.11)
Enjoyment of Respiratory Tract Sensations	0.22 (0.14)	0.42 (0.13)	0.64 (0.15)	0.58 (0.14)	1.00 (0.16)	1.22 (0.16)
Craving Reduction	0.30 (0.16)	0.30 (0.15)	0.59 (0.15)	0.57 (0.15)	0.86 (0.15)	1.16 (0.17)
Aversion	0.04 (0.05)	0.00 (0.06)	0.04 (0.06)	0.24 (0.07)	0.24 (0.08)	0.28 (0.07)
CPT Index						
Elasticity	−0.01 (0.02)	−0.02 (0.01)	−0.03 (0.03)	−0.02 (0.01)	−0.04 (0.02)	−0.04 (0.02)
Intensity	0.41 (0.82)	1.59 (0.61)	2.03 (0.69)	0.44 (0.66)	2.05 (0.76)	2.52 (0.88)
O_{max}	−4.61 (6.40)	3.93 (4.30)	−0.44 (3.49)	8.79 (4.71)	12.53 (7.83)	8.51 (4.74)
P_{max}	0.11 (0.57)	0.42 (0.52)	0.52 (0.63)	0.72 (0.68)	1.14 (0.67)	1.25 (0.58)
Breakpoint	0.36 (0.92)	0.55 (0.98)	0.91 (0.93)	1.07 (1.01)	1.63 (1.10)	2.32 (0.99)
Concurrent Choice						
Proportion of Choice for Higher Dose	.58 (.03)	.57 (.03)	.62 (.03)	.64 (.03)	.68 (.02)	.71 (.02)

Note: mCEQ – modified cigarette evaluation questionnaire, CPT – cigarette purchase task, O_{max} – Maximum Expenditure, P_{max} – price at which expenditure is maximized.

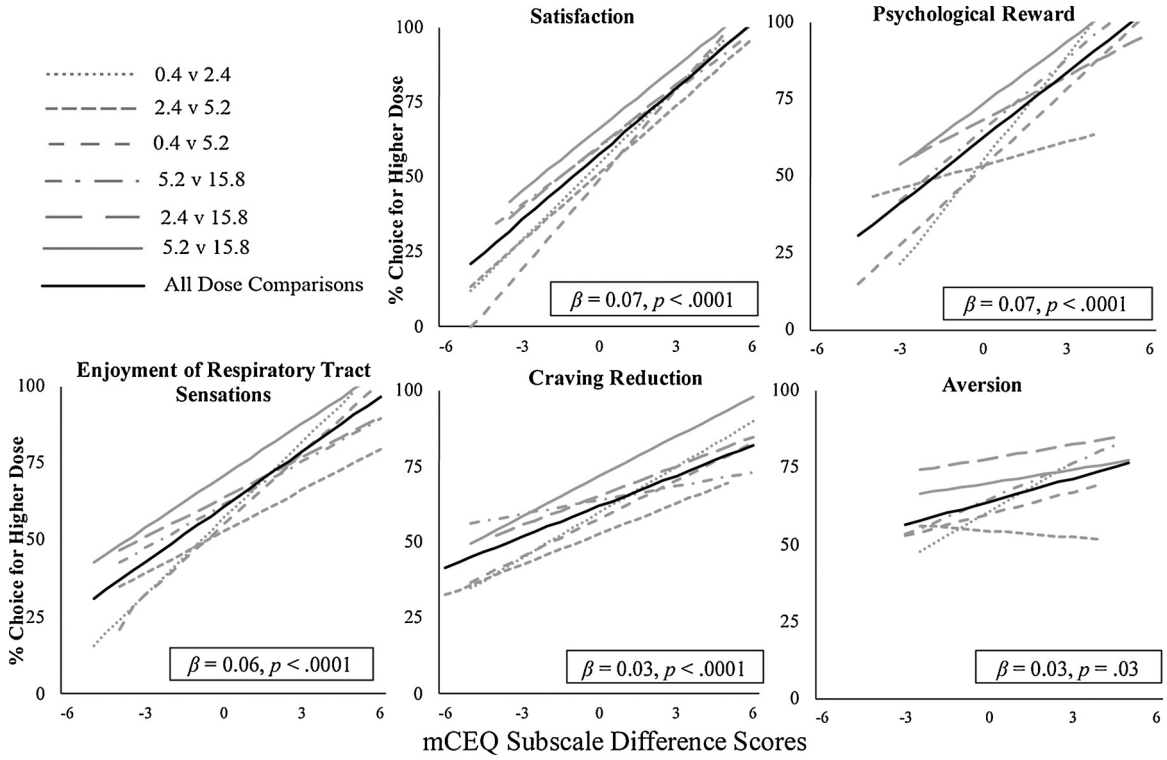

Fig. 2. Relationship between mCEQ Subscales and Choice by Vulnerable Population and Dose Comparison.
Modified Cigarette Evaluation Questionnaire (mCEQ) subscale difference scores and cigarette preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines). mCEQ subscales did not predict choice differently across the dose comparisons (Subscale X Dose Comparison, p's > 0.05).

4. Discussion

Relative reinforcing efficacy is a robust behavioral predictor of the addictive properties of nicotine-containing products and thus of considerable relevance when evaluating the abuse liability of new drugs or drug containing products. The present study tested the extent to which mCEQ subscales and CPT indices predict differences in the acute relative reinforcing effects of cigarettes that vary in nicotine content as directly measured by a concurrent choice SA procedure. These analyses provide a more detailed characterization of the mCEQ subscales and CPT indices and their potential utility in predicting the relative reinforcing effects (i.e., addiction potential) of tobacco products.

Overall, positive subjective effect measures appear to consistently correspond to concurrent choice SA preferences for cigarettes varying in nicotine content. Indeed, in the final model including mCEQ subscales and CPT indices, only the mCEQ Satisfaction and Enjoyment of Respiratory Tract Sensations subscales remained predictive of choice, with the Satisfaction subscale score being the stronger predictor of these two. Furthermore, unlike the CPT indices, the direction of the relationship between Satisfaction and Enjoyment of Respiratory Tract Sensations and SA was consistent across dose comparisons and vulnerable populations. This suggests that mCEQ subscales are more consistent than CPT indices with data from concurrent choice tasks across various contexts. These results, in combination with previous findings (Arger et al., 2017; Perkins et al., 2018), suggests that Satisfaction is the best subjective effect predictor of relative reinforcing efficacy as measured in concurrent choice procedures.

Among the five CPT indices, Elasticity appears to be unique in its ability to capture acute relative reinforcing effects measured during concurrent choice SA. It was the only CPT index to remain predictive of choice when considering all other CPT indices in a single model. However, both CPT indices that predicted choice when analyzed separately (Intensity and Elasticity) varied in their utility depending on vulnerable population and dose comparison. For example, Elasticity predicted preference for higher over lower nicotine content cigarettes at the 0.4 vs. 2.4 and 2.4 vs. 5.2 dose pairs among disadvantaged women and smokers with affective disorders, but not those with opioid dependence. Furthermore, Intensity, while predictive of choice among socioeconomically disadvantaged women of childbearing age and individuals with affective disorders, was not predictive of choice among opioid-maintained individuals.

The tendency for CPT indices to predict SA differently across vulnerable populations may be a function of its greater sensitivity to individual differences in daily smoking rates, tobacco dependence severity, and severity of co-morbid medical conditions than the mCEQ and concurrent choice procedures which appear to be relatively insensitive to these differences (e.g., Bidwell et al., 2012; Cappelleri et al., 2007; Higgins et al., 2018; MacKillop and Tidey, 2011; Streck et al., 2018). This sensitivity to individual differences suggests that the CPT is dynamic and captures facets of abuse liability beyond relative reinforcement (Bickel et al., 2000). Consistent with this, previous work by Chase et al. (2013) demonstrated that the CPT appears to capture unique features of dependence that concurrent choice does not.

While the present study provides a rigorous evaluation of the mCEQ and CPT for predicting the relative reinforcing effects of smoking, our results should be considered in light of some limitations. First, while concurrent choice SA is a laboratory proxy for drug taking in naturalistic settings, a more thorough analysis of the mCEQ and CPT would be to analyze how these measures differentially correspond to rates of use outside of the laboratory. Particularly, subjective effect measures have not been well characterized for their predictive validity of naturalistic cigarette use. Therefore, the clinical utility of these subscales and indices should be interpreted with caution pending additional validation in naturalistic settings. Second, it is unclear how well the relationships between these mCEQ and CPT and SA data extend to other tobacco products. For example, Stein et al. (2017) reported that the relationship between hypothetical purchase data and SA differed depending on the particular tobacco product being assessed and perhaps

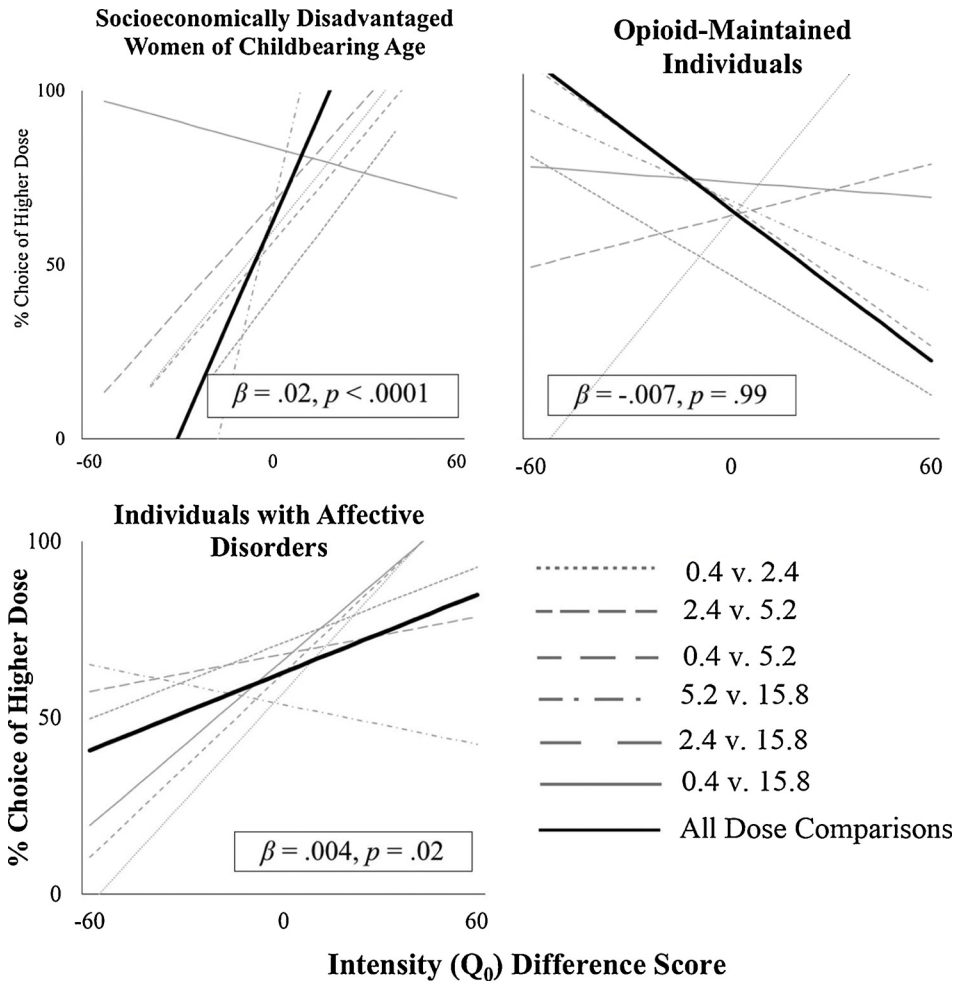

Fig. 3. Relationship between CPT Intensity and Choice by Vulnerable Population and Dose Comparison.
Intensity difference scores and cigarette choice preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines) separated by vulnerable population group. Among opioid-maintained individuals, Intensity was not predictive of choice and among socioeconomically disadvantaged women of childbearing age, Intensity was only predictive of choice at certain dose-comparisons.

participant familiarity with a product (cigarettes v. snus or nicotine gum). That said, other reports have noted consistencies across tobacco products when evaluating the relationship between subjective effects and SA (Arger et al., 2017; Hatsukami et al., 2013a, b; Perkins et al., 1996, 2018). Together, these limitations provide points for further consideration in future investigations of how subjective effects and purchase-task indices relate to relative reinforcing efficacy and the addiction potential of cigarette smoking and use of other tobacco and nicotine delivery products.

In summary, these data provide new knowledge regarding the individual components of the mCEQ and CPT in assessing and predicting the relative reinforcing effects and addiction potential of cigarette that vary in nicotine content and perhaps other tobacco and nicotine delivery products. Both instruments were sensitive to common aspects of the relative reinforcing effects of nicotine content, but when assessed together only the mCEQ Satisfaction and Enjoyment of Respiratory Tract Sensations subscales were independent predictors. One notable feature of the CPT relative to mCEQ was greater sensitivity to population differences in predicting response to reduced nicotine content cigarettes. As such, the results of the present report outline strengths and limitations of these measures which should be considered when seeking a comprehensive assessment of the addiction potential of reduced nicotine content cigarettes across populations and perhaps other tobacco and nicotine delivery products.

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Contributors

CLB collected data, created the statistical plan, interpreted results, and drafted the original manuscript, tables and figures. SHH helped conceptualize and design the parent study, helped conceptualize the statistical analyses for this secondary analysis, and helped draft the manuscript, tables and figures. DRD collected data and edited and reviewed the manuscript, tables and figures. JMS collected data and edited and reviewed the manuscript, tables and figures.

SCS helped conceptualize and design the parent study and edited and reviewed the manuscript, tables and figures. JYB helped create the statistical plan, conducted the statistical analyses, and helped interpret the results. JWT helped conceptualize and design the parent study and

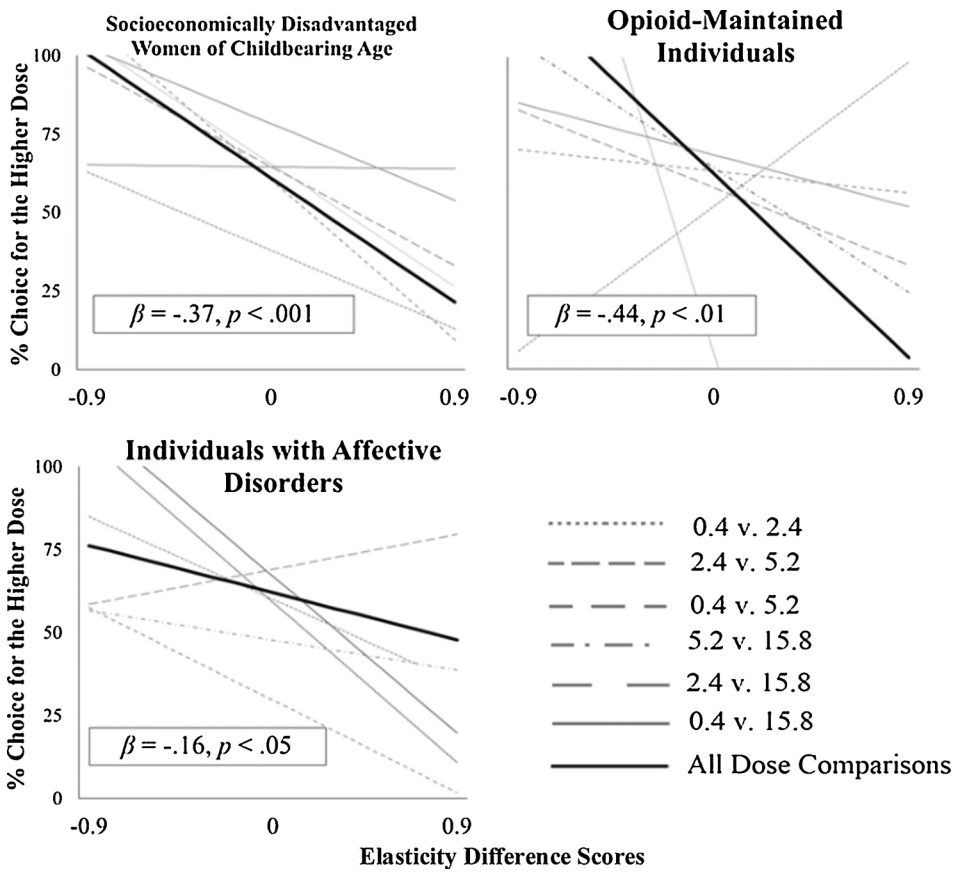

Fig. 4. Relationship between CPT Elasticity and Choice by Vulnerable Population and Dose Comparison.
Elasticity difference scores and cigarette choice preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines) broken down by vulnerable population group. Among opioid-maintained individuals, Elasticity predicted cigarette choice preference depending on the dose comparison being analyzed.

edited and reviewed the manuscript, table and figures. CAA collected data and edited and reviewed the manuscript, tables and figures. DRD consulted/advised on Cigarette Purchase Task-related analyses and interpretation. TG collected data and edited and reviewed the manuscript, tables and figures. JRH helped conceptualize and design the parent study, acted as Medical Director for the parent study, and edited and reviewed the manuscript, tables and figures. DEG helped conceptualize and design the parent study and edited and reviewed the manuscript, tables and figures. MLS helped conceptualize and design the parent study and edited and reviewed the manuscript, tables and figures. STH conceptualized and designed the parent study, conceptualized the statistical analyses for this secondary analysis, and edited and reviewed the manuscript, tables and figures. All authors have approved the final article.

Conflict of interest

JRH has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control and also consults (without payment) for Swedish Match. All other authors have nothing to declare.

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References

Arger, C.A., Heil, S.H., Sigmon, S.C., Tidey, J.W., Stitzer, M.L., Gaalema, D.E., Durand, H.J., Bunn, J.Y., Ruggieri, E.K., Higgins, S.T., 2017. Preliminary validity of the modified Cigarette Evaluation Questionnaire in predicting the reinforcing effects of cigarettes that vary in nicotine content. Exp. Clin. Psychopharmacol. 25, 473–478.

Benowitz, N.L., Jacob 3rd, P., Herrera, B., 2006. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin. Pharmacol. Ther. 80, 703–714.

Bickel, W.D., Marsch, L.A., Carroll, M.E., 2000. Deconstructing relative reinforcing efficacy and situating the measures of pharmacological reinforcement with behavioral economics: a theoretical proposal. Psychopharmacology 153, 44–56.

Bidwell, L.C., MacKillop, J., Murphy, J.G., Tidey, J.W., Colby, S.M., 2012. Latent factor structure of a behavioral economic cigarette demand curve in adolescent smokers. Addict. Behav. 37, 1257–1263.

Boren, J.J., Stitzer, M.L., Henningfield, J.E., 1990. Preference among research cigarettes with varying nicotine yields. Pharmacol. Biochem. Behav. 36, 191–193.

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

Cappelleri, J.C., Bushmakin, A.G., Baker, C.L., Merikle, E., Olufade, A.O., Gilbert, D.G., 2007. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict. Behav. 32, 912–923.

Catania, A.C., 2012. Learning, 5th edition. Sloan Publishing, Hudson, NY.

Chase, H.W., MacKillop, J., Hogarth, L., 2013. Isolating behavioral economic indices of demand in relation to nicotine dependence. Psychopharmacology 226, 371–380.

Ernst, A.F., Albers, C.J., 2017. Regression assumptions in clinical psychology research practice-a systematic review of common misconceptions. PeerJ 5, e3323.

Fischman, M.W., Foltin, R.W., 1991. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. Br. J. Addict. 86, 1563–1570.

Goodwin, R.D., Sheffer, C.E., Chartrand, H., Bhaskaran, J., Hart, C.L., Sareen, J., Bolton, J., 2014. Drug use, abuse, and dependence and the persistence of nicotine dependence. Nicotine Tob. Res. 16, 1606–1612.

Gross, J., Lee, J., Stitzer, M.L., 1997. Nicotine-containing versus de-nicotinized cigarettes: effects on craving and withdrawal. Pharmacol. Biochem. Behav. 57, 159–165.

Haney, M., Spealman, R., 2008. Controversies in translational research: drug self-administration. Psychopharmacology 199, 403–419.

Hatsukami, D.K., Heishman, S.J., Vogel, R.I., Denlinger, R.L., Roper-Batker, A.N., Mackowick, K.M., Jensen, J., Murphy, S.E., Thomas, B.F., Donny, E., 2013a. Dose-response effects of spectrum research cigarettes. Nicotine Tob. Res. 15, 1113–1121.

Hatsukami, D.K., Zhang, Y., O'Connor, R.J., Severson, H.H., 2013b. Subjective responses to oral tobacco products: scale validation. Nicotine Tob. Res. 15, 1259–1264.

Henningfield, J.E., 2014. The tobacco endgame: it's all about behavior. Prev. Med. 68, 11–16.

Higgins, S.T., Chilcoat, H.D., 2009. Women and smoking: an interdisciplinary examination of socioeconomic influences. Drug Alcohol Depend. 104, S1–S5.

Higgins, S.T., Kurti, A.N., Redner, R., White, T.J., Keith, D.R., Gaalema, D.E., Sprague, B.L., Stanton, C.A., Roberts, M.E., Doogan, N.J., Priest, J.S., 2016. Co-occurring risk factors for current cigarette smoking in a U.S. Nationally representative sample. Prev. Med. 92, 110–117.

Higgins, S.T., Heil, S.H., Sigmon, S.C., Tidey, J.W., Gaalema, D.E., Hughes, J.R., Stitzer, M.L., Durand, H., Bunn, J.Y., Priest, J.S., Arger, C.A., Miller, M.E., Bergeria, C.L., Davis, D.R., Streck, J.M., Reed, D.D., Skelly, J.M., Tursi, L., 2017a. Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction. JAMA Psychiatry 74, 1056–1064.

Higgins, S.T., Heil, S.H., Sigmon, S.C., Tidey, J.W., Gaalema, D.E., Stitzer, M.L., Durand, H., Bunn, J.Y., Priest, J.S., Arger, C.A., Miller, M.E., Bergeria, C.L., Davis, D.R., Streck, J.M., Zvorsky, I., Redner, R., Vandrey, R., Pacek, L.R., 2017b. Response to varying the nicotine content of cigarettes in vulnerable populations: an initial experimental examination of acute effects. Psychopharmacology 234, 89–98.

Higgins, S.T., Bergeria, C.L., Davis, D.R., Streck, J.M., Villanti, A.C., Hughes, J.R., Sigmon, S.C., Tidey, J.W., Heil, S.H., Gaalema, D.E., Stitzer, M.L., Priest, J.S., Skelly, J.M., Reed, D.D., Bunn, J.Y., Tromblee, M.A., Arger, C.A., Miller, M.E., 2018. Response to reduced nicotine content cigarettes among smokers differing in tobacco dependence severity. Prev. Med. 117, 15–23.

Hursch, S.R., Silberberg, A., 2008. Economic demand and essential value. Psychol. Rev. 115, 186–189.

Jacobs, E.A., Bickel, W.K., 1999. Modeling drug consumption in the clinic using simulation procedures: demand for heroin and cigarettes in opioid-dependent outpatients. Exp. Clin. Psychopharmacology 7, 412–426.

Johnson, M.W., Bickel, W.K., 2006. Replacing relative reinforcing efficacy with behavioral economic demand curves. J. Exp. Anal. Behav. 85, 73–93.

Johnson, M.W., Bickel, W.K., Kirshenbaum, A.P., 2004. Substitutes for tobacco smoking: a behavioral economic analysis of nicotine gum, denicotinized cigarettes, and nicotine-containing cigarettes. Drug Alcohol Depend. 74, 253–264.

MacKillop, J., Tidey, J.W., 2011. Cigarette demand and delayed reward discounting in nicotine-dependent individuals with schizophrenia and controls: an initial study. Psychopharmacology (Berl.) 216, 91–99.

National Center for Chronic Disease Prevention and Health Promotion (US).

Perkins, K.A., Grobe, J.E., Weiss, D., Fonte, C., Caggiula, A., 1996. Nicotine preference in smokers as a function of smoking abstinence. Pharmacol. Biochem. Behav. 55, 257–263.

Perkins, K.A., Karelitz, J.L., Kunkle, N., 2017. Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. Nicotine Tob. Res. 30, 1258–1264.

Perkins, K.A., Karelitz, J.L., Kunkle, N., 2018. Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content. J. Psychopharmacol. 32, 324–331.

Schroeder, S.A., 2016. American health improvement depends upon addressing class disparities. Prev. Med. 92, 6–15.

Schuster, C.R., Thompson, T., 1969. Self administration of and behavioral dependence on drugs. Annu. Rev. Pharmacol. 9, 483–502.

Shahan, T.A., Bickel, W.K., Madden, G.J., Badger, G.J., 1999. Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: a behavioral economic analysis. Psychopharmacology 147, 210–216.

Smith, T.T., Cassidy, R.N., Tidey, J.W., Luo, X., Le, C.T., Hatsukami, D.K., Donny, E.C., 2017. Impact of smoking reduced nicotine content cigarettes on sensitivity to cigarette price: further results from a multi-site clinical trial. Addiction 112, 349–359.

Stein, J.S., Wilson, A.G., Koffarnus, M.N., Judd, M.C., Bickel, W.K., 2017. Naturalistic assessment of demand for cigarettes, snus, and nicotine gum. Psychopharmacology 234, 245–254.

Streck, J.M., Bergeria, C.L., Parker, M.A., Davis, D.R., DeSarno, M., Sigmon, S.C., Hughes, J.R., Gaalema, D.E., Heil, S.H., Tidey, J.W., Stitzer, M.L., Rothman, M., Higgins, S.T., 2018. Response to reduced nicotine content cigarettes among smokers with chronic health conditions. Prev. Med. Rep. 12 (321), 329.

Tidey, J.W., O'Neill, S.C., Higgins, S.T., 1999. Effects of abstinence on cigarette smoking among outpatients with schizophrenia. Exp. Clin. Psychopharmacol. 7, 347–353.

Weinberger, A.H., Bandiera, F.C., Leventhal, A.M., Dierker, L.C., Gbedemah, M., Tidey, J.W., Goodwin, R.D., 2018. Socioeconomic disparities in smoking among U.S. Adults with depression, 2005–2014. Am. J. Prev. Med. 54, 765–775.