Reduced Nicotine Cigarette Purchasing Decisions

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

The 2009 Family Smoking Prevention and Tobacco Control Act gave the FDA authority to reduce public health harms of tobacco products. A key proposal is mandating nicotine reduction in cigarettes. It is hypothesized that reducing nicotine content will mitigate the overwhelming morbidity associated with smoking by decreasing smoking initiation and increasing cessation rates among established smokers. Clinical trials have provided promising support by demonstrating reductions in toxicant exposure and nicotine dependence for individuals randomized to reduced-nicotine cigarette conditions. Experimental work on reduced-nicotine cigarette pharmacodynamics has almost exclusively used blinded conditions, precluding systematic evaluation of how expectations about reduced-nicotine cigarettes may impact behavioral and subjective response. Given that real-world settings will involve unblinded products, information about expectancies is essential to inform how reduced-nicotine products will be perceived in future real-world markets. This human laboratory study will systematically determine the independent and interactive effects of expectancy and nicotine dose on reinforcing (behavioral economic demand), subjective, and topography outcomes. Participants (up to N=25) will complete 4 experimental sessions in which expectancy (labeling of “average” nicotine versus “very low” nicotine) and nicotine dose (15.8 mg/g versus 0.4 mg/g) are manipulated as within-subject variables (i.e., 4 sessions: 15.8 told average; 15.8 told low; 0.4 told average; 0.4 told low). Participants will sample a study cigarette of these combinations at the start of each session and complete craving, mood, withdrawal, and subjective drug effect measures before and after smoking. Smoking topography will also be collected during cigarette administration to determine if expectancy and dose impact how one smokes – one way that cognitive or pharmacological effects can impact smoking behavior. Demand will be evaluated with an incentivized demand task using experienced outcomes to improve experimental rigor. Behavioral economic demand analyses will differentiate between effects attributable to consumption of a good at no or little cost (“demand intensity”) and consumption following increases in cost (“demand elasticity”). We hypothesize lower demand, subjective effects, and puff volume for “very low” labels and low nicotine dose cigarettes, with the lowest demand when in combination. This study will provide critical information on the reinforcing effects of smoking due to not only nicotine content, but nicotine expectancy – a factor that has received virtually no attention in nicotine reduction research. Identifying the specific behavioral mechanisms impacted by these factors is relevant as each have very different public health implications. These data will provide clear behavioral targets for subsequent research designed to optimize public health campaigns addressing nicotine-reduction policy.

2. Objectives (include all primary and secondary objectives)

Primary objective: Determine the interaction of expectancy effects and nicotine dose on behavioral economic demand for reduced-nicotine cigarettes. Demand will be evaluated using an incentivized demand task with experienced outcomes to provide experimental rigor. We hypothesize lower demand (via intensity and elasticity) for “very low” labels and low nicotine content cigarettes, with the lowest demand when in combination.

Secondary objective: Determine the interaction of expectancy effects and nicotine dose on subjective effects and smoking topography for reduced-nicotine cigarettes. Participants will sample the study cigarette at the start of each session and complete craving, mood, withdrawal, and subjective drug effect measures before and after smoking. Smoking topography will also be collected during cigarette administration to determine if expectancy and dose impact how one smokes (another primary way cognitive or pharmacological effects can impact smoking). Based on prior research, we hypothesize lower positive subjective effects and lower puff volume for "very low" labels and reduced-nicotine cigarettes with the lowest values for their combination.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The 2009 Family Smoking Prevention and Tobacco Control Act grants the FDA authority to reduce public health harms of tobacco products. A key proposal is mandating nicotine reduction in cigarettes. The theory behind this policy was outlined by Benowitz and Henningfield (1994) who argued that regulating nicotine content below a "threshold for addiction" would help prevent development of nicotine dependence among initiating smokers and (possibly) reduce use in established smokers. Research on nicotine reduction remained limited until the 2009 Tobacco Control Act granted the FDA authority to mandate reduction, but not elimination, of nicotine should evidence support a benefit to public health. Several large-scale clinical trials then developed building on promising evidence from early Phase I/IIa studies (e.g., Benowitz et al., 2007, 2012; Hatsukami et al., 2010). One double-blind, 6-week exposure trial found that reduced-nicotine cigarettes (≤ 2.4 mg/g) decreased the number of daily cigarettes smoked compared to full-nicotine experimental or usual brand cigarettes (Donny et al., 2015). Another double-blind, 20-week trial found that immediate reduction to 0.4 mg/g cigarettes reduced toxicant exposure (i.e., breath carbon monoxide, acrolein metabolites [HPMA], and hydrocarbons [PheT]) compared to gradual or no reduction in daily smokers (Hatsukami et al., 2018).

These findings are promising for the possible public health benefits of reduced-nicotine cigarettes, which in part led to recent FDA authorization of a reduced-nicotine cigarette for public sale (Moonlight brand). However, should a reduced-nicotine content policy be enacted, whether soft (encouraging market competition) or hard (fully mandating reduced nicotine), a critical component is optimizing public health campaigns for rollout. Behavioral laboratory studies are well equipped to address such issues by determining factors contributing to expected consumer response under varying conditions. For example, behavioral research has been essential in evaluating attention and memory mechanisms contributing to point-of-sale marketing and informing FDA regulation of such tactics (Robinson et al., 2016). This study will evaluate one key and understudied cognitive-behavioral factor – expectancy effects – and how behavioral economic demand is well equipped to address the public health relevance of expectancy for nicotine-reduction policy.

Rigorous experimental work has demonstrated that expectancies can impact behavioral and subjective drug response independent of pharmacological action. This work is best exemplified by the balanced-placebo design widely used in alcohol research (Rohsenow & Marlatt, 1981). First described by Ross and colleagues (1962), this procedure involves manipulation of both drug (receive active/placebo) and expectation (told active/placebo) in a 2x2 design. An important and consistent finding of these studies is the belief that alcohol is administered irrespective of actual content results in subjective changes like increased craving as well as interactions with dose that impact reaction time and cognitive-behavioral task performance (Marlatt & Rohsenow, 1980; Testa et al., 2006). Similar independent or interactive effects involving expectancy have been observed across a variety of drugs and drug classes, including cannabinoids, stimulants, and opioids (e.g., Atlas et al., 2012; Lotshaw et al., 1996; Metrik et al., 2009, 2012; Ross et al., 1962).

Studies comparing full nicotine cigarettes to "denicotinized" cigarettes have generally found that cigarettes expected to have no nicotine have lower reinforcing effects and fewer positive subjective effects irrespective of dose (e.g., Darredeau et al., 2013; Kelemen & Kaighobadi, 2007; Perkins et al., 2004, 2008). Important to note is that in these studies, denicotinized cigarettes were Quest 3 brand, which contains trace nicotine (≤ 0.05 mg yield). Expectancy manipulations in nearly all studies, however, specified "no nicotine". The single study to use a "low nicotine" expectancy (Perkins et al., 2004), explicitly framed those cigarettes as un-liked (i.e., "you will be smoking a low nicotine cigarette that is not well-liked"). Thus, existing data prohibit direct and unbiased evaluation of expected consumer responses to reduced-nicotine products as they are likely to appear in the marketplace upon an FDA mandate.

Human laboratory work on reduced-nicotine cigarette pharmacodynamics has almost exclusively used blinded conditions, preventing systematic evaluation of expectancy and estimation of real-world response when these products would be unblinded in the marketplace. A small body of literature suggests that expectancy of low nicotine content can play a salient role. One crossover study found that participants in nicotine withdrawal that smoked blinded usual brand cigarettes labeled as "low" or "very low" nicotine reported less craving reduction compared to when labeled as "usual" (Mercincavage et al., 2016). Deeper puffs (i.e., mean puff volume) were also observed for the "usual" cigarette compared to the "low" cigarette in that study. Another study using blinded reduced-nicotine cigarettes found that participants reported lower positive subjective effects when labeled as "very low" nicotine relative to when labeled as "average" (Denlinger-Apte et al., 2017). To our knowledge, no laboratory studies on reduced-nicotine cigarettes have directly evaluated the interaction of expectancy (without an affective label) and pharmacological effects to determine the relative role of these behavioral mechanisms. Existing studies have also used an ad lib smoking exposure (e.g., "smoke as much as you want" in Denlinger-Apte et al., 2017) rather than a standardized exposure, which means that differences in the reported effects may be attributable to differential exposure across conditions.

This human laboratory study will systematically determine the independent and interactive effects of expectancy and nicotine dose on reinforcing (behavioral economic demand), subjective, and topography outcomes. Participants (N=20) will complete 4 experimental sessions in which expectancy (labeling of "average" nicotine versus "very low" nicotine) and nicotine dose (15.8 mg/g versus 0.4 mg/g) are manipulated as within-subject variables. Participants will sample a study cigarette of these combinations at the start of each session and complete craving, mood, withdrawal, and subjective drug effect measures before and after smoking. Smoking topography will also be collected during cigarette administration to determine if expectancy and dose impact how one smokes – one way that cognitive or pharmacological effects can impact smoking behavior. Demand will be evaluated with an incentivized demand task using experienced outcomes to improve experimental rigor. Behavioral economic demand analyses will differentiate between effects attributable to consumption of a good at no or little cost ("demand intensity") and consumption following increases in cost ("demand elasticity").

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

General Overview

Participants reporting current tobacco cigarette use will complete this double-blind, within-subject laboratory study. Participation will require in-person screening and 5 laboratory sessions that will take over approximately 2 weeks. We plan to recruit up to 25 participants to fully complete the study and will enroll up to 32 participants to account for possible attrition. Potential volunteers will participate in a brief telephone screening after responding to posted advertisements (e.g., community postings, radio). Those meeting initial inclusion/exclusion criteria in telephone

screening will be scheduled for in-person screening at our research unit. Laboratory screening will include health history, drug history, and physical examination. Those passing full screening will participate in 1 practice session with procedures identical to experimental sessions but using the participant's own-brand cigarette. This practice session will serve to acclimate the participant to the study procedures, account for practice effects, and provide data for exploratory comparisons with own-brand cigarette data. Following practice sessions, each participant will complete 4 experimental sessions in which nicotine content (15.8 mg/g versus 0.4 mg/g) and expectancy (participant instructed "average" versus "very low" nicotine; see details below) are manipulated as within-subject variables. The full combination of sessions will be 15.8 told average; 15.8 told low; 0.4 told average; 0.4 told low completed in a randomized order.

Practice and Experimental Session Timeline

Participants will complete 4 experimental sessions lasting about 4 hours. Upon arrival to the laboratory, carbon monoxide will be collected to verify 8-hour abstinence as indicated by a CO <50% of the value obtained a screening (e.g., Mercincavage et al., 2016). A battery of subjective effect measures will be collected prior to cigarette administration including the Minnesota Nicotine Withdrawal Scale (MNWS; Toll et al., 2007), the Questionnaire on Smoking Urges (QSU; Cox et al., 2001), and the Positive and Negative Affect Scale (PANAS; Watson et al., 1988) measuring nicotine withdrawal, cigarette craving, and mood, respectively.

Participants will then smoke one of that session's cigarette (15.8 mg/g or 0.4 mg/g). Participants will be instructed that this cigarette is either "the same level of nicotine as your usual brand" or "a very low level of nicotine compared to your usual brand" to harmonize with prior work on expectancy (Mercincavage et al., 2016). This manipulation will be necessary for the expectancy variable and success of the study protocol. A thorough debriefing about the study will occur at study completion or if a participant discontinues participation early. Dose will be double-blind such that neither research staff nor participants know the dose. Expectancy will be single-blind such that research staff who collect outcome assessments will not know the exposure participants receive (i.e., a separate member of research staff will deliver the manipulation). Participants will have 10 minutes to smoke the whole experimental cigarette. Topography will be collected including measures of total puff volume, mean puff volume, mean puff duration, mean inter-puff interval, mean maximum flow rate, and number of puffs using existing topography equipment. Subjective effect measures (MNWS, QSU, and PANAS) will be collected again following the 10-minute smoking period. Subjective effect measures about the experimental cigarettes will also be collected (i.e., 100-point visual analog scale drug effect measures such as "Strength" and "Satisfaction"). Physiological measures (e.g., CO) will be collected prior to and following cigarette administration.

Participants will complete demand procedures following the standardized cigarette administration (see details below).. A three hour smoking period will follow demand task completion in which cigarette units purchased at a randomly selected price from the demand task are available to smoke. Topography will be collected during this time, but will not be directly compared across sessions due to differences in the number of cigarette units obtained across participants and sessions depending on demand task selections. Sessions will conclude after the 3-hour period. Following completion of all experimental sessions (or earlier if participation is discontinued), participants will be debriefed about the study and experimental manipulations. Prior to debriefing, the validity of the expectancy blind and delivery will be assessed by asking participants what they believed the study purpose was. Participants will also be asked about the estimated nicotine content of cigarettes at the end of each session to evaluate validity of the manipulation.

Description of Behavioral Economic Demand

An ***incentivized purchase task*** will be used to evaluate demand involving within-session incentivized consequences. The purchase task procedure is a well-validated experimental procedure with meta-analyses supporting concurrent validity (González-Roz et al., 2019) and sensitivity to experimental manipulations (Acuff et al., 2020). The current study will use a procedure with experienced consequences to improve rigor. Participants will receive a study income ($50 of the $100 session payment) to allocate for purchasing. Instructions will stipulate that one price will be randomly selected to be *real*–meaning that the cigarette units purchased at the selected price will be available to consume during a 3-hour period and money deducted from the total session payment. Instructions will stipulate that these will be the only cigarettes available during that time and that cigarettes cannot be stockpiled (i.e., will only be available for consumption in the laboratory).

Study Cigarettes

SPECTRUM research cigarettes (22nd Century Group, RTI, Clarence, NY) at doses of 15.8 mg/g and 0.4 mg/g will be obtained from the NIDA drug supply program. The same cigarette paper, tipping paper, and dual plug (paper: acetone acetate) filters with a target pressure drop of 81 mmH_20 will be used. Doses were selected to approximate market nicotine levels (15.8 mg/g) and reduced-nicotine cigarettes recently authorized by the FDA for commercial sale (0.4 mg/g; Moonlight brand at 0.2-0.7 mg/g).

Description of procedures to minimize risk during the COVID-19 pandemic

Although it is not possible to conduct sessions remotely due to the need to collect biological measures (e.g., urine specimens) during screening and use of specialized equipment for experimental sessions (e.g., smoking and response apparatus), specific safety procedure will be put into place to minimize person-to-person while COVID-19 pandemic restrictions are in place. First, all participants will be required to wear a properly fitting face surgical grade mask while in in the laboratory. The exception to this policy will be times in which the participant is alone in the test smoking rooms with the door closed. These rooms each contain independent, strong external exhaust systems. This exception is necessary because participants will be smoking study cigarettes while in the test rooms, which is not feasible or possible while wearing a face mask. Any participant that does not have a face mask will be provided one by the study team at no cost. Second, participants will have their temperature checked using a non-invasive procedure (e.g., forehead temperature reading) and asked about potential COVID-19 symptoms upon arrival to the laboratory. Any subjects who arrive with a temperate indicative of fever or reporting symptoms indicative of COVID-19 per the JHU Clinical screening algorithm will be required to return home and participation will be paused for at least 2 weeks after which a health care professional must clear a return to participation (e.g., with a negative COVID-19 test). Third, appointment times will be staggered such that multiple participants will not be in the main laboratory room at the same time. Fourth, all equipment and surfaces will be wiped down following each session as well as at the beginning of each day with disinfectant (e.g., alcohol-based wipes or spray containing at least 70% alcohol to disinfect). Finally, all study staff will be required to wear properly fitting face masks while in the laboratory.

b. Study duration and number of study visits required of research participants.

The total study duration will be approximately 2 weeks and requires 6 study visits (one screening visits, one practice session, and four experimental sessions).

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will be instructed that this cigarette is either "the same level of nicotine as your usual brand" or "a very low level of nicotine compared to your usual brand" but blinded to actual nicotine content. This manipulation will be necessary for the expectancy variable and success of the study protocol. A thorough debriefing about the study will occur at study completion or if a participant discontinues participation early. Dose will be double-blind such that neither research staff nor participants know the dose. Expectancy will be double-blind such that research staff who collect outcome assessments will not know the exposure participants receive (i.e., a separate member of research staff will deliver the manipulation).

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A. This study does not involve therapy.

e. Justification for inclusion of a placebo or non-treatment group.

N/A. This study does not involve placebo.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from this study if they fail to comply with protocol instructions that are outlined in the consent form or if they are not medically or psychologically suitable to continue.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

The study procedures are not designed to provide therapy for cigarette smoking related problems. Participants will be individuals who do not have immediate plans to quit smoking.

Inclusion/Exclusion Criteria

Inclusion criteria:

- 21 years or older (i.e., individuals under 21 may not legally purchase tobacco products).
- Smoke five or more cigarettes per day for the past six months (e.g., Mercincavage et al., 2016).
- Biological confirmation of cigarette use: have an expired carbon monoxide (CO) level of more than 8 ppm and a urinary cotinine level of more than 100 ng per milliliter at screening.

General medical exclusion criteria:

- Intention to quit smoking in the next 30 days (unethical to recruit treatment seeking participants).
- Daily use of nicotine-containing products other than machine-manufactured combustible cigarettes.
- Serious medical or psychiatric disorder precluding participation by study physician guidance.
- Positive urine screening for illicit drugs other than cannabis or current substance use disorder (other than nicotine). Non-daily cannabis use will be allowed given increasing prevalence of cannabis use in the U.S. (Hasin, 2018). Exclusion of any cannabis use by

participants is considered a threat to external validity and inclusion of persons who use cannabis non-daily should not alter the risk profile of the study.
- Women who are pregnant, plan to become pregnant, or are breast-feeding.
- Medical contraindications to receiving tobacco products (e.g., cardiovascular disease) as assessed through a physical and self-report history.

5. Drugs/ Substances/ Devices
a. The rationale for choosing the drug and dose or for choosing the device to be used.

The Family Smoking Prevention and Tobacco Control Act 2009 gave FDA authority to limit cigarette nicotine levels to reduce levels of nicotine dependence and therefore increase smoking cessation rates and decrease the overwhelming morbidity and mortality associated with smoking (Benowitz and Henningfield, 1994). Studies have suggested reduced nicotine cigarettes result in decreased nicotine intake (Benowitz et al. 2007; Donny et al., 2015) and decreased nicotine dependence (Donny et al., 2015). Doses were selected to approximate market nicotine levels (15.8 mg/g) and reduced-nicotine cigarettes recently authorized by the FDA for commercial sale (0.4 mg/g; Moonlight brand at 0.2-0.7 mg/g). Menthol or non-menthol cigarettes will be used based on participant typical brand.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

6. Study Statistics
a. Primary outcome variable.

Behavioral economic demand curve metrics during each experimental session
a. Q0 (demand intensity)
b. α (demand elasticity)

Demand tasks will be analyzed for derived and curve-observed measures. Derived measures include demand intensity (Q0; consumption at unconstrained price) and demand elasticity (a measure of sensitivity of consumption to changes in price) and will be computed using the exponential demand equation LogQ = Log Q0+k(e^(-α Q0C)-1) (Hursh & Silberberg, 2008). The independent variable C is cost (price/cigarette), the dependent variable Q is consumption (cigarettes purchased at a particular price), the scaling parameter k indicates the range of LogQ in the observed data. Free parameters are Q0 (demand intensity) and α (demand elasticity). Should zero-dense data be observed, a modified exponentiated form of the demand equation will be considered (Koffarnus et al., 2015; Strickland et al., 2016). Observed measures include Pmax (price at maximum consumption), Omax (maximum consumption), and breakpoint (Breakpoint-1; the price of last non-zero demand).

b. Secondary outcome variables. Descriptions of Outcome Measures

Subjective Effect Measures

Subjective effect measures will include a measure of nicotine withdrawal (MNWS), smoking craving (QSU), mood (PANAS), and cigarette subjective experience (Drug Effect Questionnaire). These measures will be collected upon arrival to the laboratory (i.e., immediately prior to cigarette administration) and following the 10-minute standardized smoking period. All measures will be scored using standard procedures.

Smoking Topography

Six measures of smoking topography will be collected including: total puff volume, mean puff volume, mean puff duration, mean inter-puff interval, mean maximum flow rate, and number of puffs (Higgins et al., 2018). These measures will be collected during the 10-minute standardized cigarette smoking period using a custom smoking topography system currently in use in our laboratory.

c. Statistical plan including sample size justification and interim data analysis.

Primary Analysis: *Low nicotine expectancy and low nicotine dose will result in lower demand with lowest demand in combination:* Demand variables will be computed and transformed if non-normal (e.g., log-transform). Analyses will use a 2x2 repeated measures ANOVA with the within-subject factors of expectancy ("average" and "very low") and dose (15.8 mg/g and 0.4 mg/g). Hypothesis 1 will be supported by significant main effects indicating significantly lower demand under "very low" expectancy and 0.4 mg/g conditions. A significant interaction would also indicate different-than-additive effects of expectancy and dose. Such an interaction is plotted in Figure 3 with hypothetical data of a greater reduction in demand intensity by nicotine content under the "very low" expectancy condition.

Secondary Analysis: *Low nicotine expectancy and low nicotine dose will result in lower positive subjective effects (H2) and lower puff volume (H3) with lowest values in combination.* A 2x2 ANOVA will also be used for puff topography and subjective effect measures with similar predictions as Hypothesis 1. Measures with pre- and post-cigarette administration measures will use a 2x2x2 ANOVA including a within-subject factor of time. We expect less reduction in withdrawal and craving with low nicotine expectancy and low nicotine dose indicated by significant interactions with time.

Sample Size Justification: With respect to power, simulation of a 2x2 repeated measure ANOVA based on estimates from preliminary demand data (e.g., nicotine dose effect, SD) identified 82% power to detect a main effect under additive effects. More generally, the sample provides 80% power to detect a medium-large bivariate within-subject effects (d_z = 0.66). This project is considered a pilot project and therefore we have focused on a feasible sample size to generate signals of the behavioral relevance for expectancy in reduced-nicotine policy to inform scientific rationale for future projects. These findings will also provide evidence for the feasibility of within-session procedures with incentivized consequences for rapidly evaluating demand of experimental commodities, thereby serving as preliminary "proof-of-concept" data for a variety of proposals evaluating the reinforcing effects of novel experimental commodities. We will enroll up to 25 participants that complete the study to ensure that at least 20 provide fully systematic data on primary demand outcomes.

d. Early stopping rules.

Volunteers in this study may choose to stop study participation at any time. Participants who do not comply with study procedures, are not medically or psychiatrically suitable to continue, or

experience adverse effects from the study procedures may be discharged early from the study. Women who become pregnant will be discharged from the study.

7. Risks

a. **Medical risks, listing all procedures, their major and minor risks and expected frequency.**

The procedures employed in these studies are relatively benign. There are no specific risks related to the subject-rated effect assessments and other assessments. The primary risks to participants are those related to the well-established long-term health hazards of smoking cigarettes, as participants will be smoking cigarettes in the study. A main risk is that participants may experience side effects through minor withdrawal symptoms when asked to refrain from smoking prior to laboratory sessions. These side effects might include craving for cigarettes, nausea, headache, cough, or sore throat. These side effects would be temporary.

Breach of confidentiality about self-reported drug use and biological tests indicating recent drug use is also a risk.

Finally, full description about the intention of the study is a risk (i.e., participants will not be informed about the use of an expectancy manipulation). This is necessary for the valid and significantly rigorous study of expectation manipulations. It is possible that this may result in anger, confusion, or mistrust about the study, which will be mitigated through a complete debriefing upon completion of the study or end of participation (if participation is ended prior to completion).

b. Steps taken to minimize the risks.

Recruiting and Informed Consent. Participants are not a vulnerable population as defined by human participants protection guidelines; that is, they are not minors, pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide their voluntary informed consent. Participants will be recruited via media advertisements and posters that clearly state the study and procedures involved. The consent process will inform the participant in detail of the procedures, time involvement, compensation, risk, and benefits in our study. Particular emphasis will be given to providing information regarding the potential risks. Volunteers will also be instructed that they may discontinue participation at any time without penalty. Information will not be provided about the expectancy manipulation during the initial consent, but will be provided during a study debriefing.

Debriefing: Following completion of the study or end of participation (if participation is ended prior to completion) participants will receive a full debriefing about the study and use of the expectancy manipulation. The primary goal of this debriefing process will be to inform the participants about the true goal of the study and remove any effects of false information. The overarching goal of this process is to make sure that participants feel they were an important part of the research process and that their participation was valued. Participants will be given a simple, clear and informative explanation of the rationale for the design of the study and the methods used, and participants will also have the opportunity to ask questions. The study PI will conduct all debriefing sessions to ensure that participants are comprehensively informed and all questions answered.

Source of Cigarettes. SPECTRUM research cigarettes at doses of 15.8 mg/g and 0.4 mg/g will be obtained from the NIDA drug supply program. The same cigarette paper, tipping paper, and dual plug (paper: acetone acetate) filters with a target pressure drop of 81 mmH_20 will be used.

Cigarettes Administration Side Effects. It is unlikely that any adverse event should arise that requires medical or psychiatric treatment. In the case that any adverse effects do occur, participants will be put in contact with medical/nursing staff. Because participants will have an established history of cigarette smoking, the well-known long-term harmful effects of smoking will not constitute a new risk for participants. The medical and nursing staff at BPRU is trained in CPR and mobile emergency crash carts on the same floor of our research unit in which sessions will occur. In any case in which a participant ceases study participation due to experimental cigarette side effects the PI will make a detailed report to the IRB. Research assistants at BPRU are rigorously trained in conducting and monitoring behavioral pharmacology experiments. Expired air samples will be collected to test for the presence of alcohol (indicating current impairment), and sessions will not be conducted unless blood alcohol concentration is 0.00%.

Confidentiality. Participants' names will be recorded only during the screening, informed consent, and on necessary medical forms. Anonymous participant identification numbers will be used on all other forms and labeling of biological fluids and test results. All information gathered will be kept in locked research staff offices or file cabinets. All medical information obtained will be handled in accordance with HIPAA regulations. Only research staff will have access to participant records.

c. Plan for reporting unanticipated problems or study deviations.

The investigators will report adverse events to the IRB according to the Johns Hopkins and federal guidelines.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

N/A

e. Financial risks to the participants.

Not applicable. There are no financial risks to study volunteers.

8. Benefits

a. Description of the probable benefits for the participant and for society.

There is no direct benefit for participants in this study other than financial compensation. Evidence suggests that reduced-nicotine cigarettes may reduce the immense mortality associated with tobacco cigarette use. The goal of this project is to experimentally evaluate how expectations about reduced-nicotine cigarettes as well as actual nicotine content interact to determine behavioral and subjective response for these novel products. The proposed project can directly inform tobacco regulatory efforts by providing information about how consumers may respond to reduced-nicotine cigarettes and identify targets to optimize public health campaigns and policies concerning these product's use. This study will therefore develop and provide clinically meaningful data on the effects of cigarette expectancy and dose on smoking behavior. Ultimately, completion of this project will increase our understanding of demand for reduced nicotine cigarettes and will directly inform FDA policy.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be monetarily compensated for participation in this study. Participants will receive $30 for completing the screening session. Participants will receive up to $100 for each study session ($50 session payment + $50 experimental income for the demand task). Participants can therefore make up to $530 for completion of the full study.

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no cost to study volunteers for participating in the trial.

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