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Examining The Malleability Of Cigarette Product Preference

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EXAMINING THE MALLEABILITY OF CIGARETTE PRODUCT PREFERENCE

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Abstract

Introduction: Cigarette preference increases as a function of nicotine content, but preference can be shifted by manipulating cigarette cost. The aim of the present study is to model whether the behavioral-economic metric of unit price (cigarette cost/nicotine content) accounts for cigarette preference shifts and whether preference changes to very low nicotine content cigarettes (VLNCs) are associated with corresponding changes in smoking rate.

Methods: 169 daily smokers from populations vulnerable to smoking completed sessions in which choices between smoking normal nicotine content (NNC) (15.8mg/g) and VLNC (0.4mg/g) cigarettes were concurrently available. In Condition 1, choices for both products were available ad-lib at an equal cost of 10 responses/choice. In Condition 2, VLNCs were again available ad-lib at 10 responses/choice, but NNCs were available on a progressive-ratio (PR) schedule wherein response cost (and unit price) increased following each NNC choice (10,160,320…8400 responses/choice). Results were analyzed using ANOVAs and a binomial test ($p<.05$).

Results: Participants preferred NNCs over VLNCs in Condition 1, but shifted preference to VLNCs in Condition 2 ($p<.001$) immediately before the point in the PR progression where unit price for NNCs exceeded unit price for VLNCs ($p<.001$). Additionally, this preference shift corresponded with reduced total cigarette consumption compared to Condition 1 levels ($p<.001$).

Conclusions: These results suggest that unit price of nicotine underpins cigarette preference and may provide a metric by which regulators can predict product preference and potentially impact it through policy. These results also demonstrate that VLNCs sustain lower smoking rates than NNCs even under acute laboratory conditions.

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1. COMPREHENSIVE LITERATURE REVIEW

1.1 Overview

Since the release of the 1964 Surgeon General's Report demonstrating the health risks of cigarette smoking (U.S. Department of Health, Education, and Welfare, 1964), prevalence of cigarette smoking has steeply declined from 42.4% in 1964 to 15.5% in 2016 (Jamal et al., 2016). However, even with this sizeable reduction in prevalence, cigarette smoking remains the single largest cause of preventable death in the United States. Over 480,000 deaths per year are attributable to smoking-related causes, including 41,000 deaths attributable to secondhand smoke exposure (U.S. Department of Health and Human Services (U.S. DHHS), 2014). Unfortunately, these decreases in smoking prevalence are unevenly distributed within the U.S. population. Prevalence rates have decreased substantially among more affluent and socially stable subgroups but relatively little over this same time period in certain racial/ethnic minorities and among individuals with psychiatric conditions and have even increased in other subgroups, such as socioeconomically disadvantaged women (Chilcoat, 2009; Higgins & Chilcoat, 2009; Higgins 2014; Schroeder & Koh, 2014). As cigarette smoking continues to be a leading cause of preventable death and its harms continue to disproportionately impact more disadvantaged populations, it is important to continue investigating cigarette smoking and addiction with the overarching aim of reducing individual and population harm.

1.2 Nicotine: Reinforcing Effects, Action, and Delivery

Nicotine is the constituent in cigarettes that drives dependence and repeated use among smokers (U.S. DHHS, 1988). Nicotine, like other addictive drugs, serves as a positive reinforcer. A positive reinforcer is a stimulus that is delivered following a

behavior that strengthens or increases the probability of a response (Bouton, 2016). Nicotine has been demonstrated to function as a positive reinforcer in both preclinical and clinical studies. Across these studies, nicotine has been demonstrated to maintain voluntary drug self-administration, establish previously neutral stimuli as discriminative stimuli and conditioned reinforcers, and result in high rates of persistent drug seeking (Goldberg, Spealman, & Goldberg, 1981; Henningfield & Goldberg, 1983; Henningfield, Miyasato, & Jasinski, 1983; U.S. DHHS, 1988). In addition to demonstrating that cigarette smokers will self-administer nicotine and that administration rates are dose dependent, subjective ratings of nicotine strength and liking have been demonstrated to be dose dependent, while measures of withdrawal are inversely related to dose (Henningfield, Miyasato, & Jasinski, 1985).

Cigarettes, as a device, are well designed to deliver nicotine quickly and efficiently to the brain (Balfour, 2015; Picciotto & Mineur, 2014). When tobacco smoke from a cigarette is inhaled, smoke particles carry nicotine into the lungs, where the nicotine is absorbed into the pulmonary circulation, then arterial circulation, and travels quickly from the lungs to the brain (Henningfield, London, & Benowitz, 1990). A typical smoker will take approximately ten puffs on a cigarette over roughly five minutes taking in approximately one milligram (mg) of nicotine per cigarette (Hoffmann & Hoffmann, 1997). With nicotine having a very short distribution half-life (~ nine minutes) and a relatively short elimination half-life (~ two hours), repeated administration of cigarettes is necessary to maintain stable nicotine blood levels in dependent cigarette smokers (Feyerabend, Ings, & Russel, 1985).

In the brain, nicotine binds to nicotinic acetylcholine receptors (nACHrs). There are twelve subunits that make up these receptors; nine α subunits (α2 - α10) and three β subunits (β2 - β4). The most abundant receptors from these subunits are α4β2, α3β4, and α7 (Benowitz, 2010). The nACHr that is the main mediator for nicotine dependence is α4β2 (Dani & De Biasi, 2001). The β2 receptor subunit has been shown to be responsible for behavioral responses to nicotine (Maskos et al., 2005), while the α4 receptor subunit is an important determinant in sensitivity to nicotine (Tapper et al., 2004). Excitation of the nAChrs release a variety of neurotransmitters, including dopamine. Dopamine release underpins the reinforcing effects of nicotine as it does other reinforcing events (e.g. food consumption, sex, use of other drugs of abuse such as cocaine and heroin) (Koob, 1992; Schultz 2013; Wise, 1996). Like other drugs of abuse, nicotine stimulates dopamine release in the mesolimbic system starting in the ventral tegmental area and terminating in the nucleus accumbens (Picciotto & Mineur, 2014).

1.3 Nicotine Dependence

The level of nicotine in commercially available tobacco products is sufficient to promote and sustain dependence among users. As demonstrated in the research examining nicotine's reinforcing efficacy discussed above, those effects are dose dependent (Henningfield & Goldberg, 1983; Henningfield, Miyasato, & Jasinski, 1985). Based on that knowledge, in a landmark essay, Benowitz and Henningfield proposed that it may be possible to reduce the addiction potential of cigarettes by reducing the amount of nicotine available in cigarettes to below a threshold that would sustain dependence and repeated use (Benowitz & Henningfield, 1994). Data from non-daily (and thusly considered non-dependent) cigarette smokers was used to develop a hypothesized

'threshold of addiction' to nicotine in cigarettes (i.e. a level of nicotine consumption that would not maintain nicotine dependence). At the time of the Benowitz and Henningfield essay, approximately 10% of cigarette smokers fit the definition of 'non-daily smokers', broadly defined as those who smoke five or less cigarettes per day and who did not experience the same physical distress (i.e. withdrawal) upon abstaining from cigarette smoking as daily smokers. Using data obtained from these non-daily smokers, Benowitz and Henningfield hypothesized than an average daily intake of five mg of nicotine per day was the approximate threshold level of nicotine necessary to promote and sustain dependence (Benowitz & Henningfield, 1994). As described previously, a typical full-flavor cigarette has a nicotine delivery of approximately one mg. The nicotine delivery of a cigarette during smoking is known as a cigarette's nicotine yield. Average nicotine yield of cigarettes is determined by the United States' Federal Trade Commission (FTC), using the Cambridge Filter Method, developed in 1964. Briefly, this methodology calls for inserting a cigarette into a machine. Once inserted and lit, the machine conducts two-second, 35 mL puffs once a minute until 23-mm in length remains of the cigarette (Pillsbury, 1996). Nicotine in the machine is analyzed and the amount of nicotine delivered determines the nicotine yield of the cigarette. By this machine-measured approximation, it could be suggested that a daily intake of five or less full-flavor cigarettes could reduce nicotine intake below the approximated threshold of dependence hypothesized by Benowitz and Henningfield (1994). However, machine-determined yields have been found to not be representative of cigarette smokers' actual nicotine intake (Kozlowski, O'Connor, & Sweeney, 2001). This is attributable to the fact that cigarette smokers do not inhale smoke in a uniform way (unlike machine measured

yields) and will often alter their smoking topography by taking more frequent or larger volume puffs or smoking more cigarettes to obtain the amount of nicotine necessary to sustain dependence (Benowitz, Jacob, Kozlowski, & Yu, 1986). Indeed, that is what was observed following the introduction of light and ultra-light cigarettes to the tobacco market landscape in the 1970s. These products contained similar nicotine content to full-flavor/full strength cigarettes but were marketed by tobacco companies as a lower exposure product with reduced harm. Light and ultra-light cigarettes have lower machine measured nicotine and tar yields due to design modifications of the cigarette filter (e.g. increased ventilation to dilute the inhaled smoke) (Kozlowski & Pillitteri, 2001). However, the predicted decreases in nicotine and carbon monoxide exposure are not routinely observed with these products, as smokers often learn to block the ventilation holes with their fingers or engage in other compensatory smoking (i.e. larger puffs) to sustain desired nicotine blood levels (Benowitz et al., 2009; Scherer & Lee, 2014; Zacny & Stitzer, 1988a). As such, investigators pursuing lower nicotine exposure have to be mindful of the potential for compensatory smoking and may need to introduce products that reduce the actual nicotine content in a cigarette and not the nicotine exposure (i.e. nicotine yield) through artificial means (e.g. increased ventilation).

1.4 Nicotine Reduction

As nicotine is the constituent of dependence in cigarettes and drives repeated use, a reduction of the nicotine content in cigarettes to a level that does not sustain dependence, as outlined by Benowitz and Henningfield (1994), should be able to reduce smoking prevalence and thus related mortality and disease. In 2009, passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) gave regulatory

authority to the Food and Drug Administration (FDA) over the manufacturing, marketing, and distribution of nicotine and tobacco products. Regarding nicotine content levels in cigarettes, the FDA has the ability to lower without eliminating the amount of nicotine in cigarettes, if doing so is deemed in the interest of public health. With the FSPTCA, the FDA has the opportunity to implement a national policy of nicotine reduction that could have substantial potential for improving public health. Currently, the FDA is funding research to determine how to implement this regulatory action and to determine what the impact of regulatory action would be in both the general population of smokers and in groups that are considered especially vulnerable to smoking. As recently as March 2018, the FDA issued an Advanced Notice of Proposed Rulemaking regarding a nicotine content standard suggesting that nicotine reduction in cigarettes is being seriously considered as a regulatory action (Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, 2018).

Unlike previously described low nicotine yield products that use design features of the cigarette to lower nicotine yield but leave overall nicotine content of the cigarette unchanged, this more recent effort aims to reduce the nicotine content in cigarettes through methods such as genetically modifying tobacco to lower nicotine content. Initial studies examining cigarettes with reduced nicotine content have thus far been promising. These studies demonstrated in the general population of smokers interested in quitting in the near future and those who are not actively interested in quitting that extended exposure to cigarettes with nicotine content reduced to very low levels (0.4 mg per gram (mg/g) of tobacco) decreased cigarettes smoked per day (CPD) and nicotine dependence levels (Benowitz et al., 2012; Benowitz et al., 2007; Hatsukami, Heishman, et al., 2013;

Hatsukami, Hertsgaard, et al., 2013). Unlike prior studies with lowered machine-estimated yield cigarettes, these studies using reduced nicotine content cigarettes did not show evidence of compensatory smoking.

In addition to these earlier studies, two promising large-scale clinical trials examining extended exposure to reduced nicotine content cigarettes have been conducted using relatively healthy participants from the general population of smokers. The first of these two trials exposed participants to one of seven cigarette conditions in a between-subjects study design over a six week period; dose conditions included the participant's usual brand cigarette, a 15.8 mg/g nicotine content cigarette comparable to levels in commercial cigarettes that served as the control condition, and one of six reduced nicotine content cigarettes (5.2, 2.4, 1.3, and two at 0.4 mg/g with low and high tar levels). At the end of the six-week exposure period, those assigned to 0.4, 1.3, and 2.4mg/g nicotine content cigarette conditions smoked fewer CPD and had lower total nicotine equivalent levels (biomarker of nicotine exposure) than those in the 15.8mg/g nicotine content cigarette condition. Those in the very low (0.4mg/g) nicotine content conditions also had significantly reduced nicotine dependence scores relative to their baseline nicotine dependence scores, regardless of low or high tar condition (Donny et al., 2015).

The second of these two trials produced similar findings in that very low nicotine content cigarettes decreased nicotine exposure and nicotine dependence. However, this second trial examined nicotine reduction across two methods; immediate switching or gradual switching to very low nicotine content cigarettes over a 20-week period. Dose conditions included a 15.5mg/g nicotine content cigarette comparable to levels in

commercial cigarettes that served as a control condition, a gradual reduction condition in which cigarette nicotine content decreased incrementally every four weeks from a 15.5mg/g nicotine content cigarette to 11.7mg/g, 5.2mg/g, 2.4mg/g, and finally to a 0.4mg/g nicotine content cigarette, and an immediate reduction condition in which participants were assigned to a 0.4mg/g nicotine content cigarette for the duration of the 20-week period. Results from this trial showed significantly greater reductions in toxicant exposure in the immediate reduction condition to the 0.4mg/g nicotine content cigarette compared to both the control condition and the gradual reduction condition. CPD and dependence levels in the immediate reduction condition were lower at the end of the trial compared to the control and the gradual reduction conditions. Additionally, the gradual reduction condition had lowered exposure and dependence levels on some measures relative to the control condition, suggesting that although not as marked as the change in the immediate reduction condition, there were benefits to a gradual reduction in nicotine content over continued smoking of a normal nicotine content cigarette (Hatsukami et al., 2018).

In addition to these studies in the general population of relatively healthy smokers, there have been similar investigations in populations especially vulnerable to smoking (i.e., socioeconomically disadvantaged smokers and those with co-morbid psychiatric conditions). These vulnerable populations can have smoking rates two- to four-fold greater than the general population and often have lower cessation rates and more smoking-related health problems (Goodwin, Zvolensky, Keyes, & Hasin, 2012; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Higgins et al., 2016; Levinson, 2017; Stanton et al., 2016). Studies examining acute exposure to reduced nicotine content

cigarettes in vulnerable populations have demonstrated that these populations may respond similarly to the general population of smokers in response to cigarettes with reduced nicotine content (Higgins et al., 2017; Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2013). Tidey and colleagues demonstrated in smokers with severe mental illness (schizophrenia) that withdrawal was effectively attenuated with a very low nicotine content cigarette (0.4mg/g of tobacco) relative to a no-cigarette control condition without producing the same levels of positive subjective effects observed with participants' usual brand cigarette (Tidey et al., 2013). In the parent study that provides the data for the present study, Higgins and colleagues demonstrated in a clinical laboratory study comparing four nicotine content cigarettes under double-blind conditions (15.8, 5.2, 2.4, 0.4mg/g) that reducing the nicotine content in cigarettes dose-dependently decreased the relative reinforcing and positive subjective effects of smoking consistent with reduced addiction potential (Higgins et al., 2017). This study was conducted with three vulnerable groups (i.e., those with affective disorders as an exemplar of smokers with mental illness; those opioid dependence as an exemplar of smokers with other substance use disorders; socioeconomically disadvantaged women of reproductive age as an exemplar of smokers with economic disadvantage). Additionally, these studies, like those in the general population have demonstrated no evidence of compensatory smoking (Higgins et al., 2017; Tidey, Cassidy, & Miller, 2016).

One notable feature of the Higgins et al. (2017) study is the use of a concurrent choice arrangement to directly compare the relative reinforcing efficacy of the four-varying nicotine-content cigarettes. Following sampling of each cigarette in separate sessions under double-blind conditions, participants were exposed to two phases of

testing in the choice arrangement. In the first phase, participants completed six three-hour choice sessions. In each session they were given the choice between smoking two of the cigarettes they had previously sampled. Six sessions permitted comparisons of all possible dose pairs of the four-varying nicotine dose cigarettes. Participants were able to smoke as much or little of the two available cigarettes as they wished during each session. When they wished to smoke, they simply pointed a cursor toward the label on a computer screen for the cigarette they wanted to smoke represented by an arbitrary letter code (e.g., Cigarette A) and made 10 clicks on a computer mouse (i.e., a fixed-ratio [FR] 10 schedule of reinforcement), which allowed them to take two controlled puffs from the selected cigarette. The dependent variable was the proportion of choices allocated toward the higher dose. In the second concurrent choice test phase, participants were able to make choices between smoking the least and most preferred cigarettes, which were the lowest (0.4mg/g) and highest (15.8mg/g) dose cigarettes, respectively. This comparison was tested across three separate sessions. In these sessions, the very low nicotine dose cigarette continued to be available on an FR-10, while the highest nicotine dose cigarette was now available on a progressive-ratio (PR) schedule of reinforcement within each session. Overall, when cigarette pairs were available at an equal response cost in the first concurrent choice test arrangement, participants chose the cigarette with higher nicotine content significantly more across each of the six dose pairs (Figure 1, Panel A). However, when the higher nicotine content cigarette required greater effort to obtain than the very low nicotine content cigarette using the PR arrangement, preference was reversed, and the very low nicotine content cigarette was chosen significantly more (Figure 1, Panel B). This orderly examination of the relative reinforcing efficacy of the different nicotine

content cigarettes using a concurrent choice arrangement demonstrates how the clinical laboratory can be utilized to investigate smoker product preference and the malleability of those preferences.

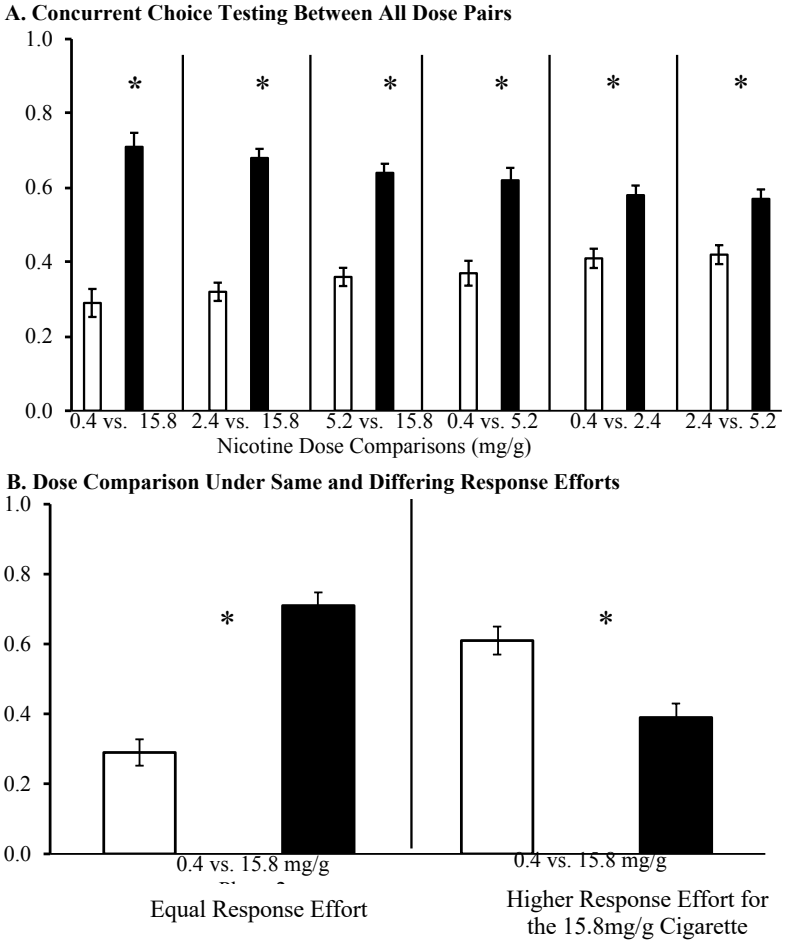

Figure 1. Data from Higgins et al. (2017). Panel A: Proportion of choices within a session across the Phase 2 concurrent choice arrangement when choices for cigarettes are under a fixed response cost (i.e. 10 mouse clicks). Panel B: Comparison of the proportion of choices allocated to each cigarette between sessions in which response cost for the 0.4mg/g and the 15.8mg/g nicotine dose cigarette is equal across the dose pair (i.e. Phase 2) and when the 15.8mg/g cigarette is shifted to a progressive ratio schedule (i.e. Phase 3). Asterisks represent significant differences in proportion of choices between cigarettes within a session ($p < .05$)

1.5 Clinical Laboratory Tasks to Examine Relative Reinforcing Efficacy and Addiction Potential

Clinical laboratory tasks have been widely utilized to examine the relative reinforcing efficacy and addiction potential of drugs in human volunteers. This allows researchers to experimentally examine behavioral responses to different substances, while rigorously controlling for potential confounding variables. As the FDA considers the development and implementation of a nicotine reduction policy, data from the clinical laboratory can provide experimental evidence regarding how cigarette smokers behave when the nicotine content of cigarettes is altered and when availability of a preferred product is constrained. Extended exposure experiments or field trials investigating reduced nicotine content products sacrifice some degree of experimental control, thus laboratory tasks can be used as an important complement to those studies. Two clinical laboratory procedures that have been very effective for assessing the addiction potential of cigarette smoking are the concurrent choice arrangement and the progressive ratio (PR) schedule. Both procedures have been used effectively in examining the relative reinforcing effects or addiction potential of smoking (Tidey, Cassidy, Miller, & Smith, 2016). Below we outline these procedures separately and when used in tandem in experiments on cigarette smoking.

1.5.1 Progressive-Ratio Schedules

PR schedules are schedules in which the response requirement increases progressively with each earned reinforcer and are used to assess reinforcer strength or value (Catania, 1998). The point in the ratio progression where responding for the reinforcer ceases is called the breakpoint. Breakpoint is known to vary as an orderly positive function of reinforcer magnitude (Brady et al., 1987; Hodos, 1961; Jones & Comer, 2013; Stafford, LeSage, & Glowa, 1998; Yokel, 1987). PR schedules represent a

well-established method for examining the relative reinforcing efficacy of a variety of drugs of abuse. Drugs or drug doses that have higher breakpoints are considered to have higher abuse liability/addiction potential (Brady, 1987; Comer et al., 2008; Stafford et al., 1998). In a seminal experiment examining breakpoint in humans, McLeod and Griffiths examined three doses of pentobarbital (200, 400, 600mg) and placebo under double-blind conditions. To obtain a single dose, participants were required to ride a stationary bike or press a set of buttons. Effort to obtain a dose increased over sessions until a breakpoint was established. Across participants, pentobarbital maintained dose-related increases in breakpoint suggesting that addiction potential increased in an orderly dose-dependent manner (McLeod & Griffiths, 1983).

Turning to examples from research on cigarette smoking, Tidey, Higgins, Bickel, & Steingard (1999) used a PR schedule to demonstrate that responding maintained by the opportunity to smoke in schizophrenic smokers was decreased in an orderly, graded manner by increases in response requirement and the concurrent opportunity to respond for an alternative non-drug reinforcer in a manner that closely paralleled the performance of smokers without serious mental illness (Bickel, DeGrandpre, Higgins, Hughes, & Badger, 1995). Those comparable effects suggested the presence of common controlling variables in cigarette smokers with and without serious mental illness. As another example, Sigmon, Tidey, Badger, & Higgins (2003) used a PR schedule to demonstrate potentially important individual differences in the response to psychomotor stimulants in cigarette smokers. Acute exposure to *d*-amphetamine increased breakpoint for responding maintained by cigarette smoking in those participants who also experienced a profile of positive mood effects (euphoria) while under the influence of the drug, but not in those

who reported no change or negative mood effects. In two final examples, PR schedules were used to characterize the substitutability of non-combusted tobacco products (Stein, Wilson, Koffarnus, Judd, & Bickel, 2017) or non-combusted tobacco products and very low nicotine content cigarettes (Johnson, Bickel, & Kirshenbaum, 2004) for normal nicotine content cigarettes with both studies demonstrating the highest breakpoints for normal nicotine content cigarettes across the products suggesting that the highest relative reinforcing efficacy among products examined was in these cigarettes.

1.5.2 Concurrent Choice Arrangements

Concurrent choice arrangements are widely used to examine relative reinforcing effects and thus can be utilized to assess the addiction potential of cigarette smoking and other substances. Concurrent choice arrangements allow participants to access two or more concurrently available reinforcers (Comer et al., 2008; Yokel, 1987). In these tasks, addiction potential is examined by having a reinforcer concurrently available with a placebo, different magnitudes of the same reinforcer, or a reinforcer and a salient non-drug alternative (such as money, social reinforcement, etc.) concurrently available (De Wit & Johanson, 1987). These tasks can either be free choice, in which a participant can make no choices if they so wish or forced choice, in which a minimum requirement of choices is an experimental requirement. Concurrent choice arrangements are effective at demonstrating drug preference under both conditions of forced choice (i.e. minimum response required) or free choice (i.e. no minimum response requirement), although overall magnitude of response appears to be higher in forced choice paradigms (Oliveto et al., 1992). As an exemplar of the concurrent choice arrangement, Johanson and Schuster (1975) examined the relative reinforcing efficacy of cocaine in rhesus monkeys

by concurrently comparing cocaine to differing doses of cocaine, saline, or varying doses of methylphenidate. When two doses of cocaine were concurrently available, the high dose of cocaine was preferred, cocaine was preferred when concurrently available with saline, and when cocaine and methylphenidate were concurrently available, drug preference was a function of which drug had a higher dose available in the choice task, suggesting the relative reinforcing efficacy of cocaine is dose dependent and comparable to methylphenidate (Johanson & Schuster, 1975). Choice arrangements have been well developed in studies with non-human animals and humans (Bickel, Higgins, & Stitzer, 1986; Comer et al., 2008; Yokel, 1987). Concurrent choice arrangements have been used to investigate the relative reinforcing effects of a variety of drugs of abuse, including cocaine (Higgins, Bickel, & Hughes, 1994; Stoops, Lile, & Rush, 2010), *d*-amphetamine (Vansickel, Stoops, & Rush, 2010), marijuana (Cooper et al., 2013), and opioids (Babalonis, Lofwall, Nuzzo, Siegel, & Walsh, 2013; Bickel et al., 1986; Jones, Sullivan, Manubay, Vosburg, & Comer, 2011; Stitzer, McCaul, Bigelow, & Liebson, 1983). Additionally, concurrent choice procedures are used to examine how relative reinforcing effects are altered under different states such as drug and medication pretreatment (Higgins & Stitzer, 1988; Higgins, Hughes, & Bickel, 1989; Tidey, O'Neill, & Higgins, 2000) or varying lengths of drug abstinence (Bradstreet et al., 2014; Chivers, Higgins, Heil, Proskin, & Thomas, 2008; Lussier, Higgins, & Badger, 2005; Yoon, Higgins, Bradstreet, Badger, & Thomas, 2009).

Addiction potential of cigarette smoking has been examined widely in concurrent choice arrangements. These arrangements have been useful in examining the reinforcing efficacy of cigarettes within the general population of cigarette smokers (Bisaga, Padilla,

Garawi, Sullivan, & Haney, 2007; Bradstreet et al., 2014; Chivers et al., 2008; Lussier et al., 2005; Johnson & Bickel, 2003; Stoops, Pooler, Vansickel, & Rush, 2011; Yoon et al., 2009) and within different specific vulnerable populations, including smokers with depression (Audrain-McGovern, Wileyto, Ashare, Cuevas, & Strasser, 2014), schizophrenia (Tidey et al., 1999), adolescents (Cassidy, Tidey, Kahler, Wray, & Colby, 2015), and more recently in studies with smokers with mental illness, comorbid substance use disorders, and low socioeconomic status (Higgins et al., 2017). These studies are important for understanding how the addiction potential of cigarette smoking may differ between or within populations.

As detailed above, the study by Higgins and colleagues (2017) examined four cigarettes of varying nicotine content using a combination of a concurrent choice arrangement where the products being compared were available at equal low effort and a concurrent choice arrangement in which the least preferred and most preferred products were compared with the former available at a low cost and the latter on a PR schedule. By combining the PR and concurrent choice arrangements, the malleability of product preference was clear with participant switching preference from the high to the low nicotine content cigarette as a function of changes in cost to obtain the former. This feature of the concurrent choice arrangement involving the PR schedule is well designed to provide additional information beyond cigarette preference under shifting constraints.

More specifically, this arrangement also provides an opportunity to examine behavior when preference is shifted to the very low nicotine content cigarette. When a very low nicotine content cigarette is more readily available than a normal nicotine content cigarette, will we be able to detect changes in cigarette consumption similar to

changes in cigarette consumption observed in studies of extended exposure? As was also detailed above, assigning daily smokers to extended use of very low nicotine content cigarettes decreases CPD (Donny et al., 2015; Hatsukami et al., 2018). Might that same effect be detected during acute exposure in the clinical laboratory? That is an unanswered question that is examined as part of the present study.

1.6 Behavioral Economic Translations of the Concurrent Choice Arrangement

An important aspect of, if not the sole rationale for, tobacco regulatory research is the ability to be able to extrapolate research results to naturalistic settings. Indeed, the rationale for establishing the Tobacco Regulatory Science Program (TRSP) in the National Institutes of Health's Office of Disease Prevention was to support research that would allow FDA to implement evidence-based tobacco regulation. With an eye towards generating such generalizable evidence, tobacco regulatory science investigators are increasingly examining behavioral economic concepts and methods of assessing addiction potential (Tidey et al., 2016). TRSP is supporting a wide range of different research areas and approaches, but behavioral economics is among those garnering support.

One such behavioral-economic concept that shows particular promise as a tool to assess addiction potential is unit price. Unit price is based on behavioral demand theory (Bickel, DeGrandpre, Higgins, & Hughes, 1990). A fundamental concept of consumer demand is the demand curve and its well-established corollary that demand for a commodity decreases as an orderly function of increases in price. In the absence of money, 'price' can be conceptualized in terms of response cost or the effort required to obtain a commodity (Collier, Johnson, Hill, & Kaufman, 1986; Hursh, 1980; Watson,

1977). Within a unit price framework, the determinant of demand is price per unit of commodity obtained as expressed in the following equation:

$$Unit\ price = \frac{reinforcer\ cost}{reinforcer\ magnitude}$$

This equation was first developed in behavioral economic research to examine food consumption in a non-human animal experimental model (Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988). Variations of this equation can take into consideration the likelihood of delivery of the reinforcer and other factors that may impact unit price, such as the force requirement of the lever (or other device) being pressed to obtain the reinforcer (Hursh et al., 1988). These aspects of the equation can be eliminated in models in which response force requirement of the lever or other device is equal across choices and probability is certain (and therefore has no impact on response cost).

According to the unit price equation, consumption should be comparable at the same unit price independent of differences in values of reinforcer magnitude and response requirement. For example, a drug has a unit price of 20 both when 20 responses are required for 1mg of the drug and when 40 responses are required for 2mg of that same drug. It is hypothesized that consumption of a reinforcer should be consistent across multiple response requirements and drug doses/reinforcer value combinations, as long as the unit price across these options is held constant (Bickel, DeGrandpre, Hughes, & Higgins, 1991).

Unit price has been shown to be effective in accounting for demand across multiple drugs of abuse in non-human and human experimental models. Regarding research in non-humans, Bickel and colleagues reanalyzed published drug self-

administration studies and demonstrated that when unit price was constant within studies employing a variety of different schedules of drug delivery and drug doses, drug administration was functionally equivalent. This finding was observed across species (rhesus monkeys, rats, squirrel monkeys) and drugs of abuse (pentobarbital, cocaine, *d*-amphetamine, phencyclidine, ketamine, ethanol, methohexital). Additionally, demand curves for each study were produced and independent of dose and response requirement, as unit price increased, consumption decreased in an orderly manner (Bickel, et al., 1990; DeGrandpre, Bickel, Hughes, Layng, & Badger, 1993).

Turning to studies in humans, this same group of investigators (DeGrandpre, Bickel, Hughes, & Higgins, 1992) used unit price to evaluate 17 studies that were examining cigarettes of different nicotine yields to determine if unit price could account for the variability in nicotine exposure reported across these studies. In this report DeGrandpre et al. (1992) determined nicotine intake by multiplying puff volume, nicotine yield, and number of cigarettes smoked or when less information was available, number of cigarettes smoked by nicotine yield. Response cost within studies for examined cigarettes were then evaluated to calculate unit prices for each cigarette within the reevaluated studies. A demand curve with unit price along the x-axis and nicotine consumption along the y-axis was created for each reevaluated study. Overall, the reanalyzed studies showed positively decelerating demand curves. As unit price increased for cigarettes, nicotine consumption decreased across studies. Other studies examining cigarette use using unit price demonstrated when differing amounts of cigarette puffs are available concurrently at varying response costs found that as a rule when there were not limitations on behavior (e.g. instructions given to participants to allocate behavior

towards certain options), behavior was in the majority of paradigms exclusively allocated to the reinforcer with the lower unit price (Bickel & Madden, 1999; Madden, Bickel, & Jacobs, 2000). These studies examining consumption and unit price within concurrent arrangements utilize cigarettes of the same nicotine content and only examined cigarettes under concurrent FR schedules (not under PR schedules). The findings in evaluations of unit price of cigarette smoking are similar to the findings of evaluation of unit price of other drugs of abuse (Bickel, DeGrandpre, & Higgins, 1993; Bickel et al., 1990; DeGrandpre et al., 1993). Importantly, unit price as a concept considers both pharmacological (i.e. amount of drug) and non-pharmalogical factors (i.e. increasing cost for drug).

There has been some exploration of the boundaries of unit price, more specifically a potential boundary where unit price may not demonstrate similar rates of consumption across functionally equivalent unit prices is when very low drug doses are involved (Bickel et al., 1990; Bickel et al., 1991; DeGrandpre et al., 1993). Relevant to tobacco regulation and nicotine reduction, a recent study in the preclinical literature on nicotine self-administration, demonstrated results showing that at very low nicotine doses (i.e. below the threshold needed to sustain responding in animals), unit prices that were equivalent to those at higher nicotine doses did not sustain demand as expected based on the unit price equation (Smith, Rupprecht, Sved, & Donny, 2016). To our knowledge, this 'low-dose' boundary has not yet been examined in human models with tobacco products, suggesting the need for further research to examine if consumption of very low nicotine content cigarettes does not adhere to the rules of unit price.

As a whole, the unit price literature suggests that response rate is not a function of reinforcer magnitude alone, but rather a function of an interaction of the cost and benefit factors of responding and that a single process appears to underlie the effects of both reinforcement magnitude and schedule manipulations (DeGrandpre et al., 1993). Tobacco regulatory science may benefit from greater examination and application of the unit price concept including when examining the potential impacts of a nicotine reduction policy. Of particular relevance to the present proposal, results obtained in the concurrent choice arrangements investigated by Higgins and colleagues (2017) could be analyzed within a unit price framework, specifically the phase where the PR schedule is employed with the normal nicotine content cigarette (15.8 mg/g) while the very low nicotine content cigarette (0.4 mg/g) remains available under a relatively low FR-10 requirement. Within a unit price framework, it can be expected that the unit price of the 0.4 mg/g nicotine content cigarette available under the FR-10 schedule will remain constant throughout experimental sessions, while the unit price of the 15.8 mg/g nicotine content cigarette available under the PR schedule will increase with each increment in the PR response requirement. It would be expected that participants in this study would behave in an orderly manner consistent with unit price and cease responding for the normal nicotine content cigarette when the unit price becomes higher than the unit price of the very low nicotine content cigarette. If that hypothesis is true, then perhaps unit price can be considered as a rule-of-thumb by FDA when considering policies that attempt to migrate tobacco/nicotine users from using more to less toxic products.

1.7 Moderating Effects of Population Differences

As the FDA considers a potential national nicotine reduction policy, it is important to investigate population differences to address potential impacts among specific groups in the face of such a broad policy. Regarding the clinical laboratory tasks discussed above, it is important to try to understand how orderly function of unit price, product preference, and consumption may be impacted by population differences both because of evidence that certain sociodemographic and psychiatric characteristics can impact smoking risk and because the FDA has prioritized examining these topics as part of a thorough evaluation of the potential impacts of a nicotine reduction policy. It is relevant to examine whether characteristics may be associated with differences in sensitivity to changes in unit price, thus maintaining behavior for the higher dose product (i.e. persisting in clicking for the higher dose product even when the unit price is lower for the low dose). Such potential subgroup differences in response to nicotine dose reductions could potentially exacerbate existing or contribute to new disparities in smoking prevalence if a national nicotine dose reduction policy were to be implemented.

In addition to increasing overall understanding of the determinants of tobacco product preference and consumption, examination of these characteristics may help policy makers to anticipate potential response differences or unintended adverse consequences within the U.S. smoker population. Some characteristics of interest are nicotine dependence severity and vulnerable populations, both of which have demonstrated some differences in smoking intensity (i.e. smoking rate when cigarettes are free of cost) on the Cigarette Purchase Task, a measure of the relative reinforcing efficacy of cigarettes (Higgins et al., 2018; Higgins et al., 2017). Additional characteristics of interest are age, menthol status (i.e. non-menthol or menthol smoker), and sex, as all of these groups are of interest

because of their differences between categories within each characteristic in regard to smoking rates, nicotine dependence, and smoking-attributable adverse health effects (Perkins, 1999; SAMSHA, 2012; Villanti et al., 2016).

2. STUDY AIMS

The overarching aim of the current study is to thoroughly examine under double-blind conditions how manipulating price (i.e., response cost) parameters in a two-option concurrent choice arrangement influences product preference and articulate implications of study results for tobacco regulation and policy. The three specific aims of the study are detailed below.

Aim 1. Examine whether changes in cigarette product preference between two research cigarettes differing in nicotine content (15.8 and 0.4 mg/g) across changing price constraints is accounted for by the behavioral economic concept of unit price.
Hypothesis: Participants will shift responding to what had been the less preferred product (i.e. the 0.4 mg/g nicotine content cigarette) when the unit price for what had been the more preferred product (i.e. the 15.8 mg/g nicotine content cigarette) becomes higher than the unit price for the less preferred product.

Aim 2. Determine if the shift in product preference to the very low nicotine content cigarette (0.4 mg/g) is associated with decreases in overall cigarette consumption.
Hypothesis: Overall cigarette consumption will decrease corresponding to preference for the lower nicotine content cigarette.

Aim 3. Examine whether sociodemographic and smoking characteristics moderate effects observed in Aims 1 and 2. *Hypothesis: While we deem examination of these potential moderators important to a thorough analysis of Aims 1 and 2, we do not have firm hypotheses about outcomes.*

3. METHODS

3.1 Participants

Participants were 169 adult daily smokers who completed a multisite (University of Vermont, Brown University, Johns Hopkins University) parent trial (Higgins et al., 2017) examining three populations with co-morbid conditions; affective disorder as an exemplar of smokers with mental illness (n = 56); opioid dependence as an exemplar of smokers with other substance use disorders (n = 60); and socioeconomically disadvantaged women of reproductive age (18-44) as an exemplar of smokers with socioeconomic disadvantage (n = 53).

Parent study inclusion criteria across the three subpopulations required participants to be at least 18 years of age and daily smokers who reported smoking at least 5 cigarettes-per-day over the past year. Smoking status was biochemically confirmed with an expired breath carbon monoxide (CO) reading of 8 parts per million (ppm) at intake. All participants had to provide a negative urine specimen at intake for the following substances (excluding any prescribed medications); cocaine, amphetamine, benzodiazepines, opiates, barbiturates, methamphetamine, phencyclidine, methadone, and buprenorphine. A positive urine specimen for marijuana was not exclusionary. At intake, all participants had to provide a breath alcohol sample < .01 for inclusion in the study. Exclusion criteria across the three subpopulations included intention to quit

smoking in next 30 days, significant use (>9) of tobacco products other than cigarettes in the past 30 days, current pregnancy, trying to become pregnant, current breastfeeding, exclusive use of "roll your own cigarettes", current suicidal ideation, and current symptoms of psychosis or dementia.

Inclusion criteria specific to the subpopulation with affective disorder were males and females 18-70 years old who met Mini International Neuropsychiatric Interview 6.0 criteria (Sheehan et al., 1998) for current or past year major depressive disorder, dysthymia, generalized anxiety disorder, post-traumatic stress disorder, panic disorder, or specific phobia, with or without agoraphobia. Inclusion criteria specific to opioid dependent subpopulation were males and females 18-70 years old who were currently receiving opioid maintenance medication for opioid dependence (i.e. methadone or buprenorphine). Participants in this subpopulation had to be stable on their opioid maintenance dose for at least 30 days prior to the study as confirmed by their maintenance provider. They also had to have <30% urine toxicology samples negative for illicit drugs (excluding marijuana) in the past 30 days as confirmed by a provider. Specific inclusion criteria for socioeconomically disadvantaged women of reproductive age were women 18-44 years old with their highest educational attainment reported as high school or less.

The study was approved by the local institutional review boards at each of the three participating research sites (University of Vermont, Brown University, Johns Hopkins University) and was reviewed by the FDA. Participants from each of the three populations were enrolled at the University of Vermont, participants from the affective disorders subpopulation were enrolled at Brown University, and participants from the

socioeconomically disadvantaged women and opioid dependent subpopulations were enrolled at Johns Hopkins University.

3.2 Research Cigarettes

Cigarettes used in the study were Spectrum research cigarettes manufactured by 22nd Century Group (Clarence, NY) and obtained from the National Institute of Drug Abuse (NIDA) following an application for an Investigational Tobacco Product with the Center for Tobacco Products, U.S. FDA. Four nicotine dose conditions were used throughout the parent study, however only two of the dose conditions were examined as part of the present study. The average nicotine content for each of the four cigarettes investigated were 15.8, 5.2, 2.4, and 0.4 mg/g of tobacco. In the current study, nicotine doses examined were the 15.8 and the 0.4 mg/g nicotine content cigarette. The 15.8mg/g nicotine content cigarette served as an experimental control with nicotine levels similar to that of commercial cigarettes. All cigarettes were available as both mentholated and non-mentholated formulations. Participants were assigned a menthol status based on their self-reported preference. Menthol content for the mentholated products are as follows: 7.22 mg of menthol per cigarette (mg/cigarette) for the 15.8 mg/g nicotine dose, 6.32 mg/cigarette of menthol for the 5.2 mg/g nicotine dose, 4.99 mg/cigarette of menthol for the 2.4mg/g nicotine dose, and 5.97 mg/cigarette of menthol for the 0.4mg/g nicotine dose (Richter et al., 2016). All non-mentholated Spectrum cigarettes have an average menthol content of 0.01 mg/cigarette across doses (Richter et al., 2016). Both mentholated and non-mentholated study research cigarettes have menthol levels within the range of menthol levels in commercially available cigarettes (Ai et al., 2016; Richter et al., 2016). All cigarettes were administered under double blind conditions.

3.3 Procedure

In the parent study, participants completed fourteen 2-4-hour experimental sessions (≥48 hours between sessions) in a within subjects design that was separated into three distinct study phases. The current study used data collected from a portion of Phase 2 and Phase 3 of the parent study. The overall and phase specific procedures conducted in the completed parent study are detailed below.

Across the study, all experimental sessions were conducted following brief abstinence (≤ 50% intake breath CO level). Prior to each session, time since last cigarette puff was equated by having participants take two ad-lib puffs of their usual brand cigarette and allowing 30 minutes to elapse prior to start study tasks (Henningfield & Griffiths, 1981). Sessions occurred no less than 48 hours apart and no more than seven days apart.

Across all sessions, upon arrival to the laboratory a brief battery of physiological measures were collected, including breath CO, breath alcohol level, heart rate, blood pressure, weight, urine toxicology screen for drugs of abuse, and urine pregnancy test, if applicable. Experimental sessions were rescheduled for participants who failed to meet breath CO criterion (≤ 50% intake breath CO level) or breath alcohol criterion (≤ 0.03%). Those with a positive drug screen for illicit substances excluding marijuana were administered a field sobriety test and if passed the session was continued. If failed, the session was rescheduled. A positive pregnancy test resulted in withdrawal from the study.

3.3.1 Phase 1 (Sessions 1-5)

Briefly, the first phase of the study consisted of a baseline session and four experimental sessions in which each of the four study cigarettes were sampled at

individual sessions. At an initial baseline session, all Phase 1 procedures (detailed below) were completed with participants using their usual brand cigarette. Following the baseline session, presentation of the study product was randomized across sessions and participants. Administration of study product was double blinded. Each cigarette was labeled with an arbitrary letter code which remained consistent throughout the study for each participant.

In each Phase 1 session, following the thirty-minute wait period and after collection of measures of withdrawal and craving using two well-validated measures, the Minnesota Nicotine Withdrawal Questionnaire (MNWS) and the Questionnaire of Smoking Urges (QSU), participants smoked the designated cigarette ad-lib through a Clinical Research Support System (CReSS) Desktop smoking topography device (Cox, Tiffany, & Christen, 2001; Hughes & Hatsukami, 1986; Lee, Malson, Waters, Moolchan, & Pickworth, 2003). This device recorded their smoking behavior, specifically capturing puff volume, duration, inter puff interval, puff velocity, and number of puffs. During smoking, participants were encouraged to write down their thoughts about each cigarette; how it tasted, how it made them feel, if they liked it. Notes for each cigarette were written on one sheet and used in the later phases of the study when multiple cigarettes were concurrently available.

Following ad-lib smoking, participants competed the modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007), a measure of subjective effects of smoking and the Cigarette Purchase Task (CPT) (Jacobs & Bickel, 1999; MacKillop et al., 2008), a measure of relative reinforcing efficacy. On the CPT, 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) for a 24-hour period. On this task, participants were instructed to assume that the product being evaluated was the only available tobacco product and this product could not be stockpiled for a later date. For the remainder of the session, CO levels were taken every fifteen minutes for an hour and measures of nicotine withdrawal and craving (MNWS, QSU) were collected.

3.3.2 Phase 2 (Sessions 6-11)

In Phase 2 sessions, participants completed the same measures of craving and withdrawal (i.e. MNWS and QSU) and engaged in the thirty-minute wait period. Following this, participants were oriented to a three-hour concurrent choice arrangement, which has been validated by prior research (Johnson et al., 2004; Lussier et al., 2005). At each session of Phase 2, two different packs of research cigarettes were made available to the participant, each with a different letter code corresponding to the letter codes assigned to the cigarettes in Phase 1. Notes from the prior sampling phase were also made available. Participants were instructed that they were free to choose as many of either cigarette as they wanted over the course of the three-hour task and if all cigarettes in a pack made available were used, another would be provided. Participants were also able to forgo smoking altogether during the session if they so desired. During the task, both available doses' letter codes were displayed on two 1.25-inch squares on a laptop computer and the computer screen displayed time remaining in the three-hour choice procedure. To make a smoking choice, participants were instructed to click ten times on a square on a computer screen that correspond to the dose they wished to smoke. Once the response requirement was completed for a smoking choice (i.e. ten clicks), the computer

displayed a screen instructing the participants to smoke. During this period, the screen also displayed a three-minute timer, which was the time participants were allotted to smoke their chosen cigarette. No other smoking choices were available during this three-minute period. Each smoking choice consisted of two puffs taken in a controlled puffing procedure, in which puffs were taken equally across choices and participants. This was to ensure that differences in nicotine exposure that are expected with smoking the different nicotine dose cigarettes was not confounded by differences in smoking topography across choices.

For each two-puff smoking choice, using the CReSS device, participants inserted the cigarette into the device and lit the cigarette without inhaling. Participants then proceeded to take a puff of the cigarette until a volume of 60 mL of smoke was inhaled, which was visually displayed on a desktop computer attached to the CReSS machine. As the puff was inhaled a second counter was displayed showing the measured puff volume as the puff was being taken. Following completion of this first puff, a timer immediately started counting down in seconds from thirty. Additionally, after each puff, participants were instructed to hold the smoke in their mouth for five seconds, which was displayed on the screen. After thirty seconds had elapsed the screen would reset, and a second puff was taken in an identical manner. Once the two earned puffs were taken, the participant was instructed to extinguished and dispose of their cigarette in an opaque jar with the appropriate letter code on it. Following the completion of the three-minute interval, participants were free to make more responses, as desired. Upon completion of each the session, the MNWS and the QSU were again administered. All six possible dose pairs (15.8mg/g vs. 0.4 mg/g; 15.8mg/g vs. 2.4mg/g; 15.8 mg/g vs. 5.2 mg/g; 5.2 mg/g vs. 2.4

mg/g; 5.2 mg/g vs. 0.4 mg/g; 2.4 mg/g vs. 0.4mg/g) were evaluated during Phase 2 and presentation of the dose pairs were randomized across participants and sessions.

3.3.3 Phase 3 (Sessions 12-14)

The experimental arrangement for Phase 3 was similar to Phase 2, with the exception that across the three sessions of Phase 3 only one dose pair was presented to the participant in these sessions; the lowest dose (0.4mg/g) and the highest dose (15.8mg/g), with the highest dose available on a progressive ratio schedule that incremented upwards each time it was chosen (10, 160, 320, 640, 1280, 2400, 4800, 6000, 7200, 8400 clicks). This progressive ratio has been established as effective for examining preference reversal in prior work (Sigmon, et al., 2003). The lowest dose remained available at fixed cost of ten clicks throughout the session.

This procedure was repeated across three sessions in Phase 3 in order to refine the estimate of what response-requirement differential between the low and high doses would reverse preference for the high dose and to discern changes over time in the development of that preference reversal. Following completion of Phase 3, participants again completed the QSU and the MNWS, as well as the CPT for both cigarettes administered.

3.4 Outcome Measures

3.4.1 Aim 1

The outcome measure for Aim 1 was obtained (a) by assessing the proportion of choices for high nicotine content cigarette (15.8 mg/g) in the Phase 2 session in which the 15.8mg/g nicotine content cigarette and the 0.4mg/g nicotine content cigarette were concurrently available and the proportion of choices for high nicotine content cigarette (15.8 mg/g) in Phase 3 and (b) by converting the FR-10 and PR schedule ratios (i.e. 10,

160, 320 ….8400) for each cigarette option in Phase 3 into unit prices, and then determining participant breakpoints in Phase 3 for the high dose cigarette (15.8mg/g) expressed as a unit price.

3.4.2 Aim 2

Smoking rate can be gleaned from the total number of choices made (two controlled cigarette puffs per choice) within each session examined in the current study (i.e. the Phase 2 session in which the 15.8mg/g nicotine content cigarette and the 0.4mg/g nicotine content cigarette were concurrently available and the Phase 3 sessions). More specifically, we examined this outcome in the Phase 2 session, in which the concurrent dose pair was the 15.8mg/g nicotine content cigarette (i.e. the normal nicotine content cigarette) and the 0.4mg/g nicotine content cigarette (i.e. the very low nicotine content cigarette) with each available at a fixed price (FR-10) and this outcome across the Phase 3 sessions where availability of the lower nicotine content cigarette (0.4mg/g) remained at FR-10 while the higher nicotine content cigarette (15.8mg/g) was available under a PR schedule.

3.4.3 Aim 3

For Aim 3, the sociodemographic and smoking characteristics of interest were nicotine dependence severity, vulnerable population, age, sex, and menthol status.

Nicotine dependence severity was examined by using the Heaviness of Smoking Index (HSI). The HSI is a measure of nicotine dependence comprised of two items; “How many cigarettes a day do you smoke?” and “How soon after you wake up do you smoke your first cigarette?” (Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989). Total possible HSI scores range from 0-6. HSI cut points previously established in

U.S. nationally representative sample of current smokers (Schnoll, Goren, Annunziata, & Suaya, 2013) and used in a separate secondary analysis of the parent study (Higgins et al., 2018) were utilized. Participants with scores of 0-2, 3, and 4-6 were categorized as mildly, moderately, and highly dependent, respectively.

Vulnerable population was defined as one of the three populations participants were categorized under in the parent study; those with affective disorder, those with opioid dependence, and women of reproductive age with low socioeconomic status. Age and sex were both collected at study screening as continuous variables through self-report (i.e. "What is your age?" and "Are you male or female?"). Menthol status was collected at screening through self-report. Participants were asked the menthol status of their usual brand cigarette and were then asked for the duration of the study what cigarette type (i.e. menthol or non-menthol) that they would prefer to smoke. Self-selected study cigarette matched self-selected usual brand cigarette on menthol status across all participants and was thus used as the variable to determine menthol status.

3.5 Statistical Analyses

This secondary analysis focuses on participants from the parent study (n = 169) (Higgins et al., 2017). All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as $p<.05$ for all analyses described below.

3.5.1. Aim 1 Analyses

To address Aim 1, cigarette choice preference was examined for the Phase 2 session in which the highest nicotine content (15.8mg/g) and lowest nicotine content (0.4mg/g) cigarette were available concurrently at identical response requirements (i.e. 10 mouse clicks) and across the three Phase 3 sessions where the response requirement for

the previously preferred product progressively increased as choices are made. A mixed model repeated measures analyses of variance (ANOVA) was used to determine if proportion of choices for the 15.8 mg/g cigarette differed significantly between the Phase 2 and 3 sessions. First, an ANOVA examining differences in the proportion of choices for the 15.8mg/g nicotine content cigarette between Phase 2 and Phase 3 was conducted. For Phase 3, an average across all sessions of proportion of choices for the 15.8mg/g nicotine content cigarette was calculated. If there was a significant main effect of phase, an ANOVA examining the effect of sessions (i.e. the Phase 2 session examining proportion of choices for the 15.8mg/g nicotine content cigarette when at equal cost to the 0.4mg/g nicotine content cigarette compared to each individual Phase 3 session where the 15.8 mg nicotine content cigarette was available under a PR schedule) was conducted to examine stability of the effect across individual Phase 3 sessions. Both ANOVAs included study site as a random effect to account for any differences across the three study sites (e.g. University of Vermont, Brown University, Johns Hopkins University) as has been done in both the parent study (Higgins et al., 2017) and prior secondary analyses using this dataset (Higgins et al., 2018; Davis et al., 2019; Streck et al., 2018).

To examine whether unit price could account for any shift in product preference observed between Phases 2 and 3, we converted the reinforcement schedules in Phase 3 into unit prices. This means that the FR-10 for the low nicotine content cigarette (0.4mg/g) and each point in the PR schedule for the high nicotine content cigarette (15.8mg/g) was converted into a corresponding unit price. Since the number of puffs is controlled and constant across choices, we can assume that the nicotine delivery per each cigarette is constant across choices and thus is not impacted by compensatory smoking or

other differences in smoking. To obtain the unit prices, the unit price equation below was used:

$$Unit\ price = \frac{reinforcer\ cost}{reinforcer\ magnitude}$$

Using this unit price equation, a choice for the 0.4mg/g nicotine content cigarette has a constant unit price of 25 (e.g.10 clicks ÷ 0.4mg/g nicotine dose) within and across all Phase 3 sessions, as the reinforcer cost and reinforcer magnitude did not change. However, a choice for the high dose cigarette had a shifting unit price at each point in the PR schedule (10 clicks, 160 clicks, 320 clicks, etc. ÷ 15.8 mg/g nicotine dose) within each three Phase 3 sessions (Table 1).

Table 1. *Unit Price Conversion of the PR Schedule in Phase 3 for the 15.8mg/g Nicotine Content Cigarette*

Progressive Ratio Schedule	Unit Price Conversion (to the nearest tenth)
10 mouse clicks	0.63
160 mouse clicks	10.12
320 mouse clicks	20.25
640 mouse clicks	40.50
1280 mouse clicks	81.01
2400 mouse clicks	151.90
3600 mouse clicks	227.85
4800 mouse clicks	303.80
6000 mouse clicks	379.75
7200 mouse clicks	455.70
8400 mouse clicks	531.65

After the conversion of each schedule point to a unit price, maximum unit price that 15.8mg/g nicotine content cigarette was obtained for was determined for each session by assessing the breakpoint for the 15.8mg/g nicotine content cigarette (i.e. the last point in the PR schedule obtained per session) across all Phase 3 sessions. To determine if responding shifted away from the 15.8mg/g nicotine content cigarette as unit

price for it increased, median maximum unit price for the 15.8mg/g nicotine content cigarette was examined to determine at what unit price that on average preference reversal occurred at across sessions. In addition to determining the median, the total number of Phase 3 sessions at which the maximum unit price that was obtained for the 15.8mg/g nicotine content cigarette occurred at a lower or equal unit price than the fixed unit price of the 0.4mg/g nicotine content cigarette was summed and divided by total number of sessions in order to obtain a proportion. An exact binomial test was used to test whether this proportion was significantly higher or lower than 0.5; that is, whether the proportion of sessions having a maximum unit price for the 15.8mg/g nicotine content cigarette that was lower than 25 (i.e. constant unit price for the 0.4mg/g nicotine content cigarette) was greater than chance.

3.5.2. Aim 2 Analyses

To examine whether the shift in product preference to the 0.4mg/g nicotine content cigarette in Phase 3 was associated with decreases in cigarette consumption, we conducted the same sequence of ANOVAs as described above for Aim 1. First, an ANOVA examining differences in total number of choices to smoke in Phases 2 and 3 was examined. If there was a significant main effect of phase, an ANOVA examining the effect of sessions (i.e. the Phase 2 session compared to each individual Phase 3 session) was conducted to examine stability of the effect across individual Phase 3 sessions. Each ANOVA included study site as a random effect to account for any differences across the three study sites (e.g. University of Vermont, Brown University, Johns Hopkins University) as has been done in both the parent study (Higgins et al., 2017) and prior

secondary analyses using this dataset (Higgins et al., 2018; Davis et al., 2019; Streck et al., 2018).

In addition to the above analyses on total consumption, it is necessary to determine whether inclusion of the PR schedule in Phase 3 may have constrained total amount of time available to smoke in Phase 3 at rates comparable to those observed in Phase 2. In Phase 3, the response requirement for the high dose increased as a function of the PR schedule. Since increases in the response requirement increase the amount of time it takes to complete each choice, total consumption may be impacted not only as a function of the changing schedule, but also due to the participants not having sufficient time to consume as much product as they did in Phase 2 (i.e. the three-hour period may expire before participants reach the total consumption that they obtained in Phase 2). In order to determine the impact of the PR schedule on total consumption, we investigated whether the proportion of time spent earning and consuming the reinforcer during Phase 3 (i.e. clicking for the opportunity to smoke, taking puffs earned, and completion associated time-out period) was significantly greater than time spent earning and consuming the reinforcer during Phase 2. To do so, we specified the total amount of time allocated to earning and consuming the reinforcer during each session. In each choice session a file was created that recorded the start of the session with a time stamp (in milliseconds) and each choice to smoke throughout the session. When a cigarette was earned, it was recorded as a single trial. The start of each trial was time stamped to the nearest millisecond. Each time that a response (i.e. mouse click) was allocated towards earning either cigarette option, the response was time stamped to the nearest millisecond. Upon completion of the number of responses required to earn a designated cigarette, the

trial ended and was time stamped. Next, there was a 3-minute period in which the participant had a chance to consume the two puffs earned, which was also time stamped. During this 3-minute consumption period, no other responding was available. After the 3-minute consumption and time out period elapsed, the start of the next trial began. In the time between the start of the new trial (i.e. when the 3-minute consumption and time-out period ended) and the first response for another reinforcer, participants were not actively trying to earn or consume reinforcer (i.e., idle time). In order to determine the total time spent earning and consuming the reinforcer in each session, we subtracted this 'idle' time from total trial time. Time that participants spent consuming and earning reinforcers per session over total session time (i.e. 3 hours) was then calculated and a proportion of total time spent consuming and earning reinforcers per session was calculated. Similar to the analyses of preference and consumption, mixed model repeated measures ANOVAs were conducted to examine differences in proportion of time earning and consuming reinforcers with an ANOVA examining the main effect of phase (i.e. Phase 2 vs. Phase 3). If there was a significant main effect of phase, an ANOVA examining the effect of sessions (i.e. the Phase 2 session compared to each individual Phase 3 session) was conducted to examine stability of the effect across individual Phase 3 sessions. ANOVAs included study site as a random effect to account for any differences across the three study sites.

3.5.3. Aim 3 Analyses

For Aim 3, sociodemographic and smoking characteristics were examined as potential moderators of Aim 1 and Aim 2 outcomes. As noted above, the potential moderating variables of interest were nicotine dependence severity, vulnerable

population, age, sex, and menthol status. HSI was calculated from the two study items: "How many cigarettes a day do you smoke?" and "How soon after you wake up do you smoke your first cigarette?" To determine HSI, scores from these two items are summed. For item 1 choice options are a) 10 or less, b) 11-20, 3) 21-30, and d) 31 or more. For item 1, a score of 0-3 is assigned depending on a participant's answer with a score of 0 being assigned to the answer choice 10 or less, a score of 1 for the answer choice 11-20, a score of 2 for the answer choice 21-30, and a score of 3 for the answer choice 31 or more. For item 2, options are a) 0-5 minutes, b) 6-30 minutes, c) 31-60 minutes, and d) more than 60 minutes with a score of 3 is answer choice is 0-5 minutes, a score of 2 if answer choice is 6-30 minutes, a score of 1 if answer choice is 31-60 minutes, and a score of 0 if the answer choice is more than 60 minutes. Total possible HSI scores range from 0-6. Scores of 0-2, 3, and 4-6 on the HSI were categorized as mildly, moderately, and highly dependent, respectively (Schnoll et al., 2013).

Vulnerable population was determined by identifying which of the three parent study populations a participant was a member of (i.e. those with affective disorders, opioid dependent individuals, women of low SES). For age, self-reported age at intake was examined as a continuous variable. For sex, self-reported sex at intake was examined as a categorical variable. For menthol status, participants were asked to select a menthol status for the duration of the study and all participants included in these analyses picked a menthol status that matched their preferred type outside of the lab.

To examine the potential moderating effect of these variables on the effect of phase on the primary dependent measures (proportion of choices for the high dose, breakpoint, total cigarette consumption, total time allocated to earning and consuming

reinforcers) the potential moderators (i.e. HSI group, vulnerable population, age, sex, and menthol status) were included as covariates in a mixed-model repeated measures ANOVAs examining main effects of phase. If there was a main effect of phase *and* the potential moderator variable was significant, the interaction term between the moderator variable and the independent variable was examined.

4. RESULTS

4.1 Participant Characteristics

Demographics and smoking characteristics are presented for the 169 participants in Table 2. Briefly, participants were on average 36 years of age and the majority of the sample was white (73%) and female (71%). Of the three vulnerable populations recruited for the parent study, 56 (33%) were those with affective disorder, 60 (36%) were opioid maintained, and 53 (31%) were socioeconomically disadvantaged women of childbearing age. Regarding smoking characteristics, on average participants smoked 15.8 cigarettes per day and 35% of the sample smoked mentholated cigarettes.

Table 2. *Demographic and Smoking Characteristics (n = 169)*

Characteristic	
Age, mean (SD)	35.6 (11.4)
Female (%)	120 (71.0)
Population	
Affective Disorders no., (%)	56 (33.1)
Opioid Maintained no., (%)	60 (35.5)
Low SES Women no., (%)	53 (31.4)
Race/Ethnicity no., (%)	
White	123 (72.8)

Native American/Alaska Native	0
Asian	1 (0.6)
Black/African-American	23 (13.6)
Native Hawaiian/Pacific Islander	1 (0.6)
Other or more than one race	15 (8.9)
Latino	6 (3.6)
Educational Attainment no., (%)	
Eighth Grade or less	4 (2.4)
Some High School	23 (13.6)
High School Graduate or Equivalent	58 (34.3)
Some College	64 (37.9)
2-year or Associate Degree	10 (5.9)
College or 4-year bachelor's degree	6 (3.6)
Graduate/Professional Degree	4 (2.4)
Marital Status no., (%)	
Married	27 (16.0)
Never Married	103 (60.9)
Divorced/Separated	35 (20.7)
Widowed	4 (2.4)
Cigarette smoked per day, mean (SD)	15.8 (7.5)
Mentholated Cigarette Smokers no., (%)	59 (34.9)
Breath Carbon Monoxide, mean (SD)	22.4 (11.9)
Age of first cigarette, mean (SD)	16.3 (4.3)
HSI, mean (SD)	2.9 ± 1.3
HSI 0-2 no., (%)	58 (32.3)
HSI 3 no., (%)	55 (32.5)

HSI 4-6 no., (%)	56 (33.1)

4.2 Aim 1 Results

4.2.1 Cigarette Preference

Proportion of choices for the 15.8mg/g nicotine content cigarette was significantly greater in the Phase 2 session in which the response requirement for the two choice options (15.8mg/g vs. 0.4mg/g) was equal compared to Phase 3 sessions ($F_{1,167} = 143.15$, $p < .001$) where response requirement for the high dose increased progressively on a PR schedule (Figure 2, Panel A). There was also a main effect of study session ($F_{3,457} = 74.63$, $p < .001$) across the four sessions (Figure 2, Panel B), with proportion of choices for the 15.8mg/g nicotine content cigarette in the Phase 2 session significantly greater (*ps* < .001) than choice for the high dose option across each Phase 3 session. There were no significant differences in the proportion of choices for the 15.8mg/g cigarette option across the three Phase 3 sessions (*ps* > .05) (Figure 2, Panel B).

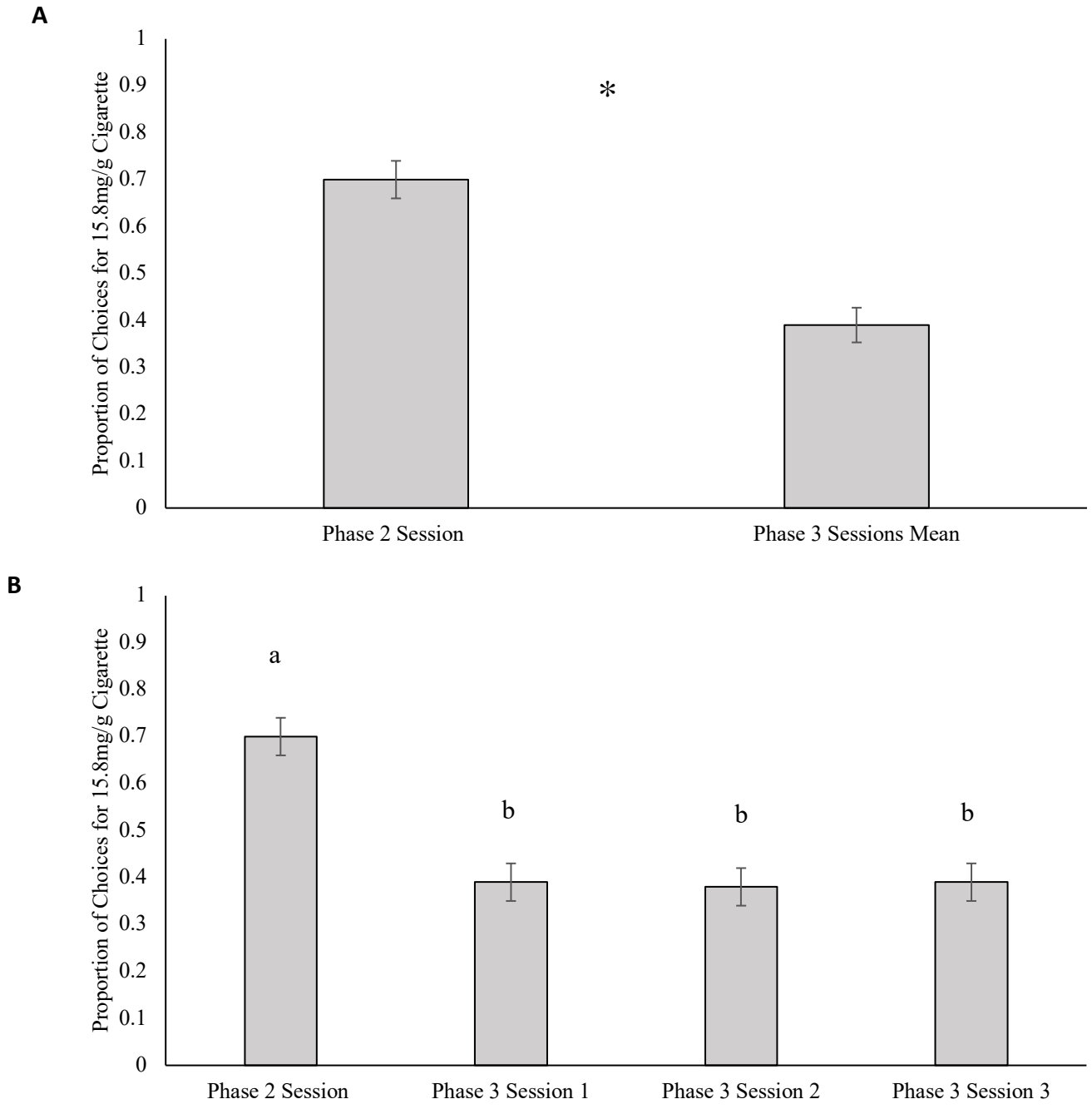

Figure 2. Proportion of choices allocated for the 15.8mg/g cigarette. Panel A: Proportion of choices allocated for the 15.8mg/g cigarette in Phase 2 and 3 of the study. Asterisk indicates significant difference at $p < .001$. Error bars represent $\pm$1 SEM. Panel B: Proportion of choices allocated for the 15.8mg/g cigarette across sessions. Data points not sharing a subscript are significantly different from one another ($p < .05$). Error bars represent $\pm$1 SEM.

4.2.2 Unit Price

The median breakpoint for the 15.8mg/g nicotine content cigarette expressed as a unit price was 20.25 (i.e. 320 mouse clicks/15.8 mg/g) across the three Phase 3 sessions (See Table 1, p. 35). The 320 mouse click response requirement is the last step in the PR schedule progression where the unit price for the 15.8mg/g nicotine content cigarette was lower than the unit price of the 0.4mg/g nicotine content cigarette, which was 25 across each Phase 3 session. The next step in the progression after 320 was a 640 mouse click response requirement, which has a unit price of 40.50.

To investigate this point further, an exact binomial test was conducted to examine whether the proportion of sessions where the maximum unit price for the 15.8mg/g nicotine content cigarette (breakpoint) was lower than the fixed unit price for the 0.4mg/g cigarette occurred at greater than chance levels. The proportion of sessions in which that was the case was 0.58, which was significantly greater than chance ($p < .001$).

4.3 Aim 2 Results

4.3.1 Total Consumption

Total cigarette consumption per 3-hour experimental session was significantly greater in the Phase 2 session in which the response requirement for the two available cigarette options were equal compared to the Phase 3 sessions in which the 15.8mg/g nicotine content cigarette was available on a PR schedule ($F_{1,166} = 98.03$, $p < .0001$) (Figure 3, Panel A). There was also a main effect of study session ($F_{3,459} = 55.45$, $p < .0001$) with total cigarette consumption in the Phase 2 session being significantly greater ($ps < .001$) than total cigarette consumption in each Phase 3 session (Figure 3, Panel B). Total

consumption for each of the three Phase 3 sessions did not significantly differ from each other (*ps* > .05).

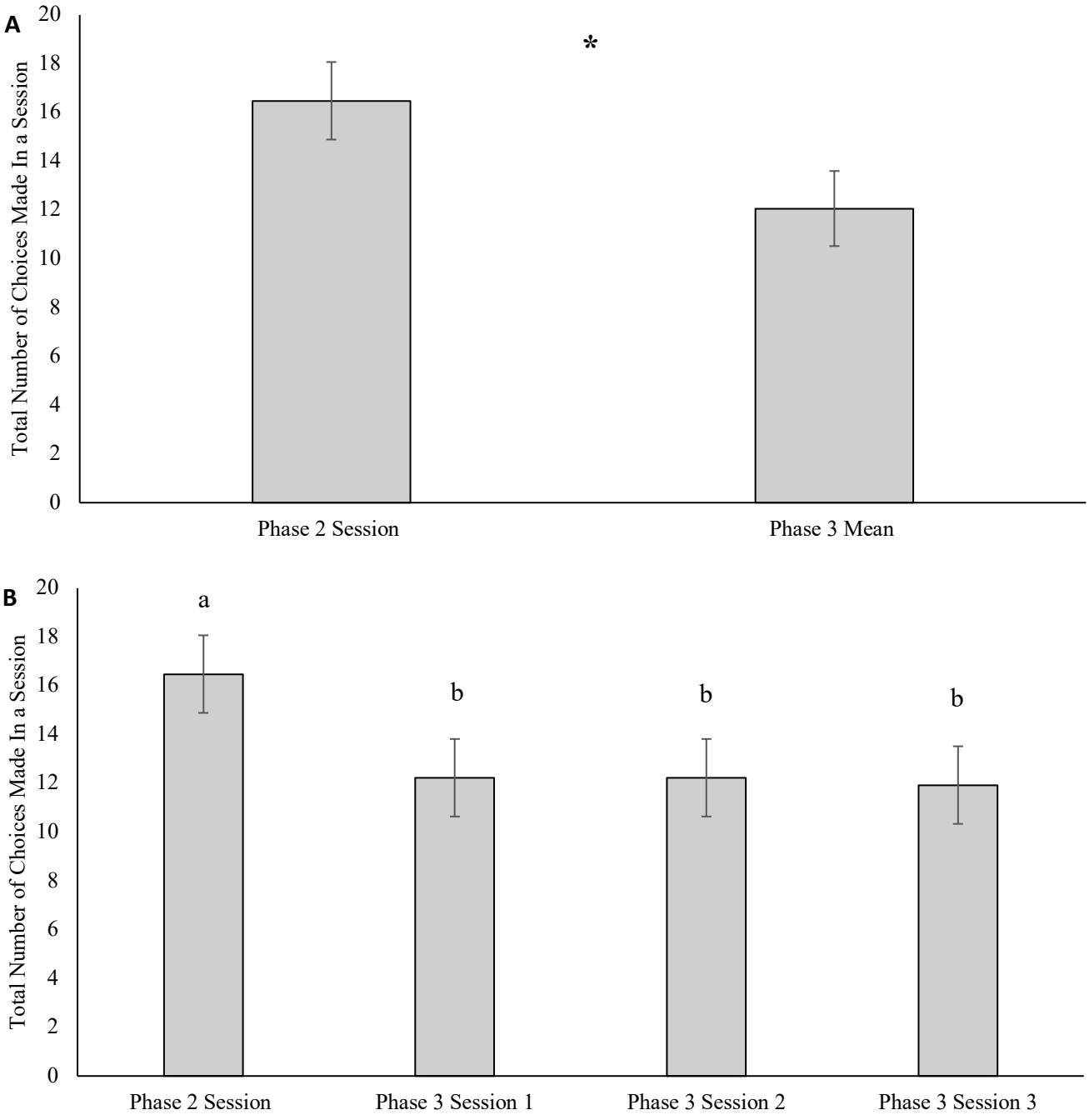

Figure 3. Total cigarette consumption across cigarettes. Panel A: Total cigarette consumption in Phase 2 and Phase 3. Asterisk indicates significant difference between Phases at $p < .001$. Error bars represent $\pm$1 SEM. Panel B: Total cigarette consumption across sessions. Data points not sharing a subscript are significantly different from one another ($p < .05$). Error bars represent $\pm$1 SEM.

4.3.2 Time Spent Earning and Consuming Reinforcers

Total time spent earning and consuming reinforcers within a session was compared across the Phases 2 and 3. There was no main effect of study phase ($F_{1,162}$ = 1.52, p = .22) (Figure 4), so session comparisons were not conducted.

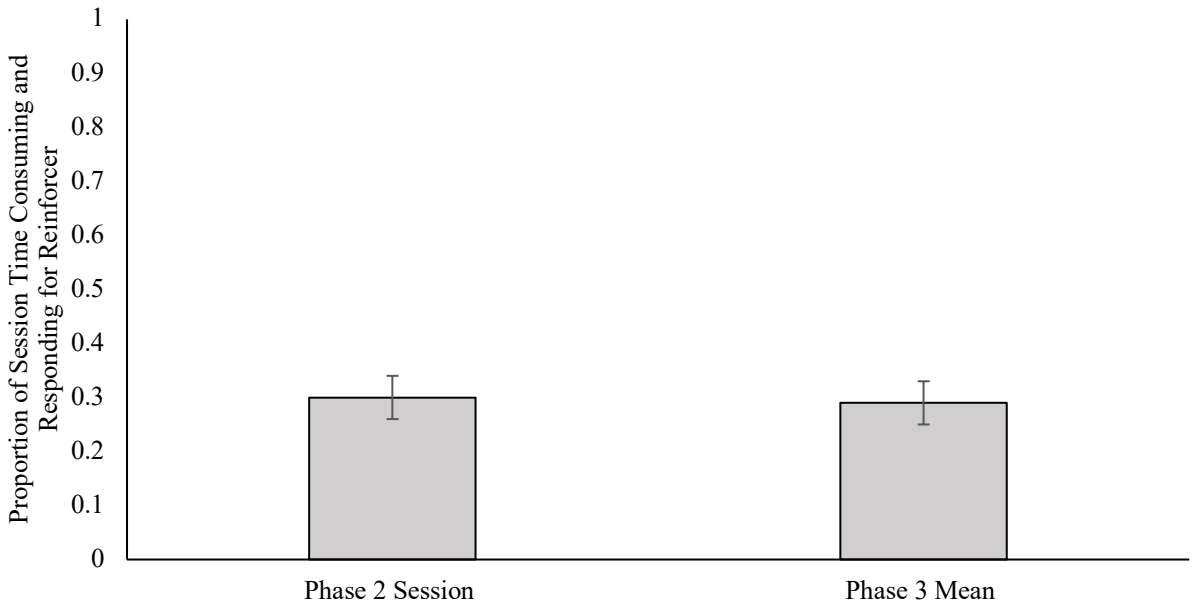

Figure 4. Proportion of total time within a session spent responding for and consuming the reinforcer in Phase 2 and Phase 3.

4.4 Aim 3 Results

When included as a covariate across analyses of phase, vulnerable population, sex, and menthol status were not significant (ps > .05). Thus, interactions with phase were not probed for these potential moderators.

Nicotine dependence was a significant covariate when included in ANOVAs examining maximum unit price (breakpoint) for the 15.8mg/g nicotine content cigarette in Phase 3, with those with greater dependence severity having greater breakpoints ($F_{2,147}$ = 4.41, p = .01). Thus, an interaction term for nicotine dependence and phase was added

to the analysis of proportion of cigarette preference for the 15.8mg/g cigarette, but was not significant ($F_{2,164} = 0.14$, $p = .87$).

Additionally, there was a significant effect of age when included as a covariate in ANOVAs examining effects of phase on total cigarette consumption, in the direction of greater consumption as age increased ($F_{1,130} = 6.65$, $p = .01$). Thus, the ANOVA was repeated including an interaction term for phase and age, but it was not significant ($F_{1,165} = 1.29$, $p = .26$).

5. DISCUSSION

As the FDA continues to consider a potential national policy setting a maximal nicotine content level in cigarettes, examining how current smokers might respond to constraints on the nicotine content of cigarettes is imperative. Previous work by our group and others demonstrate that how smokers respond to smoking is highly influenced by the nicotine content of the cigarette. That is, cigarettes with higher nicotine contents are reliably preferred over lower nicotine content cigarettes and produce greater positive subjective effects (Hatsukami, Heishman, et al., 2013, Higgins et al., 2017; Perkins, Karelitz, & Kunkle, 2018). An important caveat regarding this demonstrated reliable preference for higher over lower nicotine content cigarettes, however, is that preference appears to be malleable and can be shifted by increasing the response cost for the former (Higgins et al., 2017). The results of the present study extend that observation regarding the malleability of product preference by demonstrating that it can be accounted through the behavioral economic concept of unit price. When the unit price for the preferred product is increased to a level higher than the unit price of the previously non-preferred product, preference is shifted to the latter. Importantly, the present results also

demonstrate that when product preference is shifted to a very low nicotine content cigarette (0.4 mg/g in the present study) cigarette consumption decreases significantly (approximately one cigarette per 3-hour session in the present study). Regarding potential mechanisms underpinning reductions in consumption, the 0.4 mg/g nicotine content cigarette appears to have an insufficient magnitude of reinforcement to sustain levels of responding that were sustained by the 15.8 mg/g nicotine content cigarette, similar to what is observed in prior studies on extended exposure to the same cigarettes and doses (Donny et al., 2015; Hatsukami et al., 2018). We saw no evidence to suggest that the reduction in consumption was an artifact of constraints imposed by the experimental arrangement on the amount of time available to smoke at a desired level as there was plenty of time available for additional smoking in the Phase 2 and 3 arrangements. Additionally, it did not appear that the results on product preference or consumption were moderated by sociodemographic or smoking variables. These observations are discussed in further detail below.

We were able to confirm our hypothesis that manipulating constraints for the 15.8mg/g nicotine content cigarette shifts preference to the 0.4mg/g nicotine content cigarette suggesting that cigarette preference is malleable. Identifying that product preference between different nicotine content cigarettes is malleable raised the question of whether the mechanism underpinning such malleability could be identified. Doing so would potentially allow policy makers to develop interventions that might facilitate preference shifts to lower-risk products as part of a harm-reduction strategy. In the current study, we hypothesized that the behavioral economic concept of unit price may account for the observed preference shift in our data. As discussed above, prior research

investigating unit price demonstrates that as a rule consumption decreases as a function of increases in unit price and unit price can be manipulated by altering either the response cost of a reinforcer or the reinforcer magnitude (Bickel et al., 1990; Bickel et al., 1991; DeGrandpre et al., 1993). We were able to demonstrate that the preference shift observed in Phase 3 when the 15.8mg/g nicotine content cigarette was administered on a PR schedule of reinforcement was accounted for by the unit price derived per schedule point. On average, participants in the current study ceased responding for the 15.8mg/g nicotine content cigarette when the unit price to obtain it exceeded that of the concurrently available very low nicotine content cigarette. This is consistent with prior research using normal nicotine content cigarettes to examine cigarette smoking and unit price; in single schedule arrangements, nicotine consumption decreases as a function of unit price increases (Degrandpre et al., 1992) and in concurrent schedule arrangements preference was near exclusively allocated to the reinforcer with the lower unit price (Bickel and Madden, 1999; Madden, Bickel, & Jacobs, 2000). Additionally, prior research shows that increasing the unit price across multiple sessions of a normal nicotine content cigarette increases use of denicotinized cigarettes (similar in nicotine content to the 0.4mg/g nicotine content cigarette in the current study) (Johnson, Bickel, & Kirshenbaum, 2004). The current study's unique contribution to this literature is that we are able to demonstrate that shifts in product preference between different nicotine content cigarettes occur at the point at which unit price for the previously preferred product increases above the previously non-preferred product. To our knowledge, there are no prior studies in the literature detailing the role of unit price as the process underpinning this kind of change in product preference.

Importantly, we did not see evidence of limitations in the ability of unit price to account for preference at very low drug doses. Prior literature has demonstrated that at very low doses of drugs of abuse, including nicotine, responding may not conform to the unit price model (i.e. lowered responding as unit price increases) (Bickel et al., 1990; Bickel et al., 1991; DeGrandpre et al., 1993; Smith et al., 2016). However, the present results with human cigarette smokers suggests that unit price can account for cigarette choice even when one of the available cigarettes has sufficiently low nicotine content levels to be below that the hypothesized threshold for addiction (Benowitz & Henningfield, 1994). This is promising, as our data appears to demonstrate that one can accurately account for changes in cigarette preference using unit price as a tool even when cigarettes with a 0.4 mg/g nicotine content level are involved, which may be the level that cigarettes are capped at should a nicotine reduction policy be implemented as the literature indicates its more effective at lower addiction potential than other doses that have been examined (Donny et al., 2015; Higgins et al., 2017).

In regard to implementing a nicotine reduction policy, our findings suggest that very low nicotine content cigarettes would need to be made available at a lower unit price than normal nicotine content cigarettes if they are to garner more consumer demand. If not, we can readily predict that normal nicotine content cigarettes will dominate the market place similarly to how they dominated preference in Phase 2 of the current study.

While the FDA has not shared how they might implement a reduced nicotine content policy, their direction appears to be moving towards setting a maximal nicotine level across all commercial cigarettes that is determined to be minimally or non-addictive (Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, 2018). In a

regulatory landscape where higher nicotine content cigarettes are banned, smokers would either have to engage in a black-market purchase of the product or travel outside of the United States to obtain them. It can be assumed that having to do so would increase the unit price of these higher nicotine content products considerably allowing the legal lower nicotine content cigarettes to compete with them in the commercial marketplace. However, it is worth noting that such a scenario is conditional on meaningful enforcement of the policy banning higher nicotine content cigarettes.

If the FDA were to implement a nicotine reduction policy in which both minimally or non-addictive cigarettes and normal nicotine content cigarettes were legally available concurrently on the market, the unit price would need to be adjusted (by shifting cost) for each product to shift preference. As taxation on cigarettes is determined by state, this could prove ineffective if states do not universally shift prices to shift unit price of the two competing products.

Tobacco researchers and the FDA might want to consider future studies similar in nature to the current study, but utilizing alternative tobacco products. Cigarettes do not exist in isolation in the tobacco marketplace, so we may observe that setting a nicotine standard at very low levels may encourage smokers to begin using alternative combusted tobacco products, such as cigars, cigarillos, little cigars. For cigarette smokers, we can assume that there might be a slightly elevated unit price associated with these products; for example, cigarette smokers may not be as adept at obtaining nicotine from these alternative products, so reinforcement magnitude could be lowered. However, some of these products (e.g. cigarillos, little cigars) have many shared features with cigarettes and if any standard on nicotine content of cigarettes does not include those products, we

could very well observe them coming to serve as a more effective substitute for higher nicotine content cigarettes than very low nicotine content cigarettes. That would be an unfortunate unintended effect of a nicotine reduction policy as cigarillos and little cigars are just as toxic as conventional tobacco cigarettes (Pickworth, Rosenberry, O'Grady, & Koszowski, 2017). There is some indication the FDA appears to be moving toward a policy that would reduce the nicotine content level of all combusted tobacco products, or at least those that are used like cigarettes such as cigarillos and little cigars. Additionally, if certain tobacco products are identified as products that may reduce harm relative to cigarettes, such as appears to be the case with non-combusted tobacco products like electronic cigarettes (Nutt et al., 2014), the FDA may want to identify the unit price of these products with the intention of transitioning cigarette smokers from combusted products.

In addition to our findings regarding the malleability of product preference, we also observed that when preference shifted to the 0.4mg/g nicotine content cigarette, it was accompanied by a decrease in total cigarette consumption. This effect is consistent with results from at least two prior clinical trials examining smoking rates during extended exposure to reduced nicotine content cigarettes (Donny et al., 2015; Hatsukami et al., 2018). Both of these prior clinical trials on extended exposure (6 weeks in Donny et al., 2015; 20 weeks in Hatsukami et al., 2018) demonstrated decreases in total cigarettes smoked per day among participants assigned to the 0.4 mg/g nicotine content cigarette condition compared to cigarette conditions with nicotine content levels similar to those found in commercial cigarettes (15.8mg/g in Donny et al., 2015; 15.5 mg/g in Hatsukami et al., 2018).

One limitation of extended exposure studies, such as those described above, that does not apply to the present acute-exposure arrangement is that the majority of participants assigned to these very low nicotine content conditions supplement throughout the exposure period with non-study cigarettes in addition to smoking their assigned research cigarette. Biochemical markers of nicotine consumption, such as total nicotine equivalent and urine cotinine levels, have shown that the majority of study participants (60% and 76% of participants across two analyses) assigned to 0.4mg/g nicotine content cigarettes in extended exposure studies exhibit some level of non-compliance (Benowitz, Nardone, Hatsukami, & Donny, 2015; Nardone et al., 2016). These practices complicate quantification of real reductions in smoking rate from substitution of non-study for study cigarettes. Our findings provide a complement to these prior studies on extended exposure by demonstrating reductions in consumption when using the 0.4mg/g nicotine content cigarette in the absence of any potential confounding associated with use of non-study cigarettes. Participants in the present study decreased consumption from an average of approximately 32 puffs (16.48 mean total responses for smoking) across a three-hour session in Phase 2 to an average of approximately 24 puffs (12.23 mean total responses for smoking) across the Phase 3 sessions. This 8-puff decrease across the 3-hour session is only slightly under the typical ten puffs for one full cigarette (Hoffmann & Hoffmann, 1997; Zacny & Stitzer, 1988b). Evidence in the literature suggests that such decreases in cigarettes per day can facilitate cessation (Hughes & Carpenter, 2006) and similarly, Donny and colleagues (2015) found that in their study of extended exposure participants who were assigned to the 0.4mg/g

nicotine content cigarette were more likely to report quit attempts following completion of the study.

The current study does not provide direct evidence for why we observe a decrease in consumption when preference is shifted to the 0.4mg/g nicotine content cigarette. However, considering that 0.4mg/g of nicotine is below the hypothesized threshold of nicotine needed to sustain dependence, it seems likely that the reinforcing effects of nicotine at that level are not sufficient to sustain smoking at levels observed when cigarettes that have nicotine levels similar to what is found in commercial cigarettes, like the 15.8 mg/g dose cigarette, are not readily available (Benowitz & Henningfield, 1994). In the parent study, it was demonstrated that the 0.4 mg/g nicotine content cigarette produced significantly lower ratings of satisfaction, psychological reward, craving reduction, enjoyment of respiratory tract sensations, and significantly more aversion than the 15.8mg/g nicotine content cigarette as measured by the Modified Cigarette Evaluation Questionnaire, a well validated measure of subjective effects of smoking, which is consistent with the idea that the 0.4mg/g nicotine content cigarette produces relatively weak reinforcing and positive subjective effects (Cappelleri et al., 2007; Higgins et al., 2017). However, it is worth noting the 0.4mg/g nicotine content cigarette does not appear to be devoid of reinforcing effects. Although subjective effects are significantly lower with this product relative to normal nicotine content cigarettes, they are not zero. In the parent study, as measured by the subscales of the Modified Cigarette Evaluation Questionnaire, the mean rating (out of a maximum of 5 points) for the positive subjective effects following smoking the 0.4mg/g nicotine content cigarette was 3.2 for smoking satisfaction, 2.7 for psychological reward, 3.4 for craving reduction, and 2.9 for

enjoyment of respiratory tract sensations. Comparatively for the 15.8mg/g nicotine content cigarette, mean ratings were 4.6, 3.4, 4.6, and 4.1, respectively (Higgins et al., 2017). Additionally, in the current study, there is some selection of the 0.4mg/g nicotine content cigarette in the Phase 2 concurrent choice arrangement when response cost is equal (and thus unit price much lower for the 15.8mg/g nicotine content cigarette) suggesting there may be some level of reinforcement associated with them. This reinforcement may be due to conditioned effects, which would be expected to weaken over repeated use of the 0.4mg/g nicotine content cigarette.

A final discussion point is to note the lack of moderating effects of different socioeconomic and smoking characteristics in the current study. Although we did not enter the current study with a firm hypothesis regarding potential moderators, we wanted to examine a subset of potential moderators that might do so based on their ability to influence potential to successfully quit smoking and other aspects of using tobacco products. We found that although maximum unit price in Phase 3 increased as a function of nicotine dependence, there was no moderating effect of this variable on differences by phase in proportion of choices for the 15.8mg/g cigarette across study phases. This is similar to reports in Higgins et al., 2018, in which in the Cigarette Purchase Task there was an increase in smoking demand as dependence severity increased, but no interaction with the effects of nicotine dose changes. We also observed that while age appeared to positively influence total cigarette consumption, there again was no interaction of phase effects on total consumption. This lack of moderating effects is important, as it suggests that we can expect the functional relationships observed have relatively broad generality. Our findings are consistent with the findings of prior investigations by our group, which

suggest minimal moderating effects are observed in a variety of potential moderators, including study population (Higgins et al., 2017), cigarette menthol preference (Davis et al., 2019), presence of medical co-morbidities (Streck et al., 2018), and manuscripts in preparation examining potential moderation by sex (Streck et al., in preparation) and age (Davis et al., in preparation).

5.1 Limitations

There are a few limitations of the current study worth noting. First, this study was a secondary analysis of outcomes from a study examining the addiction potential of reduced nicotine content cigarettes in populations vulnerable to smoking. As such, results may not be generalizable to the general population of smokers. That said, it important to note again that the data reported in the current study and in studies with similar vulnerable groups (Tidey et al., 2013) follow patterns similar to those observed in studies of reduced nicotine content cigarettes in the general population of smokers (Donny et al., 2015; Hatsukami et al., 2018).

Second, being a secondary analysis the experimental arrangements were not specifically designed for the questions being addressed and. The PR schedule for the 15.8mg/g nicotine content cigarette, for example, moves from a unit price of 20.25 to 40.50 in a single step. As such, there is never a point where the unit price for the 0.4mg/g and15.8mg/g nicotine content cigarettes overlap directly (i.e., there is a never a point where the 15.8mg/g cigarette has a unit price of 25). Additionally, there are relatively large increases in unit price in the PR schedule (i.e. 20.25 to 40.50, 40.50 to 81.01). Future studies that include an overlapping unit price point and smaller steps in the PR

progression will be important to providing a more complex characterization of the influence of unit price on product preference.

Third, the current and prior studies on reduced nicotine content cigarettes (e.g., Donny et al., 2015; Hatsukami et al., 2018) have inclusion criteria designed to include daily, relatively dependent cigarette smokers who have limited use of other products. Exclusion criteria across studies is greater than 10 days of other tobacco product use, as well as non-daily cigarette use. This practice may be eliminating individuals who are more willing to substitute other tobacco products (e.g. cigars, cigarillos) for cigarettes than study participants and participants who may be considered minimally dependent. Future research should examine malleability of cigarette product preference in smokers who use multiple tobacco products as they represent an increasing proportion of tobacco product users (Kasza et al., 2017) and may have different response to reduction in the nicotine content of cigarettes than those who are exclusive cigarette users (Pacek, Wiley, & McClernon, 2019), as well as non-daily smokers. Some initial work has been done examining extended exposure in non-daily smokers with similar findings to those in the more typical smoking population (Shiffman, Kurland, Scholl, & Mao, 2018), but future research could examine if these so described very light smokers follow similar patterns regarding preference reversal and cigarette consumption.

5.2 General Conclusions

As cigarette smoking continues to be a leading cause of preventable death in the U.S., a nicotine reduction policy has the ability to markedly improve population health (Apelberg et al., 2018). The findings from the current study demonstrate a potential pathway for implementation of such a policy. First the current study suggests that the

behavioral economic concept of unit price should be utilized in contemplating potential intended and unintended consequences of a reduced nicotine content policy. Second, our data underscores the potential utility of considering unit price when contemplating nicotine reduction in cigarettes in tandem with other tobacco regulatory policies aimed towards harm reduction (e.g., what unit price differences might be needed to shift current smokers over to exclusive use of less harmful sources of nicotine). Third, data from the present study also demonstrate that similar to results from extended exposure studies, overall cigarette consumption decreases are discernible even during acute periods of exposure to very low nicotine content cigarettes. Notably, none of the aforementioned empirical observations appear to be moderated by sociodemographic or smoking characteristics suggesting broad generality. Lastly, results from the present and parent study are encouraging about the potential of a policy reducing the nicotine content of cigarettes to reach and benefit vulnerable populations who are most at risk for smoking, nicotine dependence, and experiencing the adverse health consequences of smoking.

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