CigVent Proj-003

Effects of Cigarette Filter Ventilation on Substitution in the Experimental Tobacco Marketplace in Tobacco Cigarette Smokers: Experiment 1

Study Protocol

7/13/2017

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Introduction

The Food and Drug Administration (FDA) was granted authority in 2009 to establish tobacco product standards if those standards are reasonably expected to benefit the public health. One product feature that could be changed is cigarette filter ventilation. A recent review examined the effects of cigarette filter ventilation and concluded that filter ventilation, by changing how a cigarette burns, yields more mutagens and carcinogens, and results in greater puff volume and possibly depth of inhalation, which has led to increases in peripheral lung adenocarcinomas (1). This, along with the ability to manipulate systemic levels of nicotine by altering smoking behavior, as well as misconceptions about the lower toxicity of filter ventilation, may have also contributed to the use, appeal, and abuse liability of ventilated cigarettes. The extent to which commercial cigarettes are ventilated vary substantially in the market by brand, ranging from 0 to 80%. However, smokers compensate for the lower nicotine yields associated with higher ventilation by varying their puffing behavior, number of cigarettes per day, and blocking some portion of the ventilation holes. This compensatory behavior exposes smokers to more tobacco smoke constituents than would be indicated by machine smoking tests. Regulatory action that reduces or eliminates cigarette ventilation would not only reduce exposure to smoke constituents by increasing nicotine yield per cigarette, but also change the smoker's experience, likely resulting in harsher taste that may be proportional to the ventilation in a given cigarette brand. The potentially large effect on taste and preference corresponding to cigarette ventilation could alter the appeal and abuse liability of these products and could inform regulatory actions. However, eliminating filter ventilation raises a variety of questions that constitute a gap in our knowledge and must be answered to assess the potential for adverse unintended consequences of removing filter ventilation. We will explore these questions within a behavioral economic framework.

Behavioral economic demand analyses can be used to understand the level of motivation to consume a product on either an individual or small group level, including cigarettes (2,3). This level of analysis allows for experimental manipulations to be made on variables of interest. By quantifying how consumption decreases as costs increase to obtain and consume a product, important indices of demand are obtained. These indices can be grouped into two main measures of consumption, demand intensity and demand elasticity, which are associated with use level and dependence severity (3,4,5,6). Demand intensity is the amount of the commodity consumed when available at very low cost (approaching free), and demand elasticity quantifies the degree to which the individual is willing to increase monetary or effort-based expenditures to maintain the same level of consumption as costs increase. Elasticity of demand has been shown to be a characteristic of the drug itself and independent of drug dose for many drugs including nicotine (2,7,8). While drug demand plotted as a function of unit price has been often shown to be a function of the total drug consumed, some of our prior research with cigarette demand calls this conclusion into question. A prior study we conducted (9)

compared conventional cigarettes to denicotinized cigarettes. We found that, if these denicotinized cigarettes were the only tobacco product available, the denicotinized cigarettes had comparable demand to nicotinized cigarettes. If both were available, however, participants preferred the nicotinized cigarettes. This suggests that cigarette demand is not strictly regulated by nicotine dose, and that there is substantial abuse liability associated with other aspects of cigarettes (e.g., sensory components) apart from any nicotine content. Relevant to this point and the current application, we conducted a pilot study, where conventional ventilated cigarette smokers purchased either their usual cigarettes (ventilated) or their usual cigarettes with the filter vents blocked. When each cigarette type was available alone in separate sessions, demand for both products was very similar. However, in a separate session in which both cigarette types were available concurrently at equivalent unit prices, ventilated cigarettes were clearly preferred at all prices. These findings suggest that to fully understand the abuse liability of cigarettes will require that they are studied in contexts where other products are available (e.g., substitution).

Substitution is defined as an increase in the consumption of a constant-priced product while the cost of a different commodity is increased. For example, we have shown that as the price of conventional cigarettes is increased and its consumption decreased, the consumption of nicotine gum increased even though its price remained constant (10). Substitution defines one end of a continuum of interactions between two commodities. At the other end of that continuum, commodities can also function as complements. Complementarity refers to the decreased consumption of a constant-priced product in response to an increase in the price of a different commodity. For example, the research team has previously shown that as the price of cigarettes increased, consumption of coffee decreased even though its price remained constant (11). Between these two extremes is independence, which occurs when changes in the price of one commodity have little or no effect on consumption of another commodity where price has remained unchanged. Substitution, complementarity, and independence are measured by cross-price elasticity of demand and are represented by values that are positive, negative, or near zero, respectively. Studies to date have almost exclusively examined only pairs of products and, in even fewer cases, three concurrently available commodities. For example, in one of our studies smokers had access to conventional cigarettes, denicotinized cigarettes, and nicotine gum13. When the price of conventional cigarettes increased, consumption of both denicotinized cigarettes and nicotine gum increased even though their prices were fixed. Thus, denicotinized cigarettes and nicotine gum functioned as substitutes for conventional cigarettes. Indeed, by concurrently using both products, the smoker could reproduce both the central and sensory effects of standard cigarettes by consuming the denicotinized cigarette (i.e., sensory effects) and nicotine gum (i.e., central effects). Importantly, denicotinized cigarettes functioned as a better substitute than gum (the use of denicotinized cigarettes increased the most). This effect could not have been predicted from the individual demand curves with these commodities. Only when they were measured together did these complex interactions emerge. Lastly, in this experiment consumption of conventional cigarettes was greatest when it was the

only available product, and was least when denicotinized cigarettes or both alternatives were available. This finding demonstrates that cigarette demand was altered by the presence of alternative products and that under some conditions multiple products will be used concurrently. However, this and similar studies are constrained by arbitrary circumstances of the laboratory, such as required nicotine deprivation, constrained consumption of a product (e.g., 1 cigarette puff per self-administration), long and numerous sessions (e.g., one, 3-hour session for each price examined). As such, these methods cannot and do not come close to replicating the ever more complex tobacco marketplace and underscore the gap in the understanding of how to examine these relationships among a large number of products that approximate the real world.

To address this methodological gap and to inform how various products may interact, we have developed and tested a novel method called the Experimental Tobacco Marketplace (ETM). The ETM is a systematic extension of similar marketplace methods used with other consumer products (e.g., food marketplaces used in obesity and other nutrition-related research). In experimental marketplaces, multiple products are available and the experimenter controls the prices for each. These marketplaces can be either physical or virtual stores (similar to online retailers) and permit the examination of price effects and an assessment of degree of substitution or complementarity in consumer behavior under conditions that approximate naturalistic settings. One such study (12) examined foods purchased by mothers when less healthy foods were taxed (increased price) and healthier foods were subsidized (decreased price). These authors found that taxing less healthy food reduced caloric intake and proportion of calories from fat, while increasing the amount of protein consumed. Alternatively, subsidizing healthier foods did not change the macronutrient profile of foods purchased while increasing energy intake. In a review of this emerging area of nutritional research, Epstein and colleagues noted that “price changes modify purchases of targeted foods, but research on the overall nutritional quality of purchases is mixed because of substitution effects” (p. 789; (13)). This statement suggests the importance of exploring regulatory options in complex marketplaces. The ETM developed by the investigative team is similar to an online store, that displays pictures, information, and prices for several tobacco/nicotine products. In a recent study of ours (14), smokers were endowed with an amount of money comparable to their weekly tobacco purchases. They then made tobacco product purchasing decisions while the price of conventional cigarettes was varied and the price of 5 other tobacco products remained constant. Purchasing decisions from one, randomly selected cigarette price was actualized and smokers were provided the products purchased and any unspent account balance. Smokers returned one week later to report tobacco/nicotine use and return unused products for a refund. Cigarette consumption decreased as a function of price. As the price of cigarettes increased, consumption of snus, electronic cigarettes, and nicotine lozenges showed the greatest substitution. Importantly, this approach moves beyond the constraints of previous laboratory studies by permitting the study of tobacco/nicotine preference and consumption under conditions that typically occur in most smokers’ lives, including not being nicotine

deprived, consuming the products in their natural environment, selecting the products they wish from a large number of products, and consuming the products while engaging in normal daily activities.

In this experiment, we will ascertain the impact of cigarette filter ventilation on nicotine product (including cigarettes) consumption across a range of prices to model the effect of ventilation. We will assess these effects following initial exposure to commercially available cigarettes and alternative nicotine products (e.g., e-cigarettes, snus, gum), as well as these effects over time. We will also assess these measures in each of two smoker subtypes: those who normally smoke ventilated and unventilated cigarettes (defined here as ≥20% and <10% filter ventilation, respectively). Prior research indicates that experimental exposure to "low-nicotine yield" cigarettes (including those with increased filter ventilation) produces gradual, compensatory changes in smoking topography (e.g., longer puffs or blocking of ventilation holes) that: 1) are not evident upon initial cigarette exposure, and 2) effectively increase nicotine yield to levels similar to participants' usual brand (15). The majority of this evidence suggests that asymptotic changes in smoking topography occur in two months or fewer (15-17). For this reason, after initial exposure to commercially available cigarettes, participants will receive extended exposure to these cigarettes for two months and will be assessed intermittently during this period in the ETM. Thus, in this experiment, we will examine whether the effects of ventilation differ by both smoker subtype and time.

Participants

Up to 200 smokers (plus an additional 20 to account for dropout) from the Roanoke VA area will participate in this study. To participate, smokers must:

1) provide written informed consent,

2) be 18-65 years of age,

3) be a current cigarette smoker

4) have a breath carbon monoxide (CO) level that confirms cigarette smoking

5) have stable self-reported mental and physical health,

6) and have no immediate plans to stop smoking

7) be willing to smoke commerically available cigarettes that are different from their typical brand

8) be willing to sample alternative nicotine products such as e-cigarettes

We will recruit two groups of cigarette smokers: participants whose usual brand of cigarettes have approximately 0-10% ventilation and participants whose usual brand of cigarettes have approximately 20% or greater ventilation.

Individuals who are pregnant or lactating or have plans to move out of the area during the course of the experiment will be excluded from participation. Use of other tobacco/nicotine products will not be exclusionary.

Recruitment

Participants will be recruited using a separate IRB protocol to screen cigarette smokers into a variety of smoking studies in our lab (see IRB #17-870). If participants have given prior permission (as explained in Q3.2) they will be contacted via telephone and screened using the same process mentioned above (IRB #17-870). Participants may also be recruited through flyers and ads, which which will direct potential participants to either call our lab to screen over the phone or to complete our online prescreener. Participants may also prescreen in person. These participants will be prescreening for Protocol IRB#17-870.

To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers may be addressed by providing transportation or parking costs for participants, and scheduling barriers will be minimized by offering a flexible study visit schedule. Compensation may be provided for travel costs and time. We have a history of successful recruitment of cigarette smokers into research programs. All participants will enroll on a voluntary basis

Consenting Process

Potential participants will be provided with the written consent form prior to visiting VTCRI, the Virginia Tech Corporate Research Center (VTCRC) (e.g., by email), or VT office space in Arlinginton, if they wish. They will also be given additional time in a quiet room at VTCRI or VTCRC to read the form. VTCRI research staff will review each element of the written consent form with the potential participant. Participants may have the opportunity to watch a saved video of the written consent form, read and recorded by the research staff. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. They will be encouraged to speak with whomever they wish before making this decision. Staff will reiterate that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence. If the potential participant chooses to continue with the consent process, he or she will be asked to complete a brief quiz regarding the consent form. The potential participant and person obtaining consent will review the quiz and address additional questions. The potential participant and person obtaining consent will sign the consent form after the potential participant verbally states that s/he understands the conditions of the study, has no more questions, and chooses to participate.

Procedures

Cigarettes

Commercially available ventilated filter and unventilated cigarettes will be used in this experiment. Product characteristics including blend of tobacco, additives, nicotine and tar content levels will be similar across these two products but will only differ in the degree of ventilation. Ventilated cigarettes will feature ventilation values in the 20-30% range, whereas unventilated cigarettes will feature approximately 0-5% ventilation.

Procedure

The duration of the experiment will be approximately 3 months. Participants will begin with an initial one week (approximately) exposure period to both unventilated and ventilated cigarettes as well as alternative nicotine products (e-cigarettes, snus, etc.) that will be made available throughout the experiment. Participants will be given the opportunity to sample both types of cigarettes and alternative nicotine products. In the following sessions, participants will alternate between Electronic Tobacco Marketplace (ETM) sessions and free exposure periods to their assigned cigarette, with weekly assessments throughout to track changes in smoking behavior and cigarette valuation. In total, participants will complete 10 experimental sessions (see Appendix B for experimental timeline figure). For the sake of clarity, session types are separated below. The consent and initial sessions may take place in the same or separate sessions.

At the beginning of the experiment, participants will be assigned to one of two groups: ventilated or unventilated. Group assignment will determine what cigarettes will be given to the participant after sessions in which they do not actually purchase their cigarettes of choice. Additionally, participants that typically smoke menthol cigarettes will be given a menthol version of their assigned cigarette. Cigarettes will be similar in design and will be labeled as Typa A or Type B.

At the initial session and throughout the study, urine samples may be collected and stored for testing (for tobacco use and pregnancy) and breath samples for carbon monoxide and alcohol. Self-report may be used in place of urine analyses on a case-by-case bases. Urine sample analyses for tobacco use may only take place at the VTCRI site.

Initial Assessment Session and Sampling (Session 1).

First, participants will complete the consenting process. The first session will be an assessment session to collect information from participants on patterns and degree of tobacco and other substance use, perceptions of all cigarette types available in the ETM, as well as the

results of behavioral and cognitive tasks that we think may inform or complement the results from the main study (see Appendix A for a complete list and descriptions).

Participants will also complete the initial sampling period following the initial sampling session. The goal of this period is to familiarize the participants with their randomly assigned cigarette as well as alternative nicotine products. After their assessment session, participants will be given a 7-day supply of ventilated and unventilated (3.5 days of venitlated and 3.5 days of unventialted) cigarettes and asked to use these cigarettes. The actual number of cigarettes delivered to each participant will be determined by multiplying their reported cigarettes smoked per day by 7. Therefore, the average minimum number of cigarettes that will be delivered is approximately 70 (10 cigarettes per day minimum to qualify to participate). They will be also be given a sample of the alternative nicotine products that will be made available during the Real-ETM sessions. Participants will be asked to report their favorite flavor of each product to sample. If the participant is naïve to the alternative nicotine product, they will be asked to estimate which product flavor they would prefer. To verify usage during this and all subsequent usage period (see below), participants will be asked to return spent cigarette filters in resealable bags we provide. However, while participants will be asked to smoke the cigarettes they are given and to not use any other cigarettes, they will only be asked to try the alternative nicotine products during the sampling period, they do not have to finish them. A subset of these spent filters will be randomly chosen and analyzed to permit correlation of mouth-level exposure to smoke constituents with differences in ETM purchasing behavior between ventilated and unventilated cigarettes. During this sampling period, participants will go about their daily lives, allowing them to sample these cigarettes in the social environment in which they typically operate. This “real-world” sampling period will serve to increase the generalizability of the results obtained in the ETM sessions. This duration of exposure was chosen to give participants time to begin to familiarize themselves with their assigned cigarettes. This will enable them to make informed purchasing decisions during the upcoming sessions.

Real Experimental Tobacco Marketplace Sessions (Sessions 2,6, and 10).

Following the initial sampling period, participants will complete a purchasing session in our realistic tobacco product marketplace. Participants will be seated in front of a computer to access an online marketplace with an interface similar to many online merchants. This will allow participants to browse through the products and add as many as they desire to the virtual shopping cart. Each product will have the price clearly displayed along with an image. Each ETM session will contain five pricing scenarios, in which we:

i. manipulate the price of participants’ assigned cigarettes to assess demand in a context with no other products available;

ii. manipulate the price of participants’ non-assigned cigarettes to assess demand in a context with no other products available;

iii. manipulate the price of both assigned and non-assigned cigarettes in unison to assess simple preference between the two;

iv. manipulate the price of participants' assigned cigarettes while the price of non-assigned cigarettes remains constant to assess the degree to which assigned cigarettes substitute for non-assigned cigarettes;

a. In this task, alternative nicotine products (e.g., e-cigarettes, chew, etc.) may also be available for purchase at a constant price.

v. manipulate the price of participants' non-assigned cigarette while the price of assigned cigarettes remains constant to assess the degree to which non-assigned cigarettes substitute for assigned cigarettes.

a. In this task, alternative nicotine products (e.g., e-cigarettes, chew, etc.) may also be available for purchase at a constant price.

In each of these scenarios, the price-manipulated cigarettes will be available across a range of prices (e.g., $0.12, $0.25, $0.50, $1.00, $2.00, and $4.00). Price-constant cigarettes will be set to the median cigarette price in the community. Participants will use an experimentally provided income (proportional to their real-world tobacco consumption) to purchase from the ETM. At each price, participants will be asked to make seven days of tobacco-product purchases from the ETM. After all 5 scenarios are complete for their assigned cigarette, participants will receive the products they purchased from one randomly selected price. Participants will be well informed of these procedures prior to purchasing. For those seven days after marketplace sessions, participants will be asked to only use those products they have purchased from the tobacco marketplace, and to not purchase any outside tobacco products, to not sell or give away any of their purchases, and to not ask anybody else to purchase products for them. We will strongly encourage participants to follow these procedures, and to report any deviations from these procedures, which we will incorporate into our statistical analyses. If the participant does not spend their entire income, they will be allowed to keep the remainder. In this way, participants will be spending real money and incurring a financial cost for their purchases, leading to more realistic product selections. Following the seven days of using cigarettes obtained from the ETM, participants will again visit the lab to return any unused products and report the use of experimenter provided and non-experimenter provided tobacco products.

Extended Cigarette Exposure and Experimental Tobacco Marketplace Testing (Sessions 3, 4, 5, 7, 8, and 9).

Following the first session in the ETM and its associated period of tobacco product use, participants will begin periods of freely provided exposure to their assigned cigarette (ventilated or unventilated), alternating with two additional sessions in the ETM at regular intervals. The purpose of this additional exposure between discrete ETM assessments is so that we may examine the effects of sustained exposure to participants' assigned cigarettes at

regular intervals. During the extended-exposure periods, participants will visit the lab every 7 days. At each of these sessions during extended-exposure periods, they will return any unused cigarettes, report the use of experimenter provided and non-experimenter provided tobacco products, receive cigarettes for the upcoming 7 days, and complete many of the assessments they completed at their initial assessment session.

Following sessions 5 and 9 (the sessions immediately before the Real ETM sessions) participants will be given 6 days of their assigned cigarettes and 1 day of the unassigned cigarettes in order to expose the participant to the unassigned cigarettes before the Real ETM session.

An abbreviated set of assessments will be collected on a weekly basis throughout the experiment (Appendix A) in addition to any additional scheduled session (e.g., Real ETM). These assessments will focus on measuring tobacco product use and measures of dependence and withdrawal, including a Timeline Follow-Back for the period since the last session, as well as product perceptions. We will also include a purely hypothetical version of the ETM (on non-real ETM sessions), in which participants do not receive products purchased to use outside the laboratory. Because these hypothetical ETM assessments can be repeated with greater frequency and without interrupting periods of continuous exposure to assigned cigarettes, data from hypothetical assessments will be used to inform determinations of the effects of time on valuation of ventilated and unventilated cigarettes in more detail than primary ETM assessments.

Risks and Benefits

One risk of participation is embarrassment that may come from answering sensitive questions related to medical, psychiatric, and/or drug use history. Loss of confidentiality is another risk of participation. Additionally, because the present experiment allows and sometimes involves participants self-administering cigarettes, participants might experience adverse effects associated with the use of nicotine products (e.g., nausea, vomiting, dizziness, diarrhea, weakness, and rapid heartbeat) or withdrawal from nicotine (e.g., anxiety, irritability, difficulty concentrating). These risks of effects of nicotine and withdrawal from nicotine may be more likely during periods in which participants have been asked to abstain from smoking cigarettes or when assigned to smoke cigarettes that are different from the participant's typical type. Some participants may also experience a minor increase in throat or sinus irritation.

Pregnant women will be excluded from study participation to remove the risk that tobacco and nicotine products can have on the developing fetus.

Participants will be screened, using medical history and structured interviews, for a history of medical contraindications (e.g., pregnancy, recent myocardial infarction), and current unstable medical illnesses. The study will be conducted on the campus of VTCRI, VTCRC, or VT office space in Arlington. Participants will be free to withdraw from the study at any time. In addition, if participants develop medical problems or experience adverse events during the

course of the study, assessments to determine whether participants should continue in the study and/or continue to use study products will be conducted and necessary referrals will be provided. Participants will also be told that they can stop using the study products at any time.

Using only ID numbers and keeping all data in secure locations and/or in locked offices accessible only to trained study team members will protect confidentiality. Computer databases will have coded identifiers. These screening, monitoring, and confidentiality procedures have been in effect for more than 10 years and for more than 2,000 subjects across the various protocols employed by our group across various institutions.

Participants will not directly benefit from participating in the current study. The current study, however, may help identify effective methods of assessing policies related to alternative tobacco products. Better understanding these processes could result in more informed policy decisions that aid in reducing the health and economic harm associated with tobacco products.

Data Protection

All data and participant binders will be stored in a safe place to protect confidential participant information. Safe places will include locked filing cabinets or locked rooms accessible only to study personnel. The full names of participants will not be listed on the outside of binders to protect confidentiality of study participants.

Electronic data will be saved in secure, limited access shared drives on password-protected computers accessible only to the research team.

Participant Compensation

- $40 for completion of the initial Consent and Assessment Session
- $40 for each subsequent session
- $100 bonus at the end of the study (Session 10) for successfully returning spent cigarette butts on 7 out of 9 sessions or more.

In addition, participants will receive money during the Real ETM purchase session to purchase tobacco/nicotine products (based on the participant's typical weekly expenses). The amount each participant receives will be proportional to his/her real-world nicotine product expenditure (calculated as the frequency of use of each product x market price of that product x 7 days).

Combined, the subjects could earn up to $500 by completing all aspects of the experiment. Account balances provided as part of the study to purchase study tobacco products will not be advertised as or considered compensation.

To allow for payments that are both convenient and rapidly available, we may pay participants with reloadable cards through Greenphire ClinCard (www.greenphire.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At the beginning of the study, the participant will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to the account for that participant. Funds are immediately available when added and participants can check their balance as desired. This system will allow frequent, immediately available payments. Payments may also be made via check, however, remote debit card payments will be used most often.