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EVALUATING THE UTILITY OF THE MODIFIED CIGARETTE EVALUATION
QUESTIONNAIRE AND THE CIGARETTE PURCHASE TASK FOR PREDICTING
ACUTE RELATIVE REINFORCING EFFICACY IN CIGARETTES WHICH VARY
IN NICOTINE CONTENT

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ABSTRACT

Rationale: Nicotine is the addictive component in cigarettes which maintains cigarette smoking that subsequently leads to morbidity and mortality. There are growing regulatory efforts to lower the nicotine content in cigarettes so that they are minimally addictive. Valid methods for assessing the abuse liability of cigarettes are essential to these efforts. While subjective effect measures and hypothetical purchase tasks are appealing because they are far easier to administer, it is unclear whether these methods can be used to evaluate acute relative reinforcing, a critical component of abuse liability. This secondary analysis sought to evaluate the utility of one subjective effects measure, the modified Cigarette Evaluation Questionnaire (mCEQ), and one hypothetical purchase task, the Cigarette Purchase Task (CPT), for predicting acute relative reinforcing efficacy as measured by concurrent choice Self-Administration (SA)

Method: Current smokers (N=169) belonging to one of three vulnerable populations (socioeconomically disadvantaged women of childbearing age, opioid-maintained individuals, or individuals with affective disorders) participated in a multi-site, double blind study evaluating research cigarettes with varying levels of nicotine content (0.4, 2.4, 5.2, 15.8 mg/g). In Phase I (4 sessions, 1 research cigarette per session) participants completed the mCEQ and CPT following ad-lib smoking of the research cigarette. In Phase II (6 sessions) cigarette preference was assessed using two-dose concurrent choice tests. Difference scores were calculated for each of the five mCEQ subscales and five CPT indices for all six possible dose comparisons evaluated in Phase II. We evaluated the utility of the mCEQ subscale and CPT index difference scores for predicting preference for the higher dose in a given dose comparison using a mixed-model of repeated measures analysis of variance. Finally, we used stepwise regressions to determine which subscales and indices served as independent predictors of concurrent choice SA.

Results: Among mCEQ subscales, higher Satisfaction and Enjoyment of Respiratory Tract Sensation were independently predictive of higher dose preference in the choice testing regardless of dose comparison. There was a significant Satisfaction X Vulnerable Population interaction where increases in Satisfaction difference scores corresponded to greater changes in higher dose preference among socioeconomically disadvantaged women of childbearing age compared to other Vulnerable Populations. Among CPT indices, Elasticity was the only independent predictor of choice. However, there was a significant Elasticity X Dose Comparison X Vulnerable Population interaction associated with its predictive utility where the relationship between elasticity and choice differed by dose among opioid-maintained individuals. In a final model, including all subscales and indices, Satisfaction and Enjoyment of Respiratory Tract Sensations remained the only significant predictors of choice.

Discussion: Concurrent choice testing, subjective effects and hypothetical purchase tasks capture some common features of abuse liability. Concurrent choice testing and the Satisfaction subscale were the most concordant measures. The observation that CPT indices are not robust predictors of choice in a concurrent arrangement suggests this measure may have greater utility for capturing individual differences as opposed to isolating the acute relative reinforcing effects of nicotine. Nevertheless, all three measures can contribute to efforts to assess the abuse liability of cigarettes varying in nicotine dose and important work aimed at regulating these products to improve human health.

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CHAPTER 1: INTRODUCTION

1.1. Public Health Impact of Cigarette Smoking

Nearly half a million Americans die every year from cigarette smoking-related diseases (U.S. Department of Health and Human Services [USDHHS], 2014). The most recent Surgeon General's report concluded that cigarette smoking causes numerous cancers, poor cardiovascular health, adverse reproductive health outcomes, respiratory dysfunction as well as diabetes and eye diseases (USDHHS, 2014). Smoking-related health problems cost an estimated \$300 billion dollars annually (USDHHS, 2014; Xu, Bishop, Kennedy, Simpson & Pechacek, 2015). Despite the wide array of risks and substantial costs, about 15% of Americans are current cigarette smokers (Center for Disease Control and Prevention, 2016).

Cigarettes contain over 5,000 constituents; so far, 93 have been identified as harmful or potentially harmful and subsequently categorized as a carcinogen, a cardiovascular toxicant, a reproductive or developmental toxicant, a respiratory toxicant and/or addictive (Food and Drug Administration [FDA], 2012; Talhout, Schulz, Florek, van Benthem, Wester & Opperhuizen, 2011; Royal College of Physicians, 2016). The single constituent that drives persistent use of cigarettes is nicotine (USDHHS, 1988; 2014). Indeed, thirty years ago, the Surgeon General's report concluded that "nicotine is the drug in tobacco that causes addiction" (USDHHS, 1988). Importantly, the dose of nicotine obtained from smoking a cigarette influences the addictiveness of the product (Benowitz & Henningfield, 1994, Boren, Stitzer & Henningfield, 1990, Donny et al., 2015, Higgins et al., 2017a, Higgins et al., 2017b, Perkins, Grobe, Caggiula, Wilson & Stiller, 1996, Perkins, Kunkle, Michael, Karelitz & Donny, 2016, Shahan et al., 1999).

The morbidity and mortality related to cigarette smoking can be conceptualized as a side effect of nicotine addiction (Henningfield, 2014). To address this persistent and harmful behavior, public health interventions should target nicotine and its addictive properties. In a recent commentary in *The New England Journal of Medicine*, the current Food and Drug Administration Commissioner and the Director of the Center for Tobacco Products within the Food and Drug Administration declared their intention to shape a regulatory framework to eliminate the use of combustible tobacco products (mainly cigarettes) by targeting nicotine (Gottlieb & Zeller, 2017). Consistent with this report, on March 15th, 2018, Commissioner Gottlieb issued an advance notice of proposed rulemaking to lower nicotine in cigarettes to a minimally or non-addictive level (Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, 2018).

1.2. Reducing Nicotine in Cigarettes

For decades, research has shown that reducing the amount of nicotine obtained from a cigarette reduces its addictiveness (Benowitz & Henningfield, 2013; Boren et al., 1990; Donny et al., 2015; Shahan et al., 1999). The two main approaches to reducing the amount of nicotine obtained from smoking have been reducing the nicotine yield and reducing the content.

1.2.1. Reducing Nicotine Yield. Early efforts to reduce the amount of nicotine smokers obtained from each cigarette attempted to do so by lowering the nicotine yield of a cigarette by altering its physical structure (i.e., increasing the number of holes in the filter). While the tobacco in the cigarette was the same, it was thought that smokers would obtain less nicotine because more would escape through the filter holes before reaching the smoker. These modified cigarettes were introduced to the market in the

1970s and advertised as “light” cigarettes. While they are perceived to have lower risks, studies indicate levels of exposure are comparable between “light” and “full flavor” cigarettes (Benowitz et al., 1983; Benowitz et al., 1986; Yong et al., 2016) as the reduced nicotine yield of light cigarettes is easily overcome by a smoker if he/she alters how they hold their cigarette (e.g., blocking the filter holes with their lips or fingers). Nicotine yield, therefore, does not necessarily correspond to the delivered dose (Kozlowski & O’Connor, 2002; Strasser, Ashare, Kozlowski, & Pickworth, 2005).

1.2.2. Reducing Nicotine Content. Another way to decrease the nicotine dose is to lower the nicotine content of a cigarette by manipulating how much nicotine is in that cigarette. Historically, this was done by mixing regular nicotine content tobacco with some portion of nicotine-free tobacco (e.g., Boren et al., 1990). More recently, varying nicotine concentrations are achieved by genetically modifying tobacco (e.g., Donny et al., 2015). This new method has helped accelerate research testing the long-standing hypothesis that there is a so-called nicotine dose threshold for cigarette addiction (Benowitz & Henningfield, 1994).

In their influential *New England Journal of Medicine* commentary, Benowitz and Henningfield (1994) hypothesized that reducing nicotine content to levels less than 0.7 milligrams of nicotine per gram of tobacco (mg/g) could render cigarettes less addictive with the potential to decrease cigarette use and dependence. They based this dose on the nicotine intake of cigarette smokers who smoked infrequently and self-reported no withdrawal when they abstained from smoking. Currently, the nicotine content of most commercially available cigarettes ranges from 13.5-19.5 mg/g (MacGregor et al., 2014; Malson, Sims, Murty & Pickworth, 2001). Cigarettes which fall below commercially

available levels of nicotine are referred to as reduced nicotine content (RNC) cigarettes. Cigarettes which fall below Benowitz and Henningfield's threshold are referred to as very low nicotine content (VLNC) cigarettes or, in some cases, denicotinized cigarettes.

Another factor that has focused more scientific attention on RNC cigarettes is the signing of the Family Smoking Prevention and Tobacco Control Act in 2009 by President Obama (Figure 1-1). This piece of

legislation gave the FDA the ability to reduce, but not eliminate, the nicotine in

cigarettes. Now that nicotine content regulation is within the scope of the FDA's authority, testing Benowitz & Henningfield's hypothesis is more critical than ever as results will influence regulatory policy being formulated right now.

A growing body of literature indicates that lowering the nicotine content in cigarettes renders cigarettes less addictive and decreases cigarette consumption and thereby toxicant exposure over extended periods of time (Benowitz et al., 2007; Benowitz et al., 2012; Donny et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2017; Higgins et al., 2017a; Higgins et al., 2017b). In a recent randomized controlled trial published in *The New England Journal of Medicine*, smokers who were not trying to quit and who

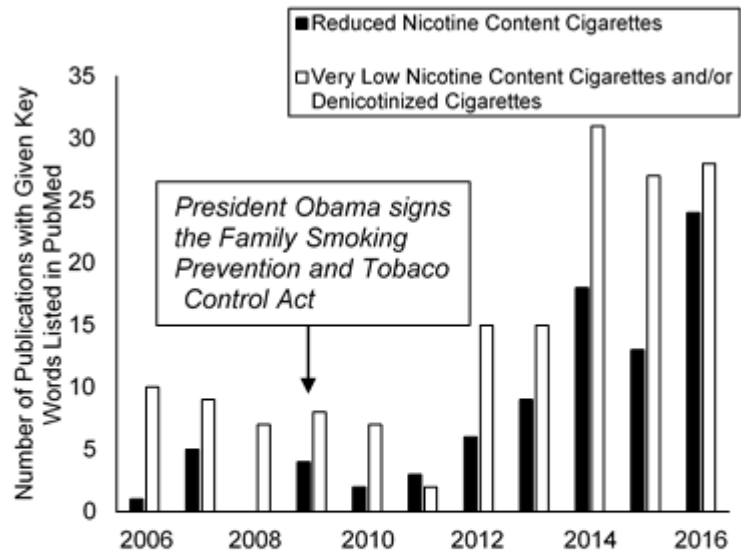


Figure 1-1. Number of articles with "reduced nicotine content cigarettes" or "very low nicotine content cigarettes" as a key term in the years 2006-2016. Denicotinized cigarettes are a term used for cigarettes with nicotine levels comparable to very low nicotine content cigarettes.

received VLNC cigarettes free of charge for 6 weeks smoked 30% fewer cigarettes per day at the end of the study compared to those who received normal nicotine content cigarettes (16 vs. 22 cigarettes per day, respectively; Donny et al., 2015). Consistently with this, smokers assigned to VLNC cigarettes had lower nicotine exposure. Finally, participants who received VLNC cigarettes were more likely to report making a quit attempt in the 30 days after completing the study. While this study is the largest and most rigorous to date, there are other long-term exposure studies reporting similar outcomes (e.g., Benowitz et al., 2007; Hatsukami et al., 2013a; Hatsukami et al., 2017).

Given increasing interest, methods for assessing the addictiveness of cigarettes varying in nicotine content are essential for predicting how these products are used among various populations of interest, in contexts when alternative sources of nicotine are available or when these products are used in conjunction with other compounds or drugs. Methods for assessing the addictive properties of nicotine-containing products are outlined below, with a focus on behavioral measures, specifically self-administration, and self-report measures, specifically subjective effect measures and hypothetical purchase tasks.

1.3. Measuring the Addictive Properties of Drugs

1.3.1. Behavioral Assessments. Addiction is characterized, in part, by high rates of drug seeking and use. In this conceptualization, an objective, behavioral proxy for the addictiveness of a drug is its reinforcing properties, or its ability to follow a behavior and increase the frequency of that behavior in the future (Schuster & Thompson, 1969). Therefore, reinforcing properties of a drug, in part, predicts the abuse liability of a drug. To better understand the addictiveness of a given drug, its

reinforcing properties can be studied preclinically and in human laboratory studies using SA experiments (Griffiths, Bigelow & Ator, 2003), whereby the delivery of a drug is contingent upon a certain operant behavior (e.g., clicking a computer mouse or pressing a lever a given number of times to earn puffs on a cigarette). While reinforcing effects measured by SA may not provide a comprehensive analysis of the abuse liability of a drug (see review by Johnson & Bickel, 2000), it has been argued that the reinforcing effects of a drug may be the most predictive facet of abuse liability (see review by Fischman & Foltin, 1991). Consistent with this, SA outcomes are predictive of drug use patterns outside of a laboratory setting (see reviews by Comer, Ashworth, Foltin, Johanson, Zacny & Walsh, 2008; Haney & Spealman, 2008).

To directly observe drug taking behavior within a laboratory session, there are often special logistical and time considerations (see review by Panlilio & Goldberg, 2007). First, SA experiments typically take place over multiple sessions to allow for multiple exposures to the drug. Furthermore, sessions may run for many hours, depending on the psychopharmacology of the drug of interest. Finally, to ensure controlled drug delivery, special facilities and equipment are often required (e.g., smoking topography devices, rooms with ventilation for smoking). The benefits of using such a paradigm, however, is that it allows researchers to isolate the reinforcing effects of a drug and to evaluate how numerous factors influence drug taking.

There are multiple SA arrangements to assess reinforcing value. Different SA arrangements can provide different insights into drugs of abuse and how their reinforcing effects may be influenced. First, drugs can be self-administered at a fixed rate (FR) of reinforcement (e.g., drug delivery after every 10 lever presses). The

Response Rate or the amount of drug earned is a proxy for the reinforcing value of the drug. Second, progressive ratio (PR) schedules can also be used to assess reinforcement. PR schedules require a subject to emit an operant on a ratio schedule of reinforcement that increases every time the drug is earned. When the demand of the schedule is too high, the subject ceases responding. The highest ratio response completed by the subject is referred to as the Breakpoint and is also a measure of the reinforcing effects of the drug. Third, relative reinforcing effects can also be measured with concurrent choice SA tasks, where two or more schedules of reinforcement are available at the same time. Concurrent choice SA tasks can include any combination of schedules of reinforcement (e.g., FR, PR). In this paradigm, relative reinforcing value can be captured by how often a given reinforcer is chosen in proportion to all choices made (Preference). In all SA paradigms, researchers can isolate factors which influence drug taking (e.g., dose, schedule of availability, and availability of other reinforcers like money, food and other drugs) to evaluate conditions which influence abuse liability. Broadly speaking, Response Rate, Breakpoint and Preference represent a laboratory-derived measure of a drug's relative reinforcing efficacy which at least partially corresponds to the drug's abuse liability.

1.3.1.1. Self-administration cigarettes that vary in nicotine content.

Cigarettes with varying levels of nicotine have been assessed in several SA paradigms. When a dose is assessed in isolation, at a fixed rate and in the presence of an alternative non-drug reinforcer (i.e., money), SA does not differ across doses (Shahan, Bickel, Badger & Giordano, 2001). Similarly, when tested in isolation under a PR schedule, cigarettes with low levels of nicotine show similar Breakpoints to cigarettes with higher

doses (Rusted, Mackee, Williams & Willner, 1998; Shahan et al., 1999; Shahan et al., 2001). Therefore, when tested separately, it appears that cigarettes with varying dose levels do not differ in their reinforcing properties. However, when two doses are concurrently available, numerous studies have shown that subjects show clear preference for cigarettes with more nicotine, even under double-blind conditions (Boren et al., 1990; Higgins et al., 2017a; Higgins et al., 2017b; Perkins et al., 1996; Perkins, Kunkle, Michael, Karelitz & Donny, 2016; Shahan et al., 1999). Thus, the more sensitive behavioral method for the relative abuse liability of cigarettes with varying doses is with a concurrent choice paradigm where two cigarettes are simultaneously available for self-administration, a finding consistent with early research conducted with non-drug reinforcers (Catania, 1963). However, while SA procedures are considered by some to be the gold standard for assessing abuse liability (Griffiths, Bigelow & Ator, 2003), they often require substantial time and labor. Additionally, SA has been criticized for being an oversimplified method for assessing abuse liability.

1.3.2. Self-Report Measures. While self-report measures are not direct assessments of drug taking behavior, they require considerably less time and labor. Two types of self-report measures, subjective effect measures and the more recently developed, hypothetical purchase tasks, have been used to characterize the abuse liability of various drugs (Jacobs & Bickel, 1999, see review by Fischman & Foltin, 1991).

1.3.2.1. Subjective effects. Subjective effect measures are a long-standing and widely used method for assessing different mood states or sensations which may or may not accompany the administration of a given drug or dose of a drug. Generally, early

observations found that positive moods or sensations (e.g., euphoria) were more frequently documented when assessing drugs which had greater addiction risk (see review by Fischman & Foltin, 1991). Subjective effect measures are easily captured after a single exposure to a drug.

To assess subjective effects of drugs, typically before and immediately following exposure to a given drug or dose of a drug, participants indicate whether a given state or sensation is present or absent or are asked to assign a score to indicate how severe a given state or sensation is on the scale provided (e.g., Likert, visual analog scale). Items can be analyzed individually or can be empirically grouped together to create specific subscales (e.g., Aversion subscale made up of individual items of dizziness and nausea).

Subjective effect scales are often tailored to capture drug-class specific effects (e.g., “limp or loose” for sedatives, “shaky or jittery” for stimulants) and can include items to evaluate effects associated with routes of administration as well (e.g., assessing throat “hit” for a cigarette, Griffiths et al., 2003; Jones, Garret & Griffiths, 1999; Rush, Frey & Griffiths; 1999). Subjective effect measures can capture drug effects and conditioned drug sensory effects, all of which contribute to the reinforcing properties of a drug (Rupprecht et al., 2015). Furthermore, subjective effects may also distinguish positively and negatively reinforcing effects from one another.

1.3.2.1.1. Subjective effects of cigarettes that vary in nicotine content.

Subjective effect measures are commonly used in studies assessing cigarettes with varying levels of nicotine (Benowitz, Jacob & Herrera, 2006; Boren et al., 1990; Butschky, Bailey, Henningfield & Pickworth, 1995; Gross, Lee & Stitzer, 1997; Hatsukami et al., 2013a; Higgins et al., 2017a; 2017b; Perkins et al., 1996; 2016; Shahan

et al., 1999). While numerous scales have been used to assess subjective effects, there are common effects which emerge across measures and reports on cigarettes with varying levels of nicotine. Enjoyment, Flavor/Taste, Liking, Satisfaction and Strength are common positive subjective effects which increase as a function of the nicotine dose delivered by a cigarette (Benowitz et al., 2006; et al., 1990; Butschky et al., 1995; Gross et al., 1997; Hatsukami et al., 2013b; Higgins et al., 2017a; 2017b; Perkins et al., 1996; 2016; Shahan et al., 1999). Common dose-dependent negative subjective effects include Aversion, Harshness, Increased Heartbeat, Jitteriness, and Light Headedness/Dizziness (Benowitz et al., 2006; Higgins et al., 2017a; Perkins et al., 1996; 2016). While both positive and negative subjective effects have been reported, positive effects are more frequently documented.

1.3.2.1.2. Subjective effect measures that predict SA of cigarettes varying in nicotine content. To our knowledge, there are two studies which assess how subjective effects correspond to SA and choice of cigarettes which vary in nicotine content.

One of the two studies which analyzed the relationship between cigarette SA preference and subjective effects was very recently published and included a VLNC (0.4 mg/g) and a normal nicotine content cigarette (15-17 mg/g) (Perkins, Karelitz & Kunkle, 2018). This study showed that subjective effect items Liking, Satisfying and How Much Flavor, significantly predicted preference for the normal nicotine content cigarette when concurrently available with a VLNC. Subjective effect items How Much Nicotine and Strong did not significantly predict choice.

The second study directly evaluating how well subjective effect data corresponds to SA of cigarettes which vary in nicotine content was conducted by our group (Arger et

al., 2017). This study will be described in more detail as it sets the stage for the current study. Arger et al. included 26 participants in a pilot study for a larger laboratory study evaluating the acute effects of cigarettes which varied in nicotine content (0.4 mg/g, 2.4 mg/g, 5.2 mg/g and 15.8 mg/g). Based on the definitions provided earlier, the 0.4 dose cigarette is considered a VLNC cigarette, the two intermediate doses are considered RNC cigarettes and the 15.8 cigarette is a normal nicotine content cigarette which approximates the dose found in commercially available cigarettes. Participants came from one of three vulnerable populations, namely socioeconomically disadvantaged women of childbearing age, opioid-maintained individuals and individuals with affective disorders, as smoking is overrepresented among and disproportionately affects these at-risk groups (Hser, Hoffman, Grella & Anglin, 2001; Lasser, Boyd, Woolhandler, Himmelstein, McCormick & Bor, 2000; Schroeder, 2016).

This study evaluated how well subjective ratings on the modified Cigarette Evaluation Questionnaire (mCEQ) measured during initial cigarette sampling sessions predicted the relative reinforcing effects of cigarettes evaluated later in the study during concurrent choice SA. The mCEQ consists of 12 questions and is designed to query the degree to which a participant experiences the reinforcing effects of smoking. The questionnaire was initially developed and used to evaluate the efficacy of pharmacotherapies which were thought to influence the reinforcing effects of cigarette smoking (mecamylamine, nicotine replacement, varenicline; Cappelleri et al. 2007; Rose et al., 1994; Westman et al., 1992). Research from our group suggests that the mCEQ is sensitive to dose differences (Higgins et al., 2017a, 2017b). However, it does not appear

to function differently among individuals with varying levels of nicotine dependence (Cappelleri et al., 2007, Higgins et al., 2018).

The twelve questions of the mCEQ generate five subscales, namely (1) Satisfaction, (2) Psychological Reward, (3) Enjoyment of Respiratory Tract Sensations, (4) Craving Reduction and (5) Aversion, each made up of 1-5 items (Table 1-1).

Table 1-1. The Five Subscales of the modified Cigarette Evaluation Questionnaire and Corresponding Questions

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 Sensations
Did smoking immediately reduce your craving for a cigarette?	Craving Reduction
Did smoking make you dizzy?	Aversion
Did smoking make you nauseous?	

Participants indicated how true a statement was using a Likert scale which ranged from 1 (Not at all) to 7 (Extremely). To evaluate different dose comparisons, subjective effect difference scores for each of the five subscales were computed by subtracting the lower dose cigarette subjective effect score from the higher dose cigarette subjective effect score, with positive scores indicating the higher dose cigarette produced greater intensity of a subjective effect and negative scores indicating the lower dose cigarette produced greater intensity of a subjective effect. For example, a participant with a Satisfaction score of 5 for the 15.8 mg/g dose and 2 for the 0.4 mg/g dose would have a Satisfaction difference score of 3. Difference scores can range from -6 to +6. Preference for the higher dose in the SA task was computed by dividing the number of times the higher dose was chosen by the total number of choices made and then multiplied by 100 to derive a

percentage. Higher percentages indicated a greater preference for the higher dose. For example, a participant who earned 8 puffs of the 15.8 dose cigarette and 2 puffs of the 0.4 mg/g dose cigarette while the two doses were concurrently available chose the higher dose 80% of the time. Three dose comparisons (i.e., 15.8 mg/g v. 5.2 mg/g, 15.8 mg/g v. 2.4 mg/g, 15.8 mg/g v. 0.4 mg/g) were included in the analyses. Dose comparisons not including the 15.8

mg/g cigarette were not examined in this study due to power concerns.

In this preliminary report, higher Satisfaction difference scores and lower Aversion difference scores predicted a

preference for the

higher dose cigarette when available concurrently with reduced nicotine content

cigarettes (Figure 1-2). Psychological Reward, Enjoyment of Respiratory Tract

Sensations and Craving Reduction effects do not appear to be predictive of concurrent choice performance.

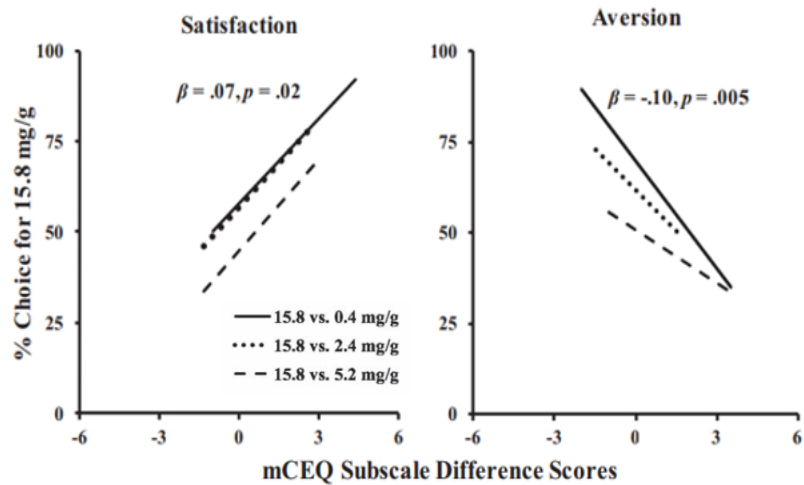


Figure 1-2. Satisfaction and Aversion subscale difference scores predicting preference for the 15.8 mg/g in three dose comparisons. These two mCEQ subscales were equally predictive of choice regardless of dose comparison. β represents the fixed effect estimate of the strength of the association between the subscale difference scores and % choice for 15.8 mg/g cigarette collapsed across dose. This figure is adapted from "Preliminary validity of the modified Cigarette Evaluation Questionnaire in predicting the reinforcing effects of cigarettes that vary in nicotine content" by Arger, C. A., et al., 2017, *Experimental Clinical Psychopharmacology*, 25(6), 473-478.

Across the two studies that have assessed how behavioral assessments correspond to subjective effects of cigarettes which vary in nicotine content, Satisfaction appears to be an important subjective effect in predicting SA preference. Negative subjective effects (i.e., Aversion) may independently predict preference as well, as documented in one of the two studies (Arger et al., 2017).

While a contribution to the literature, the study conducted by Arger and colleagues did not have a large enough sample size to evaluate how well subjective effects predict choice in intermediate dose comparisons (e.g., 0.4 mg/g v. 2.4 mg/g). Therefore, it is unclear how sensitive the mCEQ is for assessing dose comparisons which are closer in magnitude and do not approximate nicotine content found in commercially available cigarettes. In addition, because of the small sample size with small subsets of each vulnerable population (socioeconomically disadvantaged women, $n = 9$; opioid-maintained patients, $n = 11$, individuals with affective disorders, $n = 6$), the preliminary analyses could not determine if the mCEQ subscale scores are equally predictive of choice across different smoker populations.

1.3.2.2. Hypothetical purchasing tasks. Purchase tasks are another self-report method for assessing the abuse liability of cigarettes that were developed more recently. Purchase tasks assess the demand of a given reinforcer across a range of hypothetical monetary costs. This measure incorporates concepts from the field of behavioral economics which applies microeconomic theories of demand and supply to understanding the maintenance of behavior by their reinforcers. Purchase tasks can be easily and quickly administered after a single exposure to a drug.

Typically, hypothetical purchase tasks query the number of units of a given commodity (e.g., cigarettes) a participant would want in a 24-hour period at escalating price points. Purchase tasks produce a demand curve which typically shows that consumption of a commodity decreases as the price increases. Using a purchase task, drug demand is also characterized by the relationship between total expenditure as a

function of price per drug unit, captured with an inverted U-shaped curve. From these two curves, five indices can be

computed which characterize drug consumption underprice constraints: (1) Intensity (Q_0), (2) Price per drug unit when consumption becomes elastic (P_{max}),

(3) Breakpoint (4) Maximum Expenditure (O_{max}) and Elasticity (α). Intensity (Q_0)

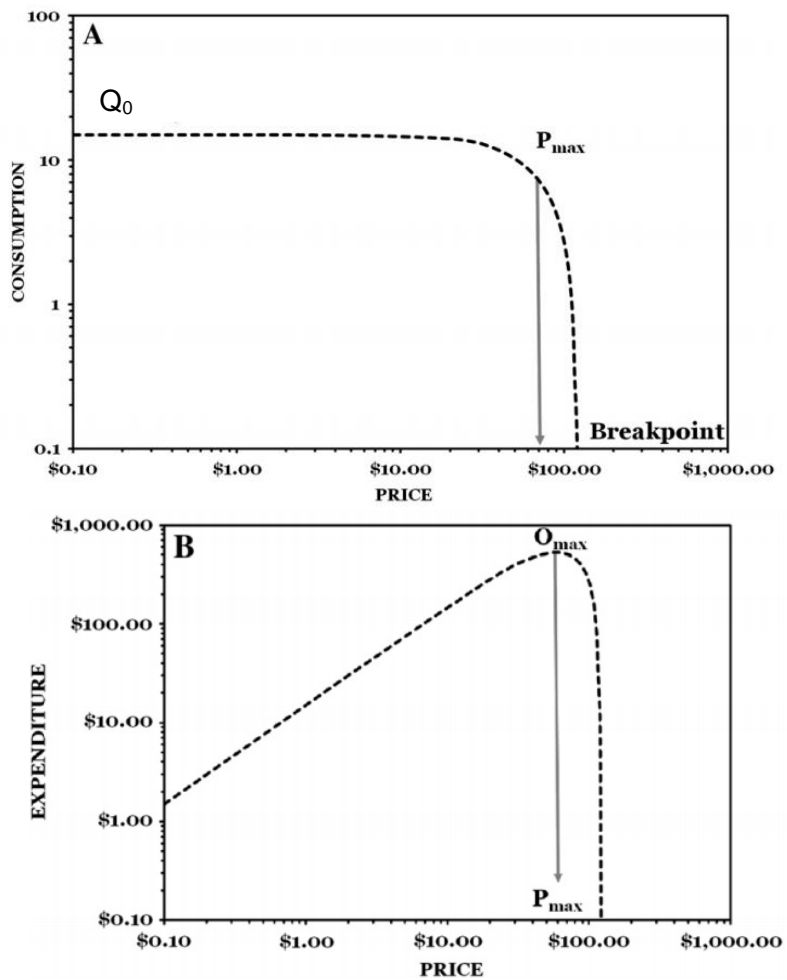


Figure 1-3. Prototypic demand curve (panel A) and expenditure curve (panel B) from which the five indices of the purchase task are derived. Adapted from “Bidwell L. C., MacKillop, J., Murphy, J. G., Tidey, J. W., Colby, S. M. (2012). Latent factor structure of a behavioral economic cigarette demand curve in adolescent smokers. *Addictive Behaviors*, 37, 1257-1263.”

captures drug consumption when there are no costs (i.e., free) and represents unconstrained consumption of the reinforcer (Figure 1 – 3, Panel A). P_{\max} is the price per drug unit when the participant incurs the most costs and represents the point at which the demand curve becomes elastic, or sensitive to price (Figure 1 – 3, Panel A and B). Breakpoint is the price point at which participants will no longer purchase any cigarettes because costs are too high (Figure 1 – 3, Panel A). O_{\max} is the largest amount of money expended in the hypothetical purchase task at a single price point and represents the largest cost a participant is willing to incur to obtain a drug (Figure 1 – 3, Panel B). Elasticity (α) is an index calculated from the other values that captures the slope of the demand curve and describes how consumption is sensitive to escalating prices (not a single point on either figure). While these five indices are often highly correlated, they represent unique facets of how the consumption of a reinforcer can be affected by monetary constraints.

1.3.2.2.1. Hypothetical purchase tasks for cigarettes that vary in nicotine content. The Cigarette Purchase Task (CPT) was developed and first tested by Jacobs and Bickel (1999) to create a less-burdensome procedure for capturing the reinforcing effects of a drug. Opioid-dependent individuals completed hypothetical purchase tasks for cigarettes and heroin and the data from those hypothetical purchase tasks were well described by a demand curve typically used to summarize SA data. Indeed, patterns of consumption followed a typical demand pattern where consumption decreased as prices increased. While this and other early purchase task studies used hypothetical scenarios, subsequent studies have confirmed that the results produced by CPT are highly correlated with real and potentially real laboratory cigarette purchasing data (Wilson et al., 2016).

Like SA procedures, CPT indices are also sensitive to environmental factors which typically influence reinforcers (e.g., deprivation, dose, presence of drug cues; Dahne, Murphy & MacPherson, 2016; Higgins et al., 2017b; MacKillop et al., 2012). These studies provide converging evidence that acute reinforcing effects are captured with this self-report method. While the CPT was originally designed to be a less burdensome complement to SA, its utility appears to extend beyond acute relative reinforcing effects as assessed by SA. Because the CPT takes into consideration the effect of environmental constraints on the consumption of cigarettes, it appears to isolate additional factors which can influence severity of cigarette use. This is evidenced by the ability of the CPT to detect individual differences like (1) cigarettes smoked per day (Dahne et al., 2016; Higgins et al., 2017b; MacKillop et al., 2008; Murphy, MacKillop, Tidey, Brazil & Colby, 2011; O'Connor et al., 2014; Secades-Villa, Pericot-Valverde & Weidberg, 2016), (2) nicotine dependence scores (Bidwell et al., 2012; Farris et al., 2017; Higgins et al., 2018; MacKillop et al., 2008; Murphy et al., 2011; O'Connor et al., 2014; Peters et al., 2017; Secades Villa et al., 2016; Secades Villa et al., 2017), (3) history of quit attempts (Bidwell et al., 2012; Higgins et al., 2017), (4) intensity of craving scores (O'Connor et al., 2014; MacKillop, Brown, Stojek, Murphy, Sweet & Niaura, 2012), (4) the presence or absence of additional substance use (Farris et al., 2017; Parker et al., 2018) and (5) presence or absence of psychopathology (Dahne et al., 2016; Farris et al., 2017; MacKillop & Tidey, 2011; Secades Villa et al., 2016, 2017). These results suggest that the CPT is a relevant tool for assessing abuse liability and clinically meaningful individual differences related to abuse liability.

Likely because it was developed more recently, the CPT has been used infrequently to characterize the abuse liability of cigarettes with varying nicotine content. For example, in the large randomized trial by Donny and colleagues (2015) that evaluated cigarettes with varying levels of nicotine and was described earlier, participants who were assigned to smoke the lowest dose cigarette (0.4 mg/g) reported that after 6 weeks of use, their assigned cigarette had significantly lower Intensity (Q_0), Maximum Expenditure (O_{max}) and Breakpoint and higher Elasticity (α) compared to cigarettes with higher doses of nicotine (Smith et al., 2016). In addition, the recent laboratory study by our group assessing cigarettes with varying levels of nicotine among vulnerable populations also captured differences in cigarette purchase task indices after a single exposure to the cigarettes. Specifically, very low nicotine content cigarettes had significantly lower Intensity (Q_0), Price at point of Elasticity (P_{max}), Breakpoint and Maximum Expenditure (O_{max}) compared to cigarettes with higher doses of nicotine (Higgins et al., 2017).

1.3.2.2.2. Purchase task indices which predict SA. While the existent literature on the CPT consistently captures a range of individual differences, there is only one study which directly tested the relationship between purchase tasks and SA data. In a study involving normal nicotine content cigarettes and other tobacco products, Breakpoint for cigarettes derived from SA under a progressive ratio schedule of reinforcement did not consistently correspond with the number of cigarettes subsequently purchased in a laboratory purchasing task (Stein et al., 2017). Specifically, Breakpoint derived from SA under a progressive ratio schedule of reinforcement positively and significantly corresponded to laboratory purchases of cigarettes at the lowest price (12¢ each), but not

at higher prices (25¢, 50¢ or \$1 each). These results were somewhat surprising but could possibly be an artifact of the study design, which assessed cigarettes and other tobacco products in isolation with SA but pairs of tobacco products in the laboratory purchasing tasks. Further, this study was limited because of its inability to describe the relationship between specific indices of the CPT and SA because in many cases the indices were inestimable with participant-level data.

The CPT may offer unique information about the abuse liability of cigarettes and could inform regulatory efforts to address the addictiveness of cigarette smoking (Tidey et al., 2016). The single study where the relationship between CPT and SA was assessed was limited to normal nicotine content cigarettes and involved general population smokers. It remains to be seen how indices derived from the CPT correspond to data collected from SA paradigms.

1.4 Aims

Our research group recently completed the laboratory-based study which was piloted in the sample evaluated by Arger and colleagues (Higgins et al., 2017b). The completed study included data from 169 individuals who completed all phases of the study. This sample size allowed us to extend the work of Arger et al. (2017) by assessing all six dose comparisons and determining the generalizability of the predictive validity of the mCEQ in various smoker populations. In addition, the CPT was collected which allowed us to exam the correspondence of CPT indices with choice preference assessed in a concurrent choice SA paradigm.

Based on previous research with the mCEQ, it was hypothesized that Satisfaction and Aversion would predict choice. Because previous studies on the topic were limited

by sample size or did not include vulnerable populations, no specific hypotheses were made regarding predictive utility as a function of dose comparison or vulnerable population.

With regards to the CPT, it was unclear what index or indices might best correspond to preference given the relative dearth of studies on the topic. Theoretically, one might hypothesize that relative Intensity (Q_0) for two cigarettes (i.e., the difference in the number of cigarettes of each dose a smoker would smoke if both cigarettes were free) would be most likely to correspond to preference for cigarettes available under an equal response cost. As there are no data to our knowledge to suggest that the relationship between Intensity and choice would vary across dose comparison nor vulnerable population, no specific hypotheses were made regarding potential interactions of Intensity with dose or vulnerable population.

CHAPTER 2: METHOD

The parent study for this secondary analysis is a large, multisite, 14-visit laboratory-based study evaluating the acute effects of cigarettes with varying levels of nicotine under double blind conditions among three vulnerable populations (socioeconomically disadvantaged women of childbearing age, opioid-maintained individuals and individuals with affective disorders, Higgins et al., 2017b). Data were collected using the same protocol utilized by Arger and colleagues (2017) that was briefly described in the Introduction. Procedures relevant to the present analyses are described in more detail below.

2.1. Participants

We used data collected from 169 smokers (53 socioeconomically disadvantaged women, 60 opioid-maintained men and women and 56 men and women with affective disorders) who completed all 14 sessions of the study. Participants were recruited via ads on Facebook, Craigslist, and in local newspapers, as well as flyers posted on community bulletin boards. The study took place at three sites: the University of Vermont in Burlington, VT; Johns Hopkins University in Baltimore, MD; and Brown University in Providence, RI. All potential participants attended a two-hour screening session. After providing informed consent, potential participants submitted breath samples (Micro⁺ Smokerlyzer; coVita/Bedfont, Haddonfield, NJ) and urine samples (NicAlert cotinine test strip; Nymox, Hasbrouck Heights, NJ) to determine smoking status; urine samples were also tested for pregnancy status. Next, potential participants completed demographic (e.g., age, race/ethnicity, education, marital status, etc.) and medical history questionnaires developed in our laboratory, and then completed a series of standardized

questionnaires about their tobacco use, including the Fagerstrom Test for Nicotine Dependence, (FTND, Heatherton, Kozlowski, Frecker & Fagerstrom 1991; Pomerleau, Majchrzak, & Pomerleau, 1989; Pomerleau, Carlton, Lutzke, Flessland & Pomerleau, 1994), and their mental health history, including the Mini International Neuropsychiatric Interview (MINI) 6.0 (Sheehan et al., 1998) and the Beck Depression Inventory (Beck, Ward & Mendelson, 1961).

To be eligible, participants self-reported using at least 5 cigarettes per day for the past year and had an intake breath carbon monoxide (CO) sample > 8 ppm. Individuals were excluded if they reported exclusively rolling their own cigarettes, using other tobacco or nicotine products 9 or more days in the last 30 days, or any smoking cessation product use in the last 30 days. All participants were without current serious mental disorders, lifetime psychosis or dementia, substance abuse, and suicidal ideation. In addition to the above-mentioned inclusion criteria, the three vulnerable populations of interest had additional population-specific inclusion criteria. 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. Finally, participants with affective disorders were between the ages of 18 and 70 and met criteria on the MINI for major depression disorder, general anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, phobia or panic disorder.

2.2. Materials

2.2.1. Research cigarettes. Spectrum nonmenthol and menthol research cigarettes were manufactured by 22nd Century (Clarence, NY) in conjunction with the National Institute of Drug Abuse. The doses used in the current protocol were 0.4, 2.4, 5.2 and 15.8 mg/g.

2.2.2. CReSS desktop smoking topography device

To implement controlled puffing procedures that would be used in later phases of the study, participants smoked all research cigarettes through the CReSS Desktop Smoking Topography Device (Borgwaldt, Richmond, Virginia). The smoking topography device is an 8" X 6" X 5" console with two tubes connected to the front (Figure 2-1, Panel A). The tubes extend about three feet and connect to a mouthpiece which holds a cigarette (Figure 2-1, Panel

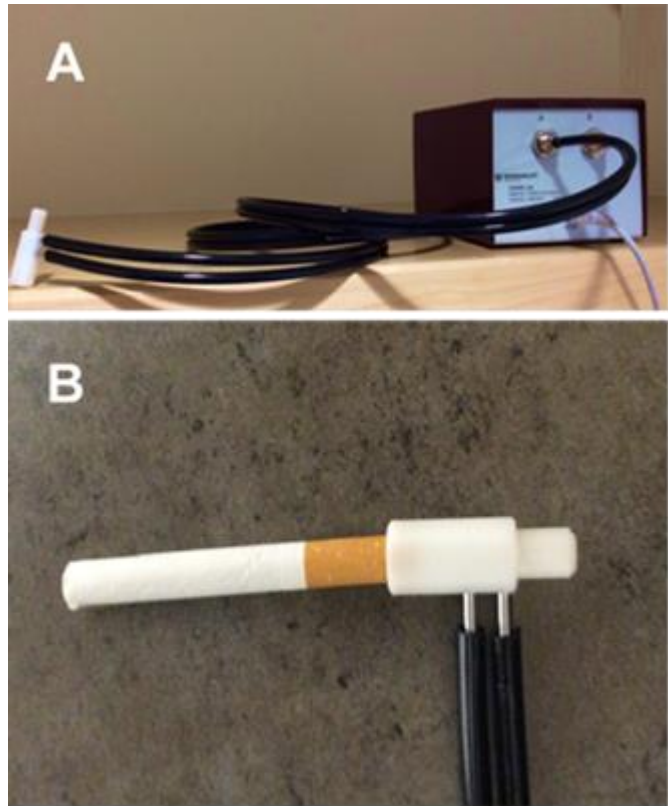


Figure 2-1. Pictures of (A) CReSS desktop smoking topography console used to measure smoking topography and (B) mouthpiece holding the cigarette which connects to the end of two tubes which connect to the console.

B). Individuals smoke the cigarette through the mouthpiece. The device can measure several parameters of puffing behavior including length, size and velocity. All data are

transferred from the console to a desktop PC via a USB cable. Puff volume is displayed on a computer screen in real time. Researchers can also display target puff volumes and timers to guide participants to puff in specific patterns. The CReSS Smoking Topography Device has been shown to have good reliability and validity (Blank, Disharoon & Eissenberg, 2008; Lee, Malson, Waters, Moolchan, & Pickworth, 2003).

2.2.3. Modified Cigarette Evaluation Questionnaire (mCEQ). As described previously, the mCEQ captures subjective effects of cigarette smoking. Participants rate each of the 12 questions (Table 1-1) on a Likert scale which ranges from 1 (not at all) to 7 (extremely). The answers are combined to form five unique subscales which quantify (1) Satisfaction, (2) Psychological Reward, (3) Enjoyment of Respiratory Tract Sensations, (4) Craving and (5) Aversion. The mCEQ was originally designed to measure changes in the reinforcing effects of smoking following a pharmacological intervention (Brauer et al., 2001, Rose et al., 1994, Rose et al., 1998, Westman et al., 1992). The most recent version was developed and validated according to data collected from three clinical trials testing the effects of varenicline for smoking cessation (total $N = 1,565$; Cappelleri et al., 2007). The subscales which make up the questionnaire used in this study demonstrate satisfactory convergent validity and have demonstrated good test-retest reliability.

2.2.4. Cigarette Purchase Task (CPT). As described in the introduction, the CPT queries how many cigarettes a participant would purchase at various given prices. The instructions when participants completed the CPT are as follows:

Think about HOW YOU ARE FEELING RIGHT NOW. The following questions how many cigarettes you would smoke if they cost various amounts of

money. ASSUME THAT: (1) The available cigarettes are your assigned study cigarettes. (2) You have the same income/savings that you have now and NO ACCESS to any cigarettes or nicotine products other than those offered at these prices. (3) You can smoke without any restrictions and without factoring in what might occur in the next 24 hours related to your participation in the study. (4) You would smoke the cigarettes that you request at this time, not save or stockpile cigarettes for a later date. Be sure to consider each price increment carefully.

Participants then provided responses for 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). Each price point was shown as price per cigarette and price per pack (e.g., \$1 per cigarette OR \$20 per pack). After completing the CPT, research assistants reviewed the data to assess any unsystematic data (e.g., increasing consumption across increasing prices, decreases in consumption as price points increased followed by increases in consumption at higher price points). If the data followed unsystematic patterns, research assistants re-explained the task and gave the participant an opportunity to change their data.

2.2.4.1. Computing CPT indices. Four of the five indices of the CPT (Intensity (Q_0), P_{\max} , Breakpoint, O_{\max} .) were empirically quantified from observed values. As discussed in the Introduction, Intensity is the quantity of cigarettes ‘purchased’ when they were free, O_{\max} is the largest sum incurred in a single price condition when hypothetically purchasing cigarettes, P_{\max} is the price point at which O_{\max} occurs and represents the point at which participants become sensitive to price and Breakpoint is the point at which

a participant first reports they would purchase zero cigarettes, presumably because the costs are too high.

To generate Elasticity, participant-level data were fit to a demand curve ($\ln Q = \ln Q_0 k(e^{-\alpha(Q_0 C)} - 1)$) where Q is the quantity consumed, Q_0 is the quantity consumed when the cigarette is 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. To log transform the data and model the demand curve, price points where participants reported smoking zero cigarettes were replaced with .001. α represents individual differences in the rate of change in consumption with changes in price (i.e., Elasticity; Hursh & Silberberg, 2008) and was derived for each participant from the demand curve based upon their responses.

2.3 Procedures

If deemed eligible at the screening visit, participants were invited to participate in the study. Participants completed each of the 14 visits under acute abstinence which was biochemically verified with at least a 50% reduction in their screening CO value; this is an abstinence criterion widely used in tobacco research (e.g., Johnson, Bickel & Kirshenbaum, 2004; Tidey, O'Neill & Higgins, 1999). The study was divided into a baseline visit and three phases (Phases 1 – Phase 3). All laboratory sessions took place in a small room (30 ft²) with a ventilation system specifically designed to allow for cigarette smoking indoors. The rooms had two computers, a laptop and a desktop computer, which were used to (1) complete questionnaires and complete the concurrent choice

program and (2) measure smoking behavior, respectively. The analyses proposed will use data from Phases 1 and 2, which are described in more detail below.

Phase 1 consisted of four visits where participants sampled a single research cigarette on distinct days and provided subjective effect ratings and CPT responses. After biochemical confirmation of acute abstinence, participants took 2 *ad lib* puffs on their usual brand cigarette. This was done to equate the time since last puff across all participants. After a 30-minute period, participants smoked the assigned research cigarette *ad lib* through the desktop smoking topography device. Each cigarette was labelled with an arbitrary letter code (e.g., A, B, C and D) which differed depending on the sequence to which each participant was randomized. While smoking the cigarette, participants were encouraged to take detailed notes on their smoking experience, which were saved for Phase 2. Immediately after smoking the cigarette, participants completed the mCEQ and CPT. In the hour that followed, participants completed other questionnaires and provided CO samples at fifteen-minute intervals; those data have been reported elsewhere (Higgins et al., 2017b). At the end of the hour, participants practiced controlled puffing procedures with specific puffing size and length requirements with the same dose research cigarette.

Phase 2 consisted of six visits where participants chose between two cigarettes, both available on a fixed-ratio schedule of reinforcement (FR-10). Each dose comparison was tested once in separate sessions (Table 2-1). Participants were randomized to a dose comparison presentation sequence. As in Phase 1, researchers

Table 2-1. Nicotine Dose Comparisons

15.8 mg/g	0.4 mg/g
15.8 mg/g	2.4 mg/g
15.8 mg/g	5.2 mg/g
5.2 mg/g	0.4 mg/g
5.2 mg/g	2.4 mg/g
2.4 mg/g	0.4 mg/g

biochemically confirmed acute abstinence at the beginning of each Phase 2 session and participants took two puffs on their usual brand cigarette and waited 30 minutes before beginning session procedures. Two different dose cigarettes labelled with the letter codes used in Phase 1 were available to smoke. Researchers provided participants with a copy of their notes from Phase 1. When participants wanted to smoke a certain cigarette, they clicked 10 times on an icon on the laptop computer which had the letter code of the corresponding cigarette (Figure 2-2). Participants then lit the selected cigarette without inhaling, placed it in the mouth piece of the desktop smoking topography device and took two controlled puffs exactly as they practiced in Phase 1 and with feedback displayed on the desktop monitor.

Participants were given 2 minutes to take the two puffs. During each 3-hour session in Phase 2, participants could make as many or as few choices for either cigarette as they wanted.

2.4 Statistics

All statistical data preparation and analyses were conducted using Statistical Analysis Software (SAS) version 9.4. Significance testing was determined at $p < .05$.

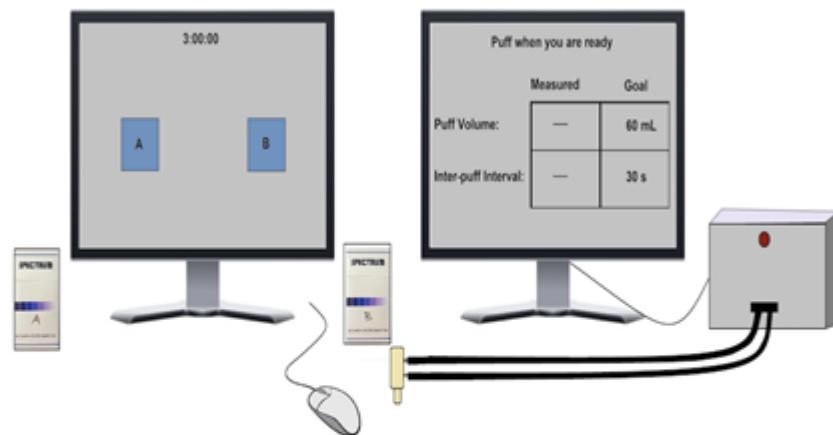


Figure 2-2. This schematic depicts the arrangement of computers, cigarettes and smoking topography machine during Phase 2. The computer on the left ran the concurrent choice program which displayed two icons with letter codes corresponding to the two cigarettes available. The computer on the right provided real-time feedback of puffing behavior with corresponding puff volume and inter-puff interval goals

2.4.1. Preparing Data for Analysis.

2.4.1.1. Predictor variables. As previously described, difference scores were calculated for each mCEQ subscale by subtracting scores for the lower dose from scores of the higher dose for each of the six dose comparisons. Difference scores can range from - 6 to + 6 and more positive difference scores indicated greater subjective effects at the higher dose.

For CPT data, Elasticity values greater than 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. 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. Demand curves for the four doses of cigarettes had R^2 s which ranged from 0.97 - 0.98, indicating that the demand curves sufficiently described the pattern of the data collected.

Once all indices were empirically quantified, difference scores were calculated for each of the five CPT indices using the same approach used for each mCEQ subscale. Ranges depended on the index being computed.

2.4.1.2. Outcome variables. To quantify relative reinforcing effects of the cigarettes using data from the concurrent choice assessment, a ratio was calculated for each of the six dose comparisons. Each ratio 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. Ratios

were multiplied by 100 to produce a percentage, with higher percentages indicating more choices for the higher dose cigarette.

$$\frac{\textit{Total Puffs Earned for Higher Dose}}{\textit{Total Puffs Earned}} \times 100$$

2.4.2. Assessing the Predictive Utility of Individual Subscales and Indices. The aims of the statistical analyses were to assess how well mCEQ subjective effect difference scores and CPT index differences scores predict preference for the higher dose in a given dose pair. Mixed effects repeated measures analysis of variance tests 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 a fixed effect. This allowed us to evaluate whether subjective effects and CPT indices were predictive of choice at all dose comparisons.

There were five variables which were included in the statistical analyses for the primary aim to account for any variability introduced by the design of the parent study. They remained in the model regardless of whether they were predictive of choice. The model included a fixed effect for session and a random effect for the sequence of dose comparison presentations since participants were randomized to receive all dose comparisons within a Latin square design. Vulnerable population group was entered as an additional fixed effect as the study included three vulnerable population groups which varied in how they were recruited and their inclusion criteria. Site (i.e., University of Vermont, Johns Hopkins University and Brown University) was also included in the model 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 in all models testing the predictive utility of the mCEQ and CPT for predicting choice.

Interaction terms were included in the model to evaluate how well mCEQ or CPT difference scores predicted choice and whether this depends on dose comparison or vulnerable population group. If any interaction terms were not significantly predictive of choice, the term was eliminated, and the model was re-run without the nonsignificant interaction term. This process was repeated until the model contained only main effects or main effects and significant interaction terms.

2.4.3. Assessing Independent Predictors of Choice. After each subscale was evaluated independently, two separate models evaluated which mCEQ subscales were independent predictors of choice and which CPT indices were independent predictors of choice. This first model included all of the subscale difference scores as a fixed effect. Non-significant subscales with the highest *p*-value were removed from the model and the model was rerun until the only subscales which remained were significant predictors of choice. This process was repeated for a second model evaluating which CPT indices were significant, independent predictors of choice.

In a final model, all five mCEQ subscales and all five CPT indices were entered as predictors of choice. Again, predictors with the largest *p*-values were removed from the model and the model was rerun until only significant subscales or indices remained in the model.

2.4.4. Power Analysis. Using data from the pilot study (Higgins et al., 2017a), similar analyses using a sample of 26 individuals resulted in a statistically significant effect of differences in Satisfaction and Aversion on the choice of cigarettes with an eta-

squared of 0.08 and 0.05, respectively (Arger et al., 2017). Our sample size of 169 is sufficient to detect a similar effect size with 90% power including all 6 dose comparisons.

CHAPTER 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 3-1).

Table 3-1. Participant Characteristics

	All (n=169)	Disadvantaged Women (n=53)	Opioid Abusers (n=60)	Affective Disorders (n=56)
Age (mean yrs \pm SD)	35.6 \pm 11.4	30.0 \pm 7.0	41.0 \pm 11.2	35.0 \pm 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	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 \pm SD)	15.8 \pm 7.5	14.5 \pm 6.3	16.5 \pm 6.1	16.3 \pm 9.5
Primary Menthol Smoker (%)	35	30	38	36
Age Started Smoking Regularly (mean yrs \pm SD)	16.3 \pm 4.3	16.4 \pm 3.7	16.2 \pm 5.5	16.2 \pm 3.1
Fagerstrm Test for Nicotine Dependence (M \pm SD)	5.0 \pm 2.2	4.6 \pm 2.3	5.3 \pm 1.8	5.0 \pm 2.3

On average, participants smoked 16 cigarettes per day and 35% of participants were primary menthol cigarette smokers. Participants started smoking regularly at 16 years old and had moderate levels of dependence according to the Fagerström Test for Nicotine Dependence. These factors did not significantly differ by group, therefore we did not control for them statistically.

3.2. Descriptive Statistics for Predictor and Outcome Variables

Table 3-2. Mean (SE) mCEQ Subscale Difference Scores by Dose Comparison

Subscale	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
Satisfaction	0.41 (0.14)	0.26 (0.13)	0.67 (0.13)	0.77 (0.14)	1.03 (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 (0.14)	0.58 (0.14)	1.00 (0.16)	1.22 (0.16)
Craving Reduction	0.30 (0.16)	0.29 (0.15)	0.59 (0.15)	0.57 (0.15)	0.96 (0.15)	1.15 (0.17)
Aversion	0.04 (0.05)	0.01 (0.06)	0.04 (0.06)	0.24 (0.07)	0.24 (0.08)	0.28 (0.07)

Table 3-3. Mean (SE) CPT Index Difference Scores by Dose Comparison

CPT Index	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
Elasticity	-0.06 (0.02)	-.02 (0.01)	-0.21 (0.01)	-0.02 (0.01)	-0.04 (0.02)	-0.04 (0.02)
Intensity	0.40 (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 (6.41)	3.93 (4.30)	-0.44 (3.49)	8.79 (4.71)	12.53 (7.83)	8.51 (4.74)
P _{max}	0.10 (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 (1.00)	1.63 (0.75)	2.32 (0.87)

mCEQ subscale and CPT index difference score means and standard errors are presented for each dose comparison in Tables 3-2 and 3-3. As reported in Higgins et al. (2017b), participants showed dose-dependent increases in all five mCEQ subscales and four of the five CPT indices (Intensity, P_{max}, Breakpoint, O_{max}). Means and standard errors for the proportion of choices for the higher dose cigarette in the six dose pairs are summarized in Table 3-4. As reported in Higgins et al. (2017b), participants showed significantly greater preference for the higher dose in a given dose pair with greater

Table 3-4. Mean (SE) Proportion of Choice for Higher Dose in a Give Dose Pair

Proportion of Choice for Higher Dose	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
	.58 (.03)	.57 (.03)	.62 (.03)	.64 (.03)	.68 (.03)	.71 (.03)

preference shown when the dose contrast was larger.

3.3. mCEQ Subscales as Predictors of Choice

When analyzed separately, all five mCEQ subscales were predictive of choice.

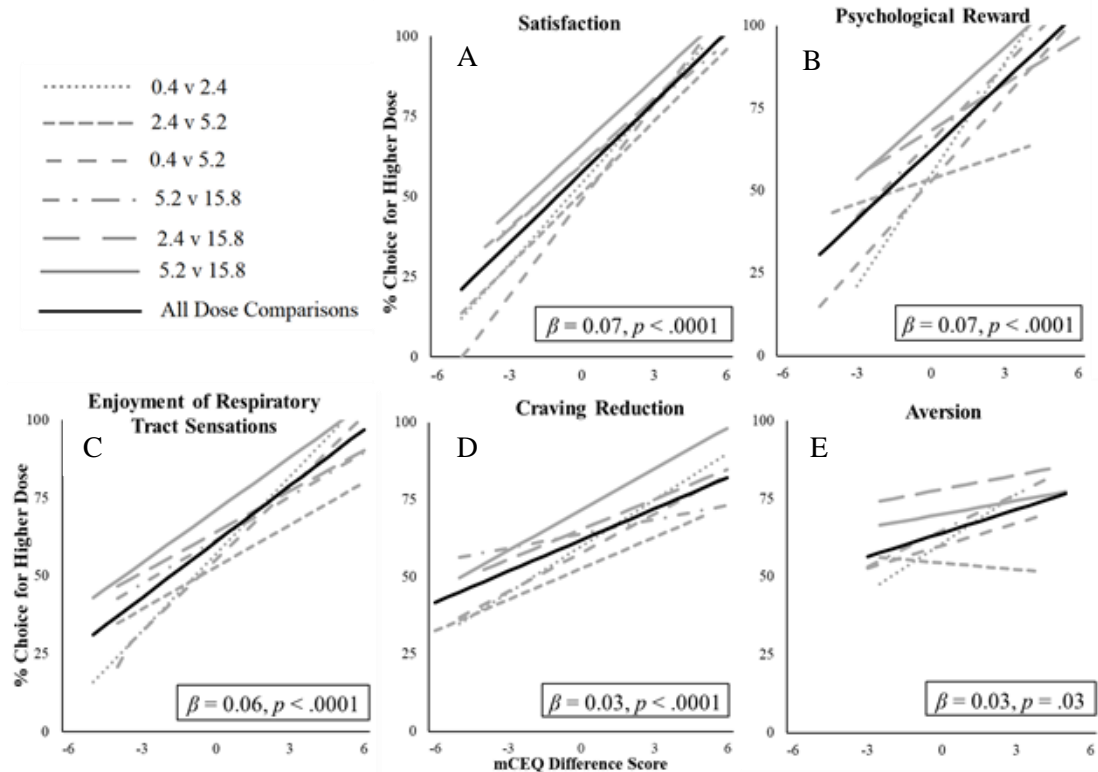


Figure 3-1. mCEQ subscale difference scores and cigarette preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines). mCEQ subscales did not predict choice differently across the dose comparisons (Subscale X Dose Comparison, p 's > .05).

3.3.1. Satisfaction. Satisfaction was significantly predictive of choice regardless of dose comparison, $\beta = .07$, $F(1, 999) = 211.16$, $p < .0001$ (Figure 3-1, Panel A). Specifically, greater differences in Satisfaction scores were associated with greater preference for the higher dose cigarettes; for every 1-point increase in Satisfaction subscale scores, preference for the higher dose cigarette increased by 7%.

The final model used to evaluate the predictive utility of Satisfaction for cigarette preference included one interaction term which was statistically significant (Satisfaction X Vulnerable Population), $F(2, 998) = 10.06$, $p < .001$ (Figure 3-2). Across all

populations, greater Satisfaction difference scores corresponded to greater preference for the higher dose cigarette. However, socioeconomically disadvantaged women appeared to show greater increases in behavioral preference as Satisfaction difference scores increased. Specifically, socioeconomically disadvantaged women showed an 11% increase in

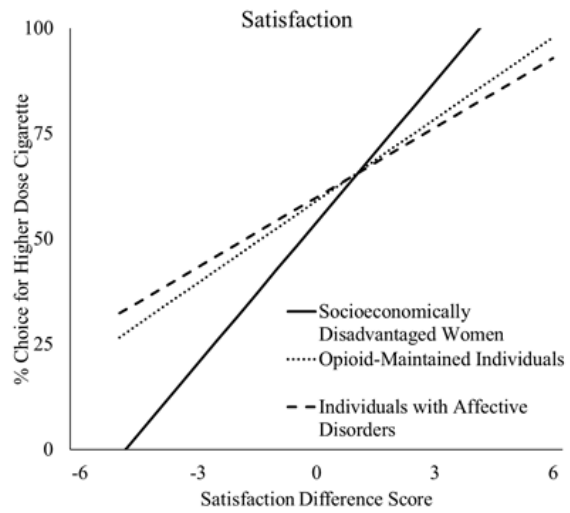


Figure 3-2. Satisfaction difference scores and cigarette preference, collapsed across dose comparisons and separated by project.

higher dose cigarette preference for every 1-point increase in Satisfaction difference scores while individuals who were opioid-maintained and individuals with affective disorders showed a 6% increase in higher dose cigarette preference for every 1-point increase in Satisfaction. Post-hoc analyses controlling for sex, age and education did not eliminate the significant interaction between satisfaction and vulnerable population for predicting choice whereby changes in Satisfaction subscale difference scores corresponded with larger increases in preference for the higher dose cigarette. Sex, age and education were considered in post-hoc analyses because participants were specifically recruited/enrolled based on these factors.

3.3.2. Psychological Reward. Psychological Reward was predictive of choice regardless of dose comparison and vulnerable population, $\beta = .07$, $F(1, 1003) = 95.01$, $p < .0001$ (Figure 3-1, Panel B). Specifically, greater differences in Psychological Reward scores were associated with greater preference for the higher dose cigarettes; for every 1

point increase in Psychological Reward, preference for the higher dose cigarette increased by 7%. The final model used to evaluate the predictive utility of Psychological Reward for cigarette preference did include any interaction terms.

3.3.3. Enjoyment of Respiratory Tract Sensations. Enjoyment of Respiratory Tract Sensations was predictive of choice regardless of dose comparison and vulnerable population, $\beta = .06$, $F(1, 1004) = 141.17$, $p < .0001$ (Figure 3-1, Panel C). Specifically, greater differences in Enjoyment of Respiratory Tract Sensations were associated with greater preference for the higher dose cigarettes; for every 1-point increase in Enjoyment of Respiratory Tract Sensations, preference for the higher dose cigarette increased by 5%. The final model used to evaluate the predictive utility of Enjoyment of Respiratory Tract Sensations for cigarette preference did not include any interaction terms.

3.3.4. Craving Reduction. Craving Reduction was predictive of choice regardless of dose comparison and vulnerable population, $\beta = .03$, $F(1, 1002) = 45.35$, $p < .0001$ (Figure 3-1, Panel D). Specifically, greater differences in Craving Reduction were associated with greater preference for the higher dose cigarettes; for every 1 point increase in Craving Reduction, preference for the higher dose cigarette increased by 6%. The final model used to evaluate the predictive utility of Craving Reduction for cigarette preference did not include any interaction terms.

3.3.5. Aversion. Aversion was predictive of choice regardless of dose comparison and vulnerable population, $\beta = .03$, $F(1, 1003) = 4.66$, $p = .03$ (Figure 3-1, Panel E). Specifically, greater differences in Aversion were associated with greater preference for the higher dose cigarettes; for every 1-point increase in Aversion, preference for the higher dose cigarette increased by 3%. The final model used to

evaluate the predictive utility of Aversion for cigarette preference did not include any interaction terms.

Because Aversion predicted choice in the opposite direction of previous findings by 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 scores were significantly predictive of choice across dose comparisons and vulnerable population. However, Nausea was significantly negatively predictive of choice, $\beta = -.02$, $F(1, 1003) = 4.23$, $p = .04$, and Dizziness scores were significantly positively predictive of choice, $\beta = .04$, $F(1, 1003) = 22.61$, $p < .001$.

3.3.6. 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 remained significant, $\beta = .06$, $F(1, 1001) = 52.32$, $p < .0001$, $\beta = .02$, $F(1, 1001) = 7.03$, $p < .01$, respectively. Higher Satisfaction and higher Enjoyment of Respiratory Tract Sensations scores for the high dose cigarette corresponded to a higher proportion of choices for the high dose cigarette. Specifically, for every 1-point increase in Satisfaction or Enjoyment of Respiratory Tract Sensation difference scores, participants selected the higher dose cigarette 6% and 2% more, respectively.

3.4. CPT Indices as Predictors of Choice

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

3.4.2. Intensity. Intensity was significantly and positively predictive of choice, $\beta = -.002$, $F(1, 944) = 19.44$, $p < .001$. Specifically, higher Intensity corresponded to a greater preference for the higher dose cigarette.

The final model used to assess the predictive utility of Intensity included a significant Intensity X Dose Comparison X Vulnerable Population interaction. This interaction revealed that Intensity is predictive in socioeconomically disadvantaged

women of childbearing

age ($\beta = .02$, $F(1, 288)$

$= 18.35$, $p < .001$) and

individuals with

affective disorders ($\beta =$

$.004$, $F(1, 312) = 5.49$,

$p = .01$), but not opioid-

maintained individuals

($\beta = -.007$, $F(1, 336) =$

0.00 , $p = .99$; Figure 3-

3). In addition, there

was a significant

Intensity X Dose

Comparison interaction

among the

socioeconomically

disadvantaged women of childbearing age, ($F(5, 276) = 3.03$, $p = .01$), where Intensity

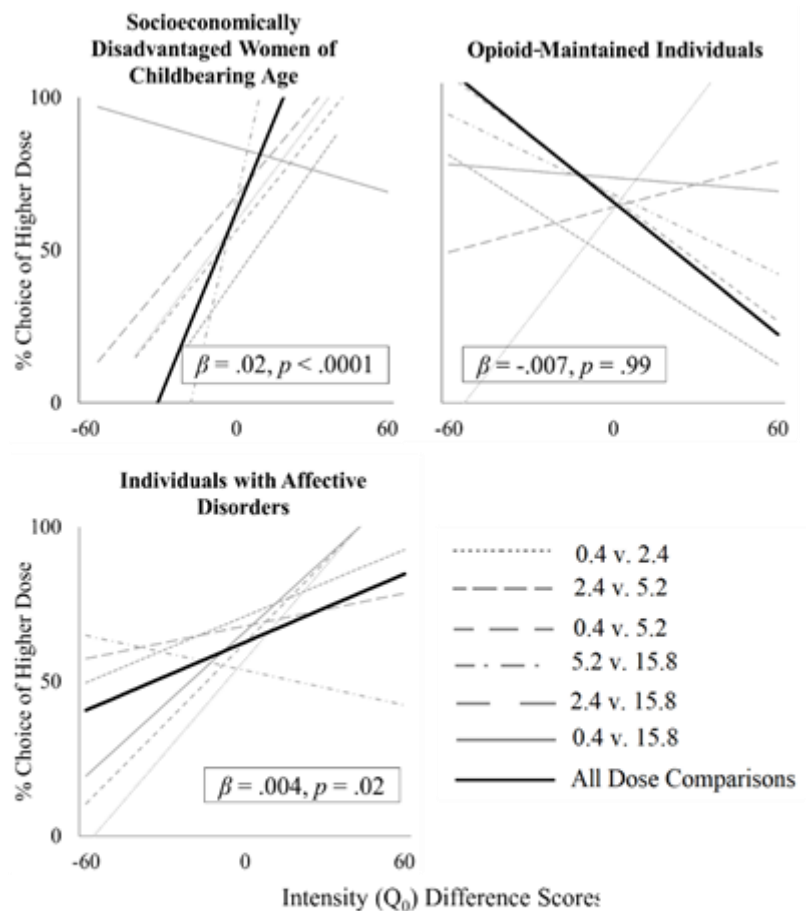


Figure 3-3. Intensity difference scores and cigarette choice preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines) broken down by vulnerable population group. Among opioid-maintained individuals, Intensity was not predictive of choice, $\beta = -.007$, $F(1, 336) = 0.00$, $p = .99$, and among socioeconomically disadvantaged women of childbearing age,

was only significantly predictive of choice in the 0.4 v. 2.4, 5.2 v. 15.8 and 2.4 v 15.8 dose comparisons.

3.4.1. Elasticity. Elasticity was significantly predictive of choice, $\beta = -.22$, $F(1, 880) = 14.25$, $p < .001$. Specifically, lower Elasticity difference scores were associated with greater preference for the higher dose cigarettes; for every 0.1 point decrease in Elasticity, preference for the higher dose cigarette increased by 2%.

The final model used to assess the predictive utility of Elasticity differed by vulnerable population and dose comparison, Elasticity X Vulnerable Population X Dose Comparison: $F(2, 998) = 10.06$, $p < .001$. In all three vulnerable populations of interest, Elasticity was significantly, negatively associated with choice (Figure 3-4). However, among opioid-maintained individuals, Elasticity was differentially predictive of choice across different dose comparisons (Elasticity X Dose Comparison: $F(5, 298) = 3.96$, $p = .002$), with Elasticity positively predictive of choice for the 2.4 v. 5.2 dose comparison and negatively predictive for 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 remained significant, $\beta = -.21$, $F(1, 880) = 14.25$, $p < .001$. Lower Elasticity scores for the high dose cigarette corresponded to a higher proportion of choices for the high dose cigarette.

3.5. Best Predictor of Choice

When all five mCEQ subscales and five CPT indices were included as predictor variables in a final model, Satisfaction and Enjoyment of Respiratory Tract Sensations were the only ones which remained predictive of choice preference for the higher dose

cigarette, $\beta = .06$, $F(1, 1001) = 53.32$, $p < .0001$., $\beta = .02$, $F(1, 1001) = 7.03$, $p < .001$, respectively.

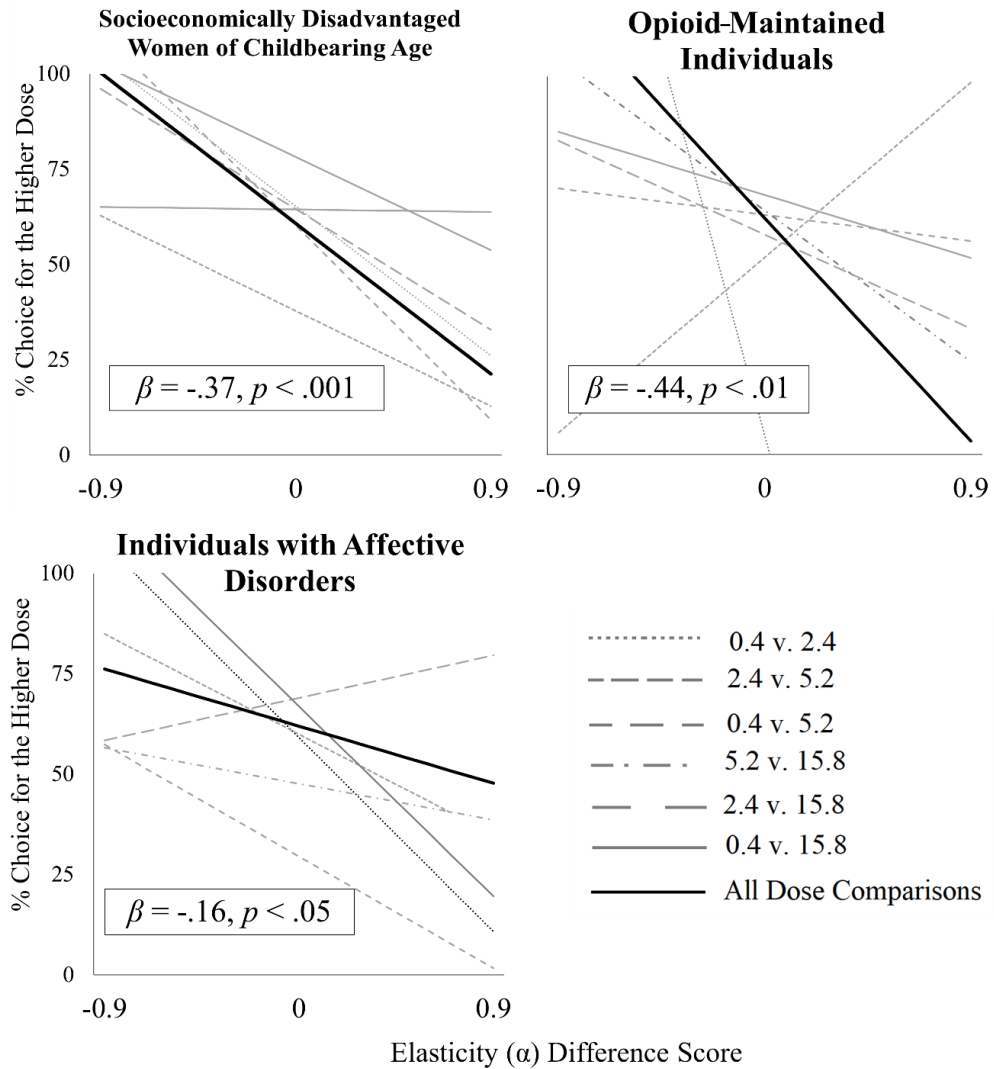


Figure 3-4. Elasticity difference scores and cigarette choice preference across six dose comparisons (gray lines) and collapsed across dose comparisons (black lines) broken down by vulnerable population group. Among opioid-maintained individuals, Elasticity predicted cigarette choice preference depending on the dose comparison being analyzed.

CHAPTER 4: DISCUSSION

In recent years, the FDA has taken steps to reduce the addictiveness of combustible products. Relative reinforcing efficacy is a robust predictor of the addictive properties of nicotine containing products. The present study tested the extent to which the mCEQ and CPT, two self-report measures, captured acute relative reinforcing effects of cigarettes which vary in nicotine content as measured by a behavioral measure, concurrent choice SA.

4.1. mCEQ Predicting Choice

Even though not all mCEQ subscales were predictive of SA when tested in the pilot sample, it is not surprising that all mCEQ subscales are significantly associated with choice, as mCEQ subscales query moods and sensations that typically accompany increases in nicotine dose (Benowitz et al., 2006; Boren et al., 1990; Butschky et al., 1995; Gross et al., 1997; Hatsukami et al., 2013b; Higgins et al., 2017a; 2017b; Perkins et al., 1996; 2016; Shahan et al., 1999). However, among all mCEQ subscales, Satisfaction and Enjoyment of Respiratory Tract Sensations subscales were the only independent predictors of choice. In addition, while Satisfaction was a significant predictor across dose, the magnitude of prediction varied by population and was significantly greater among women of childbearing age who are socioeconomically disadvantaged. Follow-up analyses determined that statistically controlling for sex, age and education did not eliminate the strength of Satisfaction in predicting choice among these populations. This suggests that sex, age and education, which were constrained among socioeconomically disadvantaged women of childbearing age due to specific inclusion criteria, did not drive the strength of the relationship between Satisfaction and choice. While the predictive

utility appears to vary in strength among certain groups, the overall pattern is consistent: the greater a Satisfaction score is for a cigarette, the more likely it will be chosen. These results paired with previous findings suggests that Satisfaction is the best subjective effect for predicting relative reinforcing efficacy measured in a concurrent choice paradigm (Arger et al., 2017; Perkins et al., 2018). Building on Arger et al. (2017), our results also showed that the relationship between Satisfaction and choice was significantly positively related at every dose comparison, including between reduced nicotine content cigarettes.

The observation that Enjoyment of Respiratory Tract Sensations was an independent predictor of choice was somewhat inconsistent with the results of Arger et al (2017). Although the direction of the relationship was similar in both set of analyses, it did not reach significance in Arger et al., perhaps due to issues around power and sample size. Similar to Satisfaction, this subscale asks about the presence or absence of a positively reinforcing subjective effect but unlike Satisfaction, this subscale is a cigarette-specific subjective effect. Participants sampled these cigarettes under acute abstinence, which has been associated with increases in coughing and throat irritation, and laboratory research demonstrates that nicotine suppresses coughing following extended abstinence (Davenport, Vovk, Duke, Bolser & Robertson, 2009). Given that both sampling and concurrent choice sessions were conducted under acute abstinence, it is possible that coughing and respiratory discomfort was heightened prior to the session and that cigarettes with higher nicotine doses better suppressed coughing and throat irritation and thereby provided more favorable sensations and therefore were more preferable.

According to our results, the subjective effects that best predict relative reinforcing effects captured in concurrent choice SA paradigms are positive effects. This finding is consistent with both previous studies which have tested this relationship (Arger et al., 2017; Perkins et al., 2018). On the other hand, negative reinforcing effects, more likely to be picked by items on the Craving Reduction and Psychological Reward subscales, were no longer predictive of choice when positive reinforcing effects were included in the model. Somewhat unexpectedly, Aversion was not independently predictive of concurrent choice SA. Follow-up analyses determined that the two items within the Aversion subscale (Nausea and Dizziness) predicted choice in opposite directions, with Nausea negatively associated with preference for the higher dose and Dizziness positively associated with preference for the higher dose. This discrepancy is consistent with results from a confirmatory factor analysis of the mCEQ which found that Aversion had less internal consistency than the other mCEQ subscales for capturing subjective effects of reinforcement (Cappelleri et al., 2007). Our discrepant findings on Aversion and choice may speak to the lack of consistency of the subscale. With regards to cigarettes varying in nicotine content, it appears that these two factors (Nausea and Aversion) should be considered separately as they function differently in terms of how they relate to actual drug taking in concurrent choice SA paradigms.

4.2. CPT Predicting Choice

The utility of the CPT indices for predicting choice varied greatly across individual indices, vulnerable populations and dose comparisons. Intensity and Elasticity, when tested separately, significantly predicted choice. While the predictive utility of Intensity and Elasticity depended on which dose comparisons were being

analyzed within each vulnerable population, Elasticity was the most consistent predictor of choice across populations. Among all three populations, the less sensitive to price (inelastic), the more often a dose was chosen. This suggests that doses which are relatively less sensitive to environmental constraints are more likely to be preferred in a concurrent choice paradigm when two doses are available at equal response costs. It is possible that the other CPT indices, P_{max} , Breakpoint and O_{max} , which were not significant predictors of choice, do not isolate the reinforcing effects of a drug and instead capture individual differences related to the greatest costs an individual is willing to incur (e.g., Murphy et al., 2012, Dahne et al., 2017, O'Connor et al., 2014). These features may be more relevant to an individual's cigarette use history and less relevant to the acute reinforcing effects of a drug. This question has not been tested directly but certainly warrants additional scientific attention.

As already noted, the relationships between Elasticity, Intensity and choice varied depending on dose comparison and/or vulnerable population. Among opioid-maintained individuals, dose comparisons which had the smallest dose discrepancies (e.g., 0.4 vs. 2.4 and 2.4 vs. 5.2), showed less consistent predictive utility of Elasticity for choice. 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. These population differences may be a function of the sensitivity of the CPT for detecting individual differences, which is not as frequently observed in mCEQ or choice preference (e.g., Higgins et al., 2018, Cappelleri et al., 2007). For example, our group recently showed that among vulnerable population smokers, the Heaviness of Smoking Index (a measure

of cigarette dependence) corresponds to differences in CPT indices but not mCEQ subscales or concurrent choice preference across a range of doses (Figure 4-1). Specifically, smokers with higher dependence severity had greater Intensity (Q_0) and Maximum Expenditure (O_{max}). One component of the HSI is cigarettes smoked per day; given that Q_0 and O_{max} correspond to this measure of dependence, it perhaps is not surprising that these two indices differentiated among different levels of dependence. In addition, as outlined in the Introduction, the CPT is predictive of many measures of the natural history of smoking (cigarettes per day, nicotine dependence, quit attempts, clinical outcomes). Therefore, beyond assessing acute effects of cigarettes which vary in nicotine and predicting choice, the CPT also characterizes individuals with varying patterns of cigarette use.

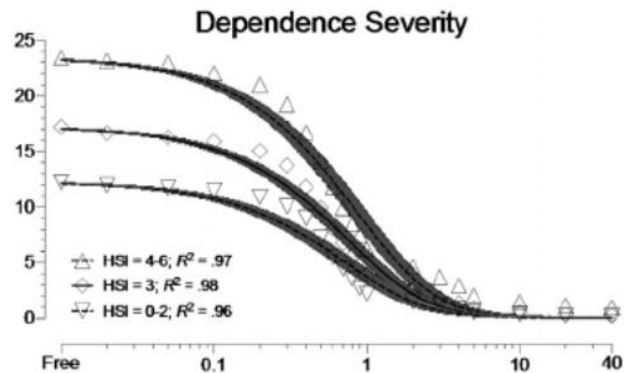


Figure 4-1 Demand curves derived from the CPT by Heaviness of Smoking Index (HSI) scores. Adapted from “Higgins, S. T., Bergeria, C. L., Davis, D. R., Streck, J. M., Villanti, A. C. ... Miller, M. E. (2018) Response to reduced nicotine content cigarettes among smokers differing in tobacco dependence severity. *Preventive Medicine*, In press.

So far, it is unclear how different indices may correspond to unique aspects of addiction. There is evidence that all five indices can serve as predictors of cigarettes smoked per day, nicotine dependence and psychopathology (Dahne et al. 2017, Murphy et al., 2012; Secades Villa et al., 2016, 2017). Our data, however, isolates Elasticity as a good measure for detecting acute relative reinforcing effects regardless of population, which distinguishes the utility of this index from the other four.

4.3. Evaluating the Best Self-Report Predictor of Choice

Satisfaction and Enjoyment of Respiratory Tract Sensations, but not Elasticity, remained predictive of concurrent choice SA. This suggests that the mCEQ subscales are best at capturing acute relative reinforcing effects of cigarettes concurrently available at equal response costs. The CPT incorporates how intensity of demand and sensitivity to environmental constraints influence the reinforcing properties of cigarettes which vary in nicotine content. While Elasticity was predictive of concurrent choice SA when tested individually, mCEQ subscales more accurately captured the component of abuse liability measured in concurrent testing. That said, increasing evidence suggests that the CPT is best for capturing unique features of abuse liability related to cigarette smoking in naturalistic settings where environmental constraints are ever present and smoking rates vary across subpopulations.

4.4. Limitations and Future Directions.

While our analyses provide a more rigorous evaluation of the mCEQ subscales and CPT indices for evaluating the acute 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, a more thorough validation of the mCEQ and CPT would be to analyze how these measures correspond to rates of use outside of the laboratory. Therefore, the clinical utility of Satisfaction, Enjoyment of Respiratory Tract Sensations and Elasticity should be interpreted with caution until there is broader validation.

Second, it is unclear how well the relationships between these mCEQ and CPT and SA data extend to other tobacco products. According to a study by Stein and colleagues

(2017), the relationship between CPT indices and SA functioned differently depending on the tobacco product being assessed and perhaps how familiar the participant is with a product (cigarettes v. snus or nicotine gum). On the other hand, other studies have found evidence of consistencies across tobacco products when evaluating the relationship between subjective effects and SA (Arger et al., 2017; Hatsukami et al., 2013c; Perkins et al., 1996; 1997; 2018).

Together, these limitations provide clear future directions for assessing how subjective effects and purchase tasks may be related to behavioral assessments of abuse liability.

4.5. Conclusions

This study compared widely used measures for abuse liability and how well they assess relative reinforcing efficacy assessed in a concurrent choice SA paradigm. All three measures provide unique insights into how cigarettes with varying levels of nicotine may maintain smoking behavior. Concurrent choice testing quantifies the acute relative reinforcing effects observed with direct drug taking, mCEQ subscales characterize the positive and negative reinforcing features of cigarette smoking, and the CPT shows how intensity of demand and environmental constraints influence the abuse liability of cigarettes which vary in nicotine content. Together these data provide clarity with regard to the individual components of the mCEQ and CPT that best describe abuse liability in cigarettes which vary in nicotine content. Furthermore, these methods (behavioral and self-report) capture unique facets of the abuse liability of cigarettes which vary in nicotine content. When all three measures are used together, researchers will be better

able to comprehensively describe the abuse potential of cigarettes with varying levels of nicotine across unique populations and within unique contexts.

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