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Effect of Flavors and Modified Risk Messages on E-cigarette Abuse Liability

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Abstract

Objectives—To measure e-cigarettes' abuse liability compared to conventional tobacco cigarettes under flavor and message conditions amenable to regulation.

Methods—Two studies used 2×2 within-subjects designs with factors of e-cigarette flavor (Study 1: tobacco vs. menthol; Study 2: cherry vs. unflavored) and message (Study 1: reduced harm vs. no message; Study 2: reduced exposure to carcinogens vs. no message) with cigarette smokers (N(total) = 36). Linear mixed effects models assessed abuse liability for tobacco products. Outcomes included the price after which consumption is zero (the maximum amount participants would pay for a tobacco product) from the multiple choice procedure (MCP) and cigarette purchase task (CPT) and demand elasticity (price sensitivity) from the CPT.

Results—In the MCP, the price where consumption reached zero was significantly lower in all e-cigarette conditions except tobacco flavor (message or no message) compared to cigarettes ($p < .05$ each). Demand elasticity was significantly higher for menthol/no message and unflavored/reduced exposure message conditions relative to cigarettes ($p < .05$ each).

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Human Subjects Statement

Both studies were approved by Virginia Commonwealth University's Institutional Review Board.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Conclusions—Flavors and modified risk messages included with e-cigarettes may affect e-cigarette abuse liability among smokers, suggesting regulatory pathways to influence demand for conventional and alternative tobacco products.

Keywords

e-cigarette; abuse liability; flavor; risk messages

INTRODUCTION

Little is known about the effects of flavor availability and product messaging of electronic cigarettes (e-cigarettes; electronic nicotine delivery devices) compared to combustible tobacco cigarettes.¹ In May 2016, the United States Food and Drug Administration (FDA) Center for Tobacco Products deemed e-cigarettes to be under their regulatory authority.² With this rule, the FDA banned use of modified risk message descriptors (“low,” “light,” “mild”) without a Modified Risk Tobacco Product (MRTP) designation and required warning labels but has not prohibited characterizing flavors in e-cigarettes. Evidence is needed to understand how future modified risk messages (ie, as part of MRTP designation³) and flavor availability affect e-cigarette abuse liability, particularly among current cigarette smokers. Abuse liability—the degree to which a psychoactive drug or formulation would be used for nonmedical purposes and lead to physical/psychological dependence⁴—is an important public health and policy outcome predicting likelihood of continued tobacco product use.⁵

To date, experimental work has assessed behavioral economic indices of e-cigarette abuse liability broadly. Behavioral economic choice procedures are appropriate for investigating individuals’ preferences for different tobacco products, for example by assessing how various delivery methods (eg, cigarette, nasal spray, gum) affect nicotine’s abuse liability.⁶ Such procedures can compare e-cigarette products to predict relative abuse liability, preference, and demand for different products under potential regulatory conditions. Two behavioral economic measures assessing abuse liability include the multiple choice procedure (MCP) and the cigarette purchase task (CPT). While both assess demand for a product at various prices, they differ in several ways, including whether or not the choices made during the procedure are reinforced, creating potential tradeoffs for investigators. However, no extant literature compares abuse liability across the MCP and CPT, despite suggestions to do so.⁷

The first published examination of e-cigarette abuse liability compared cigarette smokers’ choices between own-brand cigarette puffs and money, e-cigarette puffs and money, and e-cigarette puffs and own-brand cigarette puffs using the MCP, which reinforces choices made during the task.⁸ Results indicated that current cigarette smokers were willing to forego more money for their own-brand cigarette puffs than for e-cigarette puffs and valued 10 e-cigarette puffs at 3 own-brand cigarette puffs, suggesting lower abuse liability for e-cigarettes than own-brand cigarettes.⁸ More recently, this design was partially replicated among cigarette smokers; results were consistent with participants valuing own-brand cigarettes higher than e-cigarettes.⁹ In the CPT, smokers were asked how many cigarettes

they would smoke at a variety of incrementally increasing prices.^{5,7,10,11} The CPT produces demand elasticity and other indices measuring the relative value of the product, where higher relative value indicates greater abuse liability. For example, evidence using the CPT suggested that more nicotine-dependent smokers were less elastic and less likely to reduce their demand when cigarette price increased.⁷

E-cigarettes use liquid—generally containing nicotine, flavorings, propylene glycol and glycerin—which is heated into an aerosol and inhaled.¹² Part of their appeal is the variety of flavors in this liquid. The literature reports up to 7764 different flavors,¹³ and users cite flavor availability as a main factor influencing continued e-cigarette use and intention to quit cigarettes.^{14,15} Menthol flavoring may increase e-cigarettes' appeal, particularly at high nicotine concentrations.¹⁶ Young adult cigarette smokers respond more to e-cigarette flavor availability than do older smokers, suggesting a role for flavors in attracting youth.¹⁷ However, otherwise, there is a dearth of experimental research addressing how e-cigarette flavor affects e-cigarette use or abuse liability.

Like flavors, messaging may play a role in tobacco product choice. The FDA's MRTP draft guidance indicates that the industry can apply for either a risk modification or exposure modification order to include messages such as "reduced harm relative to cigarettes" or "reduced exposure to carcinogens relative to cigarettes" on products.³ Manufacturers of MRTPs applying for a risk modification order must demonstrate their product is significantly less harmful, presents lower risk of tobacco-related disease compared to cigarettes, and confers benefit to public health, including to tobacco users and non-users. An exposure modification order permits the sale of a modified risk tobacco product that reduces or eliminates exposure to a substance and for which a population-level decrease in tobacco product-related illness and deaths is expected.³ The FDA regulates the use of these descriptors because they suggest safety.¹⁸ While e-cigarette advertisements emphasizing health-related differences (eg, "healthier," "helps to quit smoking") between e-cigarettes and cigarettes produced the most desire in trying e-cigarettes among cigarette smokers,¹⁹ other research reported that advertisements have minimal effect on demand elasticity, or how demand responds to changes in price.²⁰ Although e-cigarette messaging may alter intention toward and use of e-cigarettes, effects on abuse liability are unclear.

This paper presents evidence on the abuse liability of e-cigarettes and cigarettes from 2 pilot studies that varied in e-cigarette flavor and modified risk message. To our knowledge, only one study has used a behavioral economics approach (willingness to pay) to examine both e-cigarette flavors and messages.²¹ We expand on that study by using 2 different behavioral economic methodologies, the MCP and CPT, to allow for a robust understanding of e-cigarette abuse liability related to flavors and messages in a sample of current cigarette smokers. We hypothesize that e-cigarettes will have lower abuse liability than cigarettes, but that modified risk messages and flavors will increase abuse liability of e-cigarettes relative to no messages and no flavors.

METHODS

Sample and Recruitment

From February 2015 to July 2016, current cigarette smokers naïve to e-cigarettes were recruited in the United States through online advertisements, flyers, and word of mouth for one of 2 pilot studies. Individuals completed an online or phone screening questionnaire determining initial eligibility, followed by an in-person screening to confirm eligibility and provide informed consent. Eligible individuals were scheduled for laboratory visits. Inclusion criteria included being 18–55 years old, smoking 5 cigarettes daily for 1 year, having a strong preference for either menthol or non-menthol cigarettes (ie, smoke one type 80% of the time), and self-identifying as African American or White. Exclusion criteria included regular e-cigarette use (ie, weekly or more often for 1 month), desire to quit smoking in the next month, chronic medical or psychiatric conditions, current pregnancy or breastfeeding, current illicit drug use (other than cannabis), and having used cannabis or alcohol 20 of the past 30 days. Participants were only eligible for 1 of the 2 studies.

A total of $N = 1169$ participants were prescreened, 169 were determined eligible, 88 were screened in-person and 62 were enrolled. Of the 62 enrolled, 44 completed Study 1 or 2. Our analytic sample consisted of 36 participants with complete data following a procedural change in the tasks, of whom 17 participated in Study 1 and 19 in Study 2. Across both studies, 27 (75.0%; 64.7% in Study 1 and 84.2% in Study 2) were male, 24 (66.7%; 58.8% in Study 1 and 73.7% in Study 2) were African American, and 28 (77.8%; 82.4% in Study 1 and 73.7% in Study 2) preferred menthol. On average, participants smoked 15.0 cigarettes per day (standard deviation [SD]=6.4; Study 1 mean 14.8 and Study 2 mean 15.3 cigarettes per day) and were 37.8 years old (SD =11.4 years; Study 1 and 2 means each 37.8 years). At screening, participants presented with an average expired air carbon monoxide (CO) of 16.1 parts per million (ppm; SD =10.4). No significant differences were observed between studies on these demographic factors, $p>0.05$.

Procedure

Each experiment included a baseline session followed by 4 additional sessions using a 2×2 within-subjects factorial design with factors of e-cigarette flavor (Study 1: tobacco vs. menthol flavor; Study 2: cherry vs. no flavor) and accompanying message (Study 1: reduced harm vs. no message; Study 2: reduced exposure to carcinogens vs. no message). Participants attended 5 sessions separated by at least 48 hours, each of which was preceded by 12 hours of nicotine/tobacco abstinence, reinforced via researcher contact 1 day prior and confirmed with expired air CO levels upon arrival to the lab (<10 ppm). This criterion has been used to verify 12-hour abstinence among cigarette smokers who smoked 10 cigarettes per day.²² While in the current studies participants had to report smoking 5 cigarettes per day, 80.6% smoked 10 cigarettes per day, and average expired air CO observed prior to study sessions was 5.6 ppm (SD =2.7). This CO level is more consistent with criteria used for 24-hour smoking abstinence (<5 ppm).²² Thus, the 12-hour nicotine/tobacco abstinence manipulation was successful.

During the 4-hour baseline own-brand cigarette session, participants completed both the MCP and CPT for their own-brand cigarette as a baseline measure of abuse liability. Following own-brand cigarette assessment, participants sampled the 2 e-cigarette flavors consistent with their study design (approximately 20 puffs of each flavor; sampling order was counterbalanced across participants). The subsequent 4 3-hour sessions assessed abuse liability for each of the 4 experimental conditions; condition order was determined with a Latin square. In each session, the CPT was completed first, followed by 5 consecutive trials of the MCP. Given that MCP choices were reinforced, the CPT was completed first so that participants would be nicotine deprived in the CPT and at least the first MCP. Subjective questionnaires assessing perceptions of tobacco products presented were administered at the conclusion of each session. These items are not included in the current analysis.

E-cigarette device and flavors—The e-cigarette device used in all e-cigarette conditions was an eGo 3.3 V, 1000 mAh battery with a 1.5-Ohm, dual-coil, 510-style cartomizer (SmokTek, Shenzhen, China) loaded with 1 mL of e-cigarette liquid containing 36 mg/mL nicotine (70% propylene glycol/30% vegetable glycerin (AVAIL Vapor LLC, Richmond, Virginia)). This specific device, cartomizer, and e-cigarette liquid nicotine concentration were selected based on previous work performed among cigarette smokers that characterized the pharmacokinetic profile of this combination of e-cigarette device and liquid characteristics.²³ This nicotine concentration, in the e-cigarettes used here after consuming 10 puffs, approximates the plasma nicotine concentration after smoking an own-brand cigarette in current smokers naïve to e-cigarettes (average “boost” of 12.5 ng/mL²³). The e-cigarette flavor conditions assigned to participants included tobacco or menthol in Study 1 and cherry and no flavor in Study 2. Menthol was chosen because it is the only “characterizing” cigarette flavor still available in the US. Cherry was chosen based on e-cigarette market research suggesting among fruit flavors purchased from the top 3 e-cigarette brands, cherry is most popular.²⁴ The unflavored condition was chosen to test how any flavor vs. no flavor impacts abuse liability. The nicotine concentration of all e-cigarette liquid, 36 mg/mL, was verified independently prior to use.

Message conditions—The FDA’s Modified Risk Tobacco Products draft guidance indicates that the industry can apply for either a risk modification or exposure modification order,³ which directly applies to the messages evaluated here. In message conditions, a card was presented showing either “No message” or “Reduced harm relative to cigarettes” in Study 1, or “No message” or “Reduced exposure to carcinogens relative to cigarettes” in Study 2, following FDA’s definition of MRTP marketing as that which communicates (in brief) lower harm or lower exposure to, or the absence of, unhealthy substances.²⁵ Messaging conditions were reinforced in the instructions to the tasks as well as in the tasks themselves (see Figure 1 for an example). Study staff introduced the day’s condition and ensured participants were aware of the condition by holding up the message card and reading it aloud.

Multiple Choice Procedure (MCP)—The MCP measures abuse liability by asking participants to make choices between a dose of a drug—here, 10 puffs of an e-cigarette or their own brand of cigarettes—and various amounts of money (Figure 1).^{5,26}

Participants were given the following instructions:

For each choice below, please circle whether you prefer 10 puffs of the e-cigarette being offered to you or to receive money. After you make your decision for each choice below, one choice will be drawn at random and you will either receive money or be given time to take 10 puffs of the e-cigarette.

The monetary amounts (prices) offered were \$0.01, \$0.02, \$0.04, \$0.08, \$0.16, \$0.32, \$0.64, \$1.28, \$2.56, \$3.84, \$5.12, \$6.40, \$7.68, \$8.96, and \$10.24. Within each of the 5 conditions, participants completed 5 MCP trials. After each trial, one randomly chosen decision was reinforced. Participants drew a number 1–15 from an opaque bag; the number corresponded to one of the decisions made between the tobacco product and various amounts of money. Participants were given a 10-minute period to receive money or consume the tobacco product, followed by a 20-minute rest period before the next MCP trial.

The last price at which participants chose tobacco product over money is the crossover point, the primary outcome for analysis.⁵ This is a conservative measure in that it represents the lower bound of the maximum amount a participant would pay to consume a tobacco product—that is, the largest dollar amount at which participants still chose the tobacco product over the money. For example, if a participant chose puffs until they chose money at \$1.28, their crossover point is the next lowest price, \$0.64. This crossover point, compared across conditions, provides an estimate of the value of different products. Participants who preferred money at every point were assigned a crossover point of \$0.00, which is lower than the lowest price in our task; participants who never reached a crossover point because they preferred puffs at every price had a crossover point of \$10.24.

Cigarette Purchase Task (CPT)—The CPT⁷ also measures abuse liability by having participants respond with how many times they would consume 10 puffs of an own-brand cigarette or an e-cigarette at incrementally increasing prices (Figure 1). The following CPT instructions for the reduced harm menthol-flavored e-cigarette condition were adapted from prior CPT studies:^{5,7,11}

Imagine a TYPICAL DAY during which you smoke. The following questions ask how many times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette if every 10 puffs cost various amounts of money. The only available e-cigarette is the reduced harm menthol-flavored e-cigarette you previously sampled. Assume that you have the same income/savings that you have now and NO ACCESS to any of your own brand cigarettes or nicotine products other than e-cigarette offered at these prices. In addition, assume that you would consume the puffs of an e-cigarette that you request on that day; that is, you cannot save or stockpile e-cigarette puffs for a later date. Please respond to these questions honestly.

How many times would you take 10 puffs of a reduced harm menthol-flavored e-cigarette at each of the following prices:

The CPT prices were the same as in the MCP except the inclusion of \$0.00. The CPT provides several abuse liability measures. *Breakpoint* is the price at which participants

would no longer consume the tobacco product being offered; this is analogous to our MCP crossover point and was defined as the last price at which participants still chose any puffs before choosing zero puffs for all subsequent prices. *Intensity* is consumption at \$0.00 (Q_0), *Omax* is the maximum amount of money hypothetically spent on the tobacco product (ie, the maximum of the price times the number of cigarettes), and *Pmax* is the price associated with *Omax*. Finally, demand curves were fit to each individual's consumption data across prices, the slope of which provided an estimate of demand *elasticity* (α).¹¹ The exponential demand equation relating consumption Q and price C is reproduced below:²⁷

$$Q = Q_0 \times 10^{k(e^{-\alpha Q_0 C} - 1)}$$

The span of the demand function in log units (k) was set at 4 to provide best fit for demand curves. Breakpoint, intensity, *Omax* and *Pmax* were observed from the data, rather than being derived from the model above.⁷

Nonsystematic CPT data were excluded based on 3 criteria: 1) trend, or whether a participant showed a general increase in consumption from the first (lowest) to last (highest) price; 2) bounce, or whether a participant reported higher consumption at sequential higher prices; and 3) reversals from zero, or whether a participant reported zero consumption at 2 consecutive prices but reported any consumption at a higher price.²⁸ These criteria were developed to exclude participants whose data could not be fit to the specified curve;²⁸ we assumed that participants whose data fail these criteria did not understand the task. However, in order to retain those whose data may indicate valid demand phenomena, we included participants with zero consumption across prices by winsorizing their elasticity estimates (replacing them at the 90th percentile), as such patterns reflect very low abuse liability. From Study 1, no participants were excluded; from Study 2, across conditions, 1 participant was excluded based on trend and reversal from zero.

Data Analysis

Linear mixed effects models were estimated to account for repeated measures within subjects and to compare abuse liability across own-brand cigarette and e-cigarette conditions with STATA command “xtmixed” assuming an independent covariance matrix, after controlling for menthol vs. non-menthol cigarette preference and, in MCP regressions, for trial number (1–5). Pairwise differences between e-cigarette conditions were tested using follow-up Wald tests for all MCP and CPT outcomes using STATA's “test” command. Finally, within each condition, paired t-tests compared the CPT breakpoint with the average of all 5 trials of the MCP crossover point. A threshold of $p < .05$ was used for all significance tests. CPT demand curves were produced using GraphPad PRISM 6 (GraphPad Software, La Jolla, California). All other analyses were conducted in STATA 12 (StataCorp LP, College Station, Texas).

RESULTS

Study 1

Average MCP crossover point was significantly lower on average for all e-cigarette conditions than for own-brand cigarettes (\$1.31 vs. \$1.61, $p < .05$; Table 1). The crossover point was also lower for menthol e-cigarettes compared to own-brand cigarettes (\$1.23, $p < .05$). When analyzing flavor effects by message condition, participants would pay, on average, \$0.42 (95% confidence interval [CI] $-\$0.74, -\0.11) less for the menthol e-cigarette with no message and \$0.32 (95% CI $-\$0.64, -\0.01) less for the menthol e-cigarette with reduced harm message (Figure 2, Panel A). Neither tobacco e-cigarette condition average MCP crossover point was significantly different from own-brand cigarettes; there were also no significant pairwise differences between e-cigarette conditions.

In the CPT, average elasticity across all e-cigarette conditions was significantly higher than for cigarettes, indicating participants were more willing to reduce their demand for e-cigarettes when prices increased (0.07 vs. 0.01, $p < .05$; Table 1). Participants were also more price-responsive in the menthol-flavored (0.09, $p < .05$) and no message conditions (0.08, $p < .05$) compared to own-brand cigarettes. When analyzing flavor and message conditions together, only the menthol with no message condition showed significantly higher demand elasticity compared to own-brand cigarettes (Table 2). Pairwise comparisons of e-cigarette demand elasticities revealed significant differences between the menthol/no message and tobacco/no message conditions ($p < .05$), and between menthol/no message and menthol/reduced harm message conditions ($p < .05$). Specifically, elasticities in the tobacco/no message and menthol/reduced harm message conditions were significantly lower, indicating participants were less willing to reduce their demand for these products when prices increased than in the menthol/no message condition. The only other CPT measure with significant differences between own-brand cigarettes and e-cigarette conditions was intensity. Here, participants reported wanting nearly 7 to 10 fewer 10-puff bouts with any e-cigarette compared to own-brand cigarettes when each product was offered for \$0.00 ($ps < .05$).

Paired t-tests revealed significant differences between the CPT breakpoints and MCP crossover points: MCP crossover points were significantly lower than the CPT breakpoint for each condition ($ps < .05$).

Study 2

Average MCP crossover point was again lower on average for e-cigarette conditions compared to own-brand cigarettes (\$0.61 vs. \$1.47, $p < .05$; Table 1). The crossover point for cherry flavored e-cigarettes was significantly higher than for e-cigarettes without a flavor (\$0.71 vs. \$0.51, $p < .05$). Examining flavor effects by message condition, average differences ranged from approximately \$1.00 lower in the no flavor/reduced exposure to carcinogens message condition (95% CI $-\$1.16, -\0.84) to approximately \$0.73 lower in the cherry/reduced exposure to carcinogens message condition (95% CI $-\$0.90, -\0.57 ; Figure 2, Panel B). Follow-up pairwise comparisons of condition regression coefficients revealed that, relative to the no flavor/reduced exposure to carcinogens message condition,

the average MCP crossover point was significantly higher in both cherry conditions, regardless of message ($p < .05$, Table 2). Relative to the no flavor/no message condition, average MCP crossover point was significantly higher for cherry/reduced exposure to carcinogens message condition ($p < .05$).

Only the no flavor/reduced exposure to carcinogens message condition showed a significantly different demand elasticity in the CPT relative to own-brand cigarettes (Table 2). This finding suggests lower abuse liability of this e-cigarette flavor/message combination: small increases in price yielded larger decreases in consumption. Follow-up pairwise comparisons for demand elasticity indicated significantly higher estimates for the no flavor/reduced carcinogen exposure message condition relative to all other e-cigarette conditions ($p < .05$). For intensity, all e-cigarette conditions showed lower consumption at \$0.00 compared to own-brand cigarettes. When the product was hypothetically free, participants would have consumed between 5 and 9 fewer 10-puff e-cigarette bouts compared to own-brand cigarettes ($p < .05$).

Like in Study 1, paired t-tests showed that average MCP crossover points were significantly lower than CPT breakpoints in each condition ($p < .05$).

DISCUSSION

The current studies replicate previous findings that e-cigarettes have lower abuse liability compared to conventional tobacco cigarettes,^{8,9,21} and provide evidence that e-cigarette flavors and modified risk messages may affect behavioral economic measures of abuse liability among current cigarette smokers. In the MCP, crossover points were significantly lower for most e-cigarette conditions compared to own-brand cigarettes, regardless of flavor or message. The exception was tobacco-flavored e-cigarettes. One might expect menthol e-cigarettes to be closer in abuse liability to own-brand cigarettes—that is, smokers would have valued them more highly—than tobacco e-cigarettes, because most of our sample preferred menthol cigarettes. However, perhaps the tobacco-flavored e-cigarette was more similar in taste to cigarettes, while the menthol e-cigarette may not have matched the flavor profile of menthol cigarettes as closely, or perhaps the specific brand of menthol-flavored e-cigarette liquid used was unappealing even to menthol-preferring smokers.²⁹ While the current analyses controlled for own-brand cigarette menthol preference, this variable's coefficient was not significant and results were not sensitive to excluding it, suggesting that own-brand cigarette flavor preference did not drive the lower abuse liability of menthol e-cigarettes.

There were no significant differences in MCP crossover points when comparing tobacco and menthol e-cigarette flavors, but cherry flavor increased abuse liability relative to unflavored e-cigarettes. Further, this finding persisted in the presence of a reduced exposure message and was replicated in the CPT measure of demand elasticity, suggesting a potential role for e-cigarette flavor. The differences in flavors examined could explain some of the discrepancies between studies: perhaps the difference in appeal between cherry and no flavor is greater than the difference in appeal between tobacco and menthol flavor,³⁰ which are more familiar flavors for cigarette smokers. Indeed, in additional post-hoc analyses

combining data from both studies, we found that the difference in MCP crossover point between no flavor and cherry flavor was statistically significant ($p = .02$), but the difference between tobacco and menthol flavor was not significant ($p = .10$, results available from the authors upon request). Regulators may consider how restricting flavor availability will affect e-cigarette and cigarette use, given stark differences in the appeal of various e-cigarette flavors among smokers.

Relative to own-brand cigarettes, demand elasticity was significantly higher for the menthol e-cigarette with no message and unflavored e-cigarette with message. Follow-up tests revealed that compared to a menthol e-cigarette with no message, introducing a reduced harm message or restricting flavors to tobacco increased abuse liability as measured by lower demand elasticity. However, compared to an unflavored e-cigarette with a reduced carcinogens message, removing a modified risk message increased abuse liability as measured by a lower demand elasticity, while introducing a cherry flavor increased abuse liability as measured by higher MCP crossover points. These results suggest tradeoffs in the abuse potential of e-cigarettes across combinations of flavors and risk messages.

The current findings highlight differences between the MCP and CPT, despite conceptual similarities. CPT breakpoints were significantly higher than mean MCP crossover points in each condition. Notably, in the CPT, most e-cigarette conditions were not significantly different from own-brand cigarettes, despite large, significant differences between own-brand cigarette and e-cigarette conditions in the MCP. Several differences between the CPT and the MCP might contribute to this. First, in the MCP, after each trial participants were reinforced for one randomly drawn choice they made, while our CPT did not provide reinforcement; this incentive-compatible design may have caused participants to reveal more accurately their demand for tobacco products in the MCP than CPT.³¹ Previous research has found diverging results for hypothetical versus reinforced purchase tasks. A study using an alcohol purchase task found a strong correlation between hypothetical (non-reinforced) and actual (reinforced) demand for alcohol.³² However, a study of hypothetical (non-reinforced), real (all choices reinforced) and potentially real (one choice randomly chosen for reinforcement) cigarette purchase tasks found a strong correlation between demand elasticity for real and potentially real cigarettes, but not between demand for hypothetical cigarettes and demand for real or potentially real cigarettes.³³

Further, the MCP was administered after the CPT; the extra period of nicotine/tobacco abstinence before MCP administration may have affected demand in the MCP. The CPT may also be conceptually more difficult for participants than the MCP. Participants only completed one CPT trial per condition, but 5 MCP trials, which may have allowed participants some practice, so their results may reflect greater understanding of the task. Finally, the difference in time horizons between the tasks likely affected participants' estimates of consumption: the MCP asks participants to make choices to be immediately reinforced, while the CPT asks participants how much they would consume over an entire day. Given the continuing development of abuse liability assessment methods, future research should continue to assess the strengths and weaknesses of various behavioral economics choice procedures to inform regulatory policy.

Few studies have examined abuse liability of e-cigarettes compared to cigarettes among smokers. Two, using the MCP, found significantly higher abuse liability for cigarettes than for e-cigarettes.^{8,9} Our work corroborates this, adding that the lower abuse liability of e-cigarettes may be sensitive to flavors and modified risk messages. While we have not identified any studies that directly measure e-cigarette demand elasticity using the CPT, we note that our elasticity estimates for own-brand cigarettes are similar to those found in CPT studies of cigarettes.^{11,20} However, our study may not be entirely comparable to others: other studies define breakpoint as the first price at which demand is fully suppressed to zero,^{10,11} but to be comparable to our MCP, we defined breakpoint more conservatively as the last price at which participants still chose any amount of the tobacco product, immediately before consumption reached zero.

Beyond the CPT and MCP, one discrete choice experiment found that increasing the set of available flavors increased the choice of e-cigarettes over cigarettes or nicotine replacement therapy for young adults and those who have not used e-cigarettes in the past month.¹⁷ Further, the presence of a modified risk warning label was not associated with differences in choice of e-cigarettes over other tobacco products.¹⁷ In a study using another behavioral economic measure of demand, willingness to pay, smokers valued the availability of flavors and the harm reduction potential of e-cigarettes, and would pay significantly less for an e-cigarette without these attributes.²¹ Collectively, these examinations and the present studies demonstrate that both flavors and modified risk messaging can affect smokers' abuse liability for e-cigarettes.

Limitations

These were pilot studies so sample sizes were small, limiting statistical power and prohibiting analysis of potential interactions such as those between race or own-brand preference and flavor condition. However, crossover points for own-brand cigarettes were similar between Study 1 and 2, as were demographic characteristics and sample sizes, suggesting observed differences in abuse liability across e-cigarette flavors and messages were attributable to condition effects and not differences in demographic characteristics. We also did not adjust for multiple comparisons in our 6 post-hoc analyses given the exploratory nature of the study and power limitations arising from our sample size. Due to low enrollment, the inclusion criteria was altered halfway through recruitment to include people who smoked at least 5, rather than 10, cigarettes per day. While it is possible that receipt of a modified risk message condition early in the study persisted into later sessions when no message was present, our main results in both studies were not sensitive to order effects from the Latin Square design, particularly in regard to receiving a modified risk message.

Due to the convenience sample and design, results from this study may not generalize to other locations, to people of other races, to non-smokers, or to smokers with more e-cigarette experience. Further, our flavors were not representative of the panoply of flavors available in the US market currently. In addition, as recruitment spanned more than 1 year, e-cigarette liquids were reordered and replaced (nicotine levels re-confirmed) to ensure expired liquids were not used; for the cherry flavor, the identical flavor combination

originally ordered was unavailable from the vendor when ordering the second batch. A similar cherry flavor was used for 12 participants.

Likewise, the language used in our messages may not represent what might appear on actual packaging of e-cigarettes under a risk modification order. The experimental messages were intended to align directly with FDA definitions for Modified Risk Tobacco Products, not to determine the particular phrasing most appropriate for e-cigarette packaging. Other research evaluates the merits of specific e-cigarette messages;^{34–36} our research complements this by showing that modified risk messages in general can affect abuse liability.

Recently, the first study to develop the CPT for use with e-cigarettes noted that regular e-cigarette users do not find the number of puffs useful for conceptualizing their demand.³⁷ We used puffs as the unit of e-cigarette demand but participants were not regular e-cigarette users and therefore other units of demand, such as milliliters of e-liquid,³⁷ would not be appropriate for our study. Research is needed to determine the units that properly quantify demand for e-cigarettes among non-users and to validate these tasks for e-cigarettes.

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Appendix

Appendix Table 1

Adjusted Associations between E-cigarette Flavor and Message Conditions and Multiple Choice Procedure or Cigarette Purchase Task Measures.

	Multiple Choice Procedure	Cigarette Purchase Task				
	B (95% CI)	B (95% CI)				
Measure	Crossover point (US \$)	Demand elasticity (alpha)	Intensity (number of 10-puff bouts)	Omax (US \$)	Pmax (US \$)	Break- point (US \$)
Study 1 Condition						
Own-brand cigarettes	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>
Tobacco/No Message	−0.29 (−0.61, 0.03)	0.03 (−0.03, 0.10)	−6.59 (−11.85, −1.32)	−4.70 (−16.47, 7.07)	−0.35 (−1.83, 1.13)	−0.71 (−2.02, 0.61)
Tobacco/Message	−0.16 (−0.48, 0.15)	0.05 (−0.02, 0.11)	−9.29 (−14.56, −4.03)	−9.53 (−21.31, 2.24)	0.20 (−1.28, 1.68)	−0.88 (−2.19, 0.44)
Menthol/No Message	−0.42 (−0.74, −0.11)	0.11* (0.05, 0.17)	−7.94 (−13.21, −2.68)	−9.68 (−21.46, 2.09)	−0.82 (−2.30, 0.66)	−0.76 (−2.08, 0.55)
Menthol/Message	−0.32 (−0.64, −0.01)	0.04 (−0.02, 0.10)	−6.59 (−11.85, −1.32)	−6.50 (−18.27, 5.27)	−0.31 (−1.79, 1.17)	−0.93 (−2.25, 0.38)
Study 2 Condition						
Own-brand cigarettes	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>	<i>referent</i>
No flavor/No Message	−0.92 (−1.08, −0.76)	0.02 (−0.12, 0.17)	−8.83 (−12.42, −5.25)	−3.70 (−9.64, 2.25)	−1.02 (−2.52, 0.49)	−0.97 (−2.65, 0.72)
No flavor/Message	−1.00 (−1.16, −0.84)	0.18 (0.03, 0.32)	−7.61 (−11.19, −4.03)	−3.98 (−9.92, 1.96)	−0.54 (−2.04, 0.97)	−0.73 (−2.41, 0.96)
Cherry/No Message	−0.80 (−0.96, −0.64)	0.03 (−0.12, 0.17)	−7.06 (−10.64, −3.47)	−5.21 (−11.15, 0.73)	−0.44 (−1.94, 1.07)	−0.65 (−2.33, 1.04)
Cherry/Message	−0.73 (−0.90, −0.57)	0.03 (−0.12, 0.18)	−5.78 (−9.36, −2.20)	−4.40 (−10.34, 1.54)	−0.92 (−2.43, 0.58)	−0.87 (−2.56, 0.81)

Note: **Bolded values** indicate a significant difference relative to own-brand cigarettes determined using linear mixed effects models adjusted for own-brand cigarette menthol/non-menthol preference, and MCP estimates are also adjusted for trial (1–5) ($p < .05$).

Elasticity estimates do not include those whose data were identified as non-systematic. US \$ = United States dollars. *CI* = confidence interval.

IMPLICATIONS FOR TOBACCO REGULATION

Our results contribute to an early corpus of literature pointing to both flavors and messages playing important roles in e-cigarette abuse liability among current cigarette smokers; however, more evidence is warranted. The extent to which the vast array of potential combinations of flavor availability and modified risk messaging may interact to influence the abuse liability of e-cigarettes among cigarette smokers is so far unclear. As e-cigarette regulations move forward, considering how these factors and others (eg, nicotine concentration) affect abuse liability is important. Experimental and epidemiological investigations targeting smokers and non-smokers will be required. Our study adds empirical evidence that adult cigarette smokers value e-cigarettes less than their own brand of cigarettes, but this pattern is sensitive to the presence of different flavors and messages about the relative harm of e-cigarettes.

Multiple Choice Procedure

For each choice below, please select whether you prefer 10 puffs of a menthol-flavored e-cigarette or to receive money. After you make your decision for each choice below, one choice will be drawn at random and you will either receive money or be given time to take 10 puffs of the menthol-flavored e-cigarette.

Choice	Puffs	Receive Money
1	10 puffs of a reduced harm menthol-flavored e-cigarette	\$0.01
2	10 puffs of a reduced harm menthol-flavored e-cigarette	\$0.02
3	10 puffs of a reduced harm menthol-flavored e-cigarette	\$0.04
13	10 puffs of a reduced harm menthol-flavored e-cigarette	\$7.68
14	10 puffs of a reduced harm menthol-flavored e-cigarette	\$8.96
15	10 puffs of a reduced harm menthol-flavored e-cigarette	\$10.24

Cigarette Purchase Task

Imagine a TYPICAL DAY during which you smoke. The following questions ask how many times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette if they cost various amounts of money. The available e-cigarette is the reduced harm menthol-flavored e-cigarette you previously sampled. Assume that you have the same income/savings that you have now and NO ACCESS to any cigarettes or nicotine products other than those offered at these prices. In addition, assume that you would consume puffs of an e-cigarette that you request on that day; that is, you cannot save or stockpile cigarettes for a later date. Please respond to these questions honestly. How many times would you take 10 puffs of a reduced harm menthol-flavored e-cigarette if they were ____ each at the following prices?

Price per 10 puffs: \$0 (free)	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$0.01	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$0.02	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$0.04	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$7.68	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$8.96	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)
Price per 10 puffs: \$10.24	__ (Number of times you would take 10 puffs of a reduced harm menthol-flavored e-cigarette)

Figure 1.
Examples of Multiple Choice Procedure and Cigarette Purchase Task for a Reduced Harm Menthol-flavored E-cigarette.

Figure 2. Multiple Choice Procedure Predicted Mean Crossover Points by Study and Condition. Note: Crossover points reflect mean (+SEM) in US \$ (United States dollars). Asterisks (*) indicate a significant difference relative to own-brand cigarettes using linear mixed models adjusted for own-brand cigarette menthol/non-menthol preference and MCP trial (1–5) and brackets indicate a significant pairwise difference between those 2 e-cigarette conditions using Wald test ($p < .05$).

Table 1

Predicted Means for Multiple Choice Procedure and Cigarette Purchase Task Outcomes.

Multiple Choice Procedure		Cigarette Purchase Task	
Measure	Predicted mean (95% CI)	Predicted mean (95% CI)	
Measure	Crossover point (US \$)	Demand elasticity (alpha)	Intensity (number of 10-puff bouts)
Measure	Omax (US \$)	Pmax (US \$)	Breakpoint (US \$)
Study 1			
Own-brand cigarettes	1.61 (0.88, 2.34)	0.01 (−0.05, 0.07)	16.24 (10.92, 21.55)
All e-cigarette conditions	1.31 (0.61, 2.03)	0.07 (0.03, 0.12)	8.63 (4.41, 12.85)
Tobacco	1.38 (0.67, 2.10)	0.05 (0.01, 0.10)	8.29 (3.69, 12.90)
Menthol	1.23 (0.52, 1.95)	0.09 (0.04, 0.14)	8.97 (4.36, 13.58)
Message	1.36 (0.65, 2.07)	0.06 (0.01, 0.11)	8.29 (3.69, 12.90)
No Message	1.25 (0.54, 1.97)	0.08 (0.03, 0.13)	8.97 (4.36, 13.58)
Study 2			
Own-brand cigarettes	1.47 (1.14, 1.81)	0.01 (−0.09, 0.11)	16.67 (12.31, 21.02)
All e-cigarette conditions	0.61 (0.29, 0.93)	0.08 (0.02, 0.13)	9.35 (5.58, 13.11)
No Flavor	0.51 (0.19, 0.84)*	0.11 (0.04, 0.19)	8.44 (4.48, 12.41)
Cherry	0.71 (0.38, 1.93)*	0.04 (−0.04, 0.12)	10.25 (6.28, 14.21)
Message	0.61 (0.29, 0.94)	0.11 (0.04, 0.19)	9.97 (6.00, 13.94)
No Message	0.61 (0.28, 0.93)	0.04 (−0.04, 0.11)	8.72 (4.75, 12.69)

Note: **Bolded values** indicate a significant difference relative to own-brand cigarettes determined using linear mixed effects models adjusted for own-brand cigarette menthol/non-menthol preference, and MCP estimates are also adjusted for trial (1–5) ($p < .05$). Symbols (*) indicate a significant pairwise difference between those 2 e-cigarette conditions using Wald test ($p < .05$). Elasticity averages do not include those whose data were identified as non-systematic. US \$ = United States dollars. CI = Confidence interval.

Table 2

Predicted Means for Multiple Choice Procedure and Cigarette Purchase Task Outcomes by Flavor/Message Condition.

Multiple Choice Procedure		Cigarette Purchase Task	
Predicted mean (95% CI)	Predicted mean (95% CI)		
Measure	Crossover point (US \$)	Demand elasticity (alpha)	Intensity (number of 10-puff bouts)
Study 1 Condition			
Own-brand cigarettes	1.61 (0.88, 2.34)	0.01 (−0.05, 0.07)	16.24 (10.92, 21.55)
Tobacco/No Message	1.32 (0.58, 2.05)	0.05 (−0.01, 0.11)*	9.65 (4.34, 14.96)
Tobacco/Message	1.44 (0.71, 2.18)	0.06 (−0.00, 0.12)	6.94 (1.63, 12.25)
Menthol/No Message	1.19 (0.45, 1.92)	0.12 (0.06, 0.18)**	8.29 (2.98, 13.61)
Menthol/Message	1.28 (0.55, 2.02)	0.05 (−0.01, 0.11)#	9.65 (4.34, 14.96)
Study 2 Condition			
Own-brand cigarettes	1.47 (1.14, 1.81)	0.01 (−0.09, 0.11)	16.67 (12.31, 21.02)
No flavor/No Message	0.55 (0.22, 0.89)^	0.03 (−0.07, 0.14)#	7.83 (3.48, 12.19)
No flavor/Message	0.48 (0.14, 0.81)**	0.19 (0.09, 0.29)**^	9.06 (4.70, 13.41)
Cherry/No Message	0.67 (0.34, 1.01)*	0.04 (−0.06, 0.14)*	9.61 (5.26, 13.97)
Cherry/Message	0.74 (0.40, 1.08)^#	0.04 (−0.06, 0.14)^	10.89 (6.53, 15.24)
	</		

Note: **Bolded values** indicate a significant difference relative to own-brand cigarettes determined using linear mixed effects models adjusted for own-brand cigarette menthol/non-menthol preference, and MCP estimates are also adjusted for trial (1–5) ($p < .05$).

Symbols (*, #, ^) indicate a significant pairwise difference between those 2 e-cigarette conditions using Wald test ($p < .05$). No significant differences relative to own-brand cigarettes or between e-cigarette conditions were observed for Omax, Pmax, or Breakpoint. Elasticity averages do not include those whose data were identified as non-systematic. US \$ = United States dollars. CI = Confidence interval. Regression coefficients can be found in the Appendix.