Official Title: Using very low nicotine content cigarettes disrupt the pain-smoking reinforcement cycle

Protocol#: Pro00108705

NCT#: NCT05032755

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Research Abstract

Please type your Research Abstract here:

The Research Abstract should summarize the main points of your study in one paragraph. The following guidelines may help you:

1. Purpose and objective (1-2 sentences)
2. Study activities and population group (2-4 sentences)
3. Data analysis and risk/safety issues (1-2 sentences)

Tobacco smoking and chronic pain are highly comorbid conditions. Nicotine has been shown to provide mild, short-term anti-nociceptive effects, which may contribute to powerful negative reinforcement learning. Conversely, smoking withdrawal exacerbates pain, presenting a potential barrier to smoking cessation. The goal of the proposed research is to examine whether switching to Very Low Nicotine Content (VLNC) cigarettes can directly weaken the pain-smoking reinforcement cycle, and attenuate withdrawal-induced hyperalgesia, among smokers with chronic pain, in order to better understand the mechanisms underlying smoking-pain comorbidity. Adult, non-treatment seeking daily smokers with chronic (> 3 months) non-cancer back pain will complete 1-week of baseline ecological momentary assessment (EMA) while smoking their usual brand of cigarettes to familiarize them with study procedures; they will then be randomized to 4-weeks of Normal Nicotine Content (NNC) or VLNC cigarettes. EMA will continue during weeks 1 and 4 of study cigarette use, and will assess smoking behavior and urge, negative affect, and pain intensity and interference. Participants will attend weekly in-person visits to obtain biomarker verification of cigarette compliance, and will complete measures of nicotine dependence, self-efficacy and motivation to quit, and pain-related coping. At the start of the study and at the end of 4-weeks of study cigarette use, a 24-hr smoking abstinence test will be used to assess withdrawal symptoms and withdrawal-induced hyperalgesia. Participants will also be contacted by telephone 3 months after study participation to assess quitting behaviors, including actual quit attempts and use of cessation strategies. Analyses will examine the effects of NNCs versus VLNCs on pain and smoking-related measures assessed during EMA, weekly visits, and pre- and post-intervention abstinence tests. Risks of the study include withdrawal symptoms during the 24-hr abstinence sessions and during initial use of VLNCs, risks associated with smoking investigational cigarettes, and risks associated with the collection of personal information.

Research Summary

State your primary study objectives

1. To examine the effects of NNCs versus VLNCs on smoking and pain over 4 weeks of study cigarette use and following a 24-hour abstinence challenge.
2. To examine the effects of NNCs versus VLNCs on the bidirectional, within-person associations between momentary reports (as assessed with EMA) of smoking urge/behavior, pain, and negative affect.

State your secondary study objectives

1. To examine the effects of NNCs versus VLNCs on changes in smoking and pain-related cognitions, including interest in quitting smoking, abstinence self-efficacy, and smoking to cope with pain.

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

The purpose of the study is to evaluate the effects of switching to VLNC cigarettes as a potential strategy for disrupting the pain-smoking reinforcement and withdrawal cycle among smokers with chronic back pain. Adult daily smokers with chronic (> 3 months) non-cancer back pain will be randomly assigned to 4-weeks of Normal Nicotine Content (NNC) or VLNC investigational cigarette use. Participants will attend weekly assessment visits during this time, and will complete EMA assessments during a baseline week of usual brand smoking, and during weeks 1 and 4 of study cigarette use. Participants will also complete assessments of pain and withdrawal following 24 hours abstinence at the start of the study and after 4 weeks of study cigarette use.

Aim 1 will examine effects of NNCs versus VLNCs on smoking and pain over the 4 weeks of study cigarette use and during the 24-hour abstinence tests.

Hypothesis 1a: VLNCs will lead to reductions in nicotine dependence and frequency of smoking over the course of study cigarette use, whereas no change will be observed for NNCs.

Hypothesis 1b: Relative to the pre-intervention baseline, smokers assigned to VLNCs will report decreased pain intensity and interference and fewer withdrawal symptoms during the post-treatment 24-hr abstinence test compared with smokers in the NNC condition.

Aim 2 will examine effects of NNCs versus VLNCs on the bidirectional, within-person associations between momentary reports (as assessed with EMA) of smoking urge/behavior, pain and negative affect.

Hypothesis 2a: VLNCs will reduce the magnitude of the within-person associations between momentary reports of pain/negative affect and smoking urge/intent to smoke.

Hypothesis 2b: VLNCs will reduce the magnitude of the within-person association between recent smoking and reports of decreased pain and negative affect.

Exploratory Aim 3 will examine the effects of NNCs versus VLNCs on changes in smoking and pain-related cognitions, including interest in quitting smoking, abstinence self-efficacy, and smoking to cope with pain.

Hypothesis: Following VLNCs, participants will report increased motivation and intention to quit smoking, greater abstinence self-efficacy, and decreased use of smoking as a pain-related coping strategy.

Background & Significance

- Should support the scientific aims of the research

Tobacco smoking and chronic pain are highly comorbid conditions, and carry a combined annual price tag of more than $900 billion in health-care costs and lost productivity. Epidemiological studies demonstrate that smoking rates among individuals seeking treatment for chronic pain are at least twice those of the general population. Moreover, regular tobacco use is an independent risk factor for development of chronic pain conditions. Smoking and pain have been proposed to influence each other through a reciprocal positive feedback loop, in which pain increases motivation to smoke, and smoking worsens pain over time. Laboratory studies suggest that nicotine has mild anti-nociceptive effects, which are likely to contribute to powerful negative reinforcement of smoking behavior with repeated use. At the same time, initial smoking abstinence (12-24 hrs) is associated with *increased* pain that is correlated with craving and severity of withdrawal, presenting a significant barrier to cessation. Together, the combination of nicotine's analgesic effects and increased pain during withdrawal are likely to perpetuate smoking, contributing to worsening pain, while decreasing expectations that smoking cessation is possible. **Once this cycle is instantiated in habitual behavior, there are no known strategies for disrupting it, and effective smoking cessation interventions are extremely limited.**

The primary objective of this project is to experimentally evaluate the effects of switching to 4 weeks of very low nicotine content (VLNC) cigarettes on the pain-smoking reinforcement and withdrawal cycle among non-treatment seeking smokers with chronic back pain. Our previous work demonstrated that VLNCs decrease nicotine dependence and withdrawal in both treatment-seeking and non-treatment seeking populations, representing a powerful tool for decoupling the reinforcing effects of nicotine from the behavior of smoking. Importantly, VLNCs are effective at reducing craving by maintaining the sensorimotor and behavioral aspects of smoking, whereas the minimal level of nicotine delivery facilitates extinction of

smoking behavior leading to decreased dependence with repeated use. Although VLNCs carry the same health risks as normal nicotine content (NNC) cigarettes, evidence indicates that switching to VLNCs increases interest in quitting, promotes abstinence self-efficacy, and improves cessation, suggesting that VLNCs may be a useful intermediate step for smokers unable to quit.

Despite the utility of VLNCs as a smoking cessation aid in the general population, the effect of VLNCs on real-world pain and smoking behavior among individuals with chronic pain has not been investigated. Laboratory studies of acute pain manipulations suggest that VLNCs provide intermediate pain relief relative to NNCs or no smoking, suggesting that VLNCs may help to attenuate withdrawal-induced hyperalgesia among smokers with chronic pain. However, there is tremendous need to extend mechanistic findings from laboratory studies to examine the complex interactions between pain perception and real-world smoking behavior among individuals with chronic pain. VLNCs provide an opportunity to directly examine the relative contribution of nicotine and non-nicotine factors to the association between smoking and pain in the real world, representing a critical first step to developing targeted interventions that can reduce smoking and improve pain outcomes in this population.

The proposed project will apply well-validated, rigorous and reproducible methods, including ecological momentary assessment (EMA), randomization to VLNC or normal nicotine content (NNC) cigarettes, and stringent biochemical verification of adherence, to examine proximal clinically-relevant outcomes as a precursor to further intervention development. This research will disentangle the relative contribution of nicotine and non-nicotine factors to smoking/pain comorbidity—information critical to advancing our understanding of the mechanisms driving smoking/pain comorbidity, and will pave the way for a large-scale randomized clinical trial incorporating VLNCs to promote smoking cessation in the context of chronic pain.

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

Overview of Study Design. Participants will complete an initial screening session in which informed consent will be obtained, eligibility is confirmed, and baseline pain and smoking measures are collected. Eligible participants will then be scheduled for a training session/initial abstinence test session. Participants will be asked to abstain from smoking for 24 hours prior to this session. They will complete survey measures, and then will receive training on the EMA procedures and the Metric Wire software will be installed on their smartphone device. Participants will then complete a 1-week baseline period of EMA while smoking their usual brand of cigarettes. Following the baseline period, participants will return for an in-person visit and will be randomly assigned to smoke VLNCs (n=24) or NNCs (n=24) for the next four weeks. Participants will complete 4 weekly lab visits, during which study cigarettes will be supplied and study measures collected. In addition, EMA will continue to be conducted during weeks 1 and 4 of study cigarette use. At the end of study cigarette use, participants will complete a second abstinence challenge session to assess pain and withdrawal following 24 hrs abstinence from smoking. Finally, participants will be contacted by telephone 3 months after completing the study to provide information about quitting behaviors. Details of study sessions are described below and are presented in Table 1.

Screening Session (up to 3 hours). Participants will first complete a phone screening interview, during which the study will be described in detail and preliminary participant characteristics (e.g., age, smoking and pain status and number of cigarettes smoked per day) will be assessed. Those participants who meet preliminary criteria for participation will be scheduled for a comprehensive screening session. During this session all aspects of the study will be described, a photo ID will be documented to confirm age and identify, and informed consent will be obtained. Breath and urine samples will be collected to confirm a) negative urine drug screen (other than marijuana); b) breath alcohol level (BAL) equal to 0.000 (required at all visits); c) breath CO > 10 ppm; and d) negative pregnancy test for females who are capable of becoming pregnant. Use of illegal drugs will be exclusionary. Marijuana use will not be exclusionary, but participants must agree to not use marijuana for 48 hours prior to sessions and must avoid any additional tobacco such as cigarillos. In addition, daily marijuana users will be excluded. Tobacco use history and medical history will be obtained, and vital signs (heart rate, blood pressure) will be measured. A psychiatric screening will be conducted using the M.I.N.I. Pain and smoking-related self-report measures will be administered via Redcap. Pain intensity and interference inclusion criteria will be assessed with the Graded Chronic Pain Scale (GCPS). History of chronic back pain will be confirmed through the participant's medical record or by provider. If the participant is a non-Duke patient or is a Duke patient not recruited using Duke MyChart, a release form will be signed. If participants are recruited using Duke MyChart, a release form is not necessary. Consent, interviews and survey measures may be obtained remotely. If these measures are completed remotely, breath CO and urine samples, along with pregnancy testing and breath alcohol level will be obtained during a separate, in-person screening component. All screening materials will be reviewed by the study physician and PI prior to enrollment.

Baseline Abstinence/Training Session. Following screening, participants will complete a baseline abstinence challenge session, in which they are asked to abstain from smoking for 24 hours prior to the session. Expired CO < 6 ppm or 50% reduction from baseline will be used to verify abstinence. Participants will complete measures of craving, pain, and withdrawal. At the conclusion of the session, Metric Wire software will be installed on their smartphone, and they will be trained in the procedures for EMA.

Weekly Sessions. After one week of baseline EMA while smoking of usual brand cigarettes, participants attend an in-person visit (V1), during which they will be randomized to NNC or VLNC condition, given a supply of study cigarettes, and provided with a schedule of 4 weekly follow-up visits (V2 through V5). During each of the weekly visits participants will complete self-report measures and a timeline follow-back of past-week smoking, other tobacco use and alcohol/substance use; additional study cigarettes will be supplied; and breath CO and urinary measures of nicotine exposure will be collected. Adverse events will be monitored, as well as changes in medical history including new or discontinued medications, new treatments for current medical problems, or other study participation.

Post-Intervention Abstinence Session. Immediately following the final weekly visit, participants will be asked to abstain from smoking for 24 hours prior to attending a final laboratory abstinence session. Procedures and measures will be identical to those used in the initial abstinence session.

Follow-Up 3-Month Phone Call. Participants will be contacted by phone 3 months after completing the study to provide information about current smoking, recent quit attempts, and cessation strategies used.

Table 1. Schedule of Events and Procedures

CIGARETTES		**UB**	**NNC or VLNC Cigarettes**				
REMOTE ASSESSMENT		EMA			EMA		
IN-PERSON VISITS	Screening	24hr ABS Test 1/ Training (A1)	Visit Week 1 (V1)	Visit Week 2 (V2)	Visit Week 3 (V3)	Visit Week 4 (V4)	Visit Week 5 (V5)	24hr ABS Test 2 (A2)
Study Day	-30 to -1	0	7	14	21	28	35	36
Window (in days)		0	(± 2)	(± 2)	(± 2)	(± 2)	(± 2)	(± 1)
PROCEDURES								
Informed Consent	X							
Eligibility	X							
Demographics	X							
Medical History	X							
Tobacco History	X							
Breath CO Sample	X	X	X	X	X	X	X	X
Breath Alcohol	X	X	X	X	X	X	X	X
Urine Drug Screen	X							

Psych Assessment (MINI)	X							
Cognitive Function (WRAT)	X							
Metric Wire install and EMA training		X						
STUDY CIGARETTES								
Randomization			X					
Study Cigarettes Supplied			X	X	X	X		
Product Accountability				X	X	X	X	
Timeline Follow-back			X	X	X	X	X	
Urine Sample (TNEs)*				X	X	X	X	
SAFETY ASSESSMENTS								
Medications	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Pregnancy Test	X		X					
Respiratory Health/ Side Effects Forms	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
PRIMARY AND SECONDARY OUTCOME MEASURES								
Cigarette Dependence	X		X	X	X	X	X	
Craving/Withdrawal	X	X	X	X	X	X	X	X
Pain Intensity/ Interference	X	X	X	X	X	X	X	X
Quit Self-Efficacy	X		X		X		X	
Motivation to Quit	X		X		X		X	
Pain-Related Cognitions	X	X	X		X		X	X

UB: Usual brand cigarettes; **NNC:** Normal nicotine content research cigarettes; **VLNC:** Very low nicotine content research cigarettes; **EMA:** Ecological momentary assessment; **CO:** Carbon monoxide; **M.I.N.I.:** Mi ni International Neuropsychiatric Interview; **WRAT:** Wide Range Achievement Test-4 (Word Reading Subtest); **TNEs:** Total Nicotine Equivalents

*Note that urine samples will be collected at all visits to increase perception that study cigarette adherence may be biochemically verified at any time, but only weekly visits 4 and 5 of the VLNC group will be analyzed for TNEs.

Study Procedures. Details of specific procedures involved in the study are described below.

VLNCs and NNC Cigarettes. SPECTRUM cigarettes will be ordered through NIDA (NOT-DA-14-004) and will have the following nicotine content and yield: *NNC cigarette condition*. NRC600/601 (non-menthol /menthol) has a nicotine content of approximately 15.8 mg/g tobacco with reported nicotine yield (ISO) of 0.8 ± 0.15 mg and a tar yield of 10.5 ± 1.5. This NNC dose was chosen because it is similar to full flavor cigarettes and is associated with similar rates of smoking, nicotine levels and dependence as the usual brand cigarettes. *VLNC cigarette condition*. NRC102/103 (non-menthol/menthol) has a nicotine content of approximately 0.4 mg/g tobacco with reported nicotine yield (ISO) of 0.03 ± 0.01 mg and a tar yield of 9 ± 1.5. This dose was chosen because prior studies have shown that the VLNC dose relative to NNC showed significant reductions in cigarettes smoked per day, nicotine exposure and cigarette dependence. These cigarettes have been used previously in our lab in several studies (R01 DA042532; R01 DA048454; U54 DA031659).

Study Cigarette Adherence**.** Compliance data will be examined using methods standardized in our prior research (e.g., comparing daily reports, returned product packaging, and timeline follow-back; providing feedback on inconsistencies). To encourage adherence to study cigarettes, urine samples will be collected at each study visit; participants will be told that 2 will be randomly selected for biomarker analysis to identify non-compliance. As in our prior work,[27] participants in the VLNC group will receive $600 bonus payment contingent on biochemical verification of self-reported adherence, defined as total nicotine equivalents at or less than 12 nmol/mL at weekly visits 4 and 5. This cutoff allows for only minimal use of non-study cigarettes, while ensuring adequate sensitivity to detect adherence. To encourage honest reporting, participants disclosing non-study cigarette or other tobacco use will receive a reduced bonus of $200. We have used this tiered incentive approach in a prior 20-week study and observed biochemical verification indicating 54-69% compliance. Adherence in the proposed research will likely be higher given the shorter duration of use. Biochemical analysis is not available to confirm exclusive use of NNC cigarettes; thus bonuses in the NNC group will be based solely on self-report. Compliance is more likely in the NNC condition given that rates of usual-brand and NNC smoking were nearly identical in our prior study. Effects of compliance will be examined in sensitivity analyses restricted to those with verified VLNC adherence.

Ecological momentary assessment. Participants will complete EMA
using their smartphone during the 1-week baseline, and during the first and final weeks of study cigarette use. As in our prior research, the MetricWire application platform will be used for acquiring both prompted and smoking-initiated assessments. *Prompted assessments*: Participants will specify their typically wakeful hours at screening. They will be prompted 5 times daily at random intervals averaging 150 minutes in length. Participants will be asked to indicate how recently they have smoked (1 item), whether this was a study or non-study cigarette (1 item), and whether they are about to smoke (1 item). Participants will then be asked to rate their current urge to smoke (1-item), negative affect (4 to 6 items), positive affect (2 to 4 items), and pain (2 to 4-items; see examples in Table 2). Responses will be on a 9-point scale ranging from "not at all" to "extremely." Participants can delay responding for a brief period of time (e.g., 15 minutes), after which the response will be coded as missing. *Smoking-initiated assessments*: Participants will be prompted three times each day to indicate the next time they are about to smoke; participants will then respond to a similar set of items as in the prompted assessments before and/or after smoking the cigarette. *End of day/Morning assessments*: Throughout study cigarette use, participants will be prompted at the end of the day to report how many cigarettes they smoked that day, how many were usual brand versus study cigarettes, and any occasions of non-cigarette tobacco use. Participants will also be asked to rate their severity of withdrawal symptoms over the past 24 hours and the quality of their sleep the night before. If needed, this assessment may be prompted the following morning for participants to report on the prior day. *Compensation*. Participants will be compensated $5 per day for completing at least 4 prompted assessments. Participants will earn an additional $50 per week for completing 4 out of 5 prompted assessments and the end of day/morning assessment every day. This reinforcement schedule is consistent with that used previously in our lab, which has yielded an 88% completion rate.

Carbon Monoxide Breath Testing: Participants will be asked to inhale and hold their breath for 15 seconds, and then exhale into a commercially available breath CO monitor (e.g., Covita Smokerlyzer). This device is fitted with a disposable mouthpiece and cleaned thoroughly between participants. Given that this test requires participants to remove their mask, face to face contact will be minimized during this test under COVID restrictions. Participants will be instructed how to self-administer the test, which they will then

complete alone in a room with closed door or outside in a private, designated area. Participants will be observed completing the test via Zoom video (when indoors) or through the glass door to the designated outdoor area.

Questionnaires: A standard battery of questionnaires and interview measures will be administered via Redcap to evaluate psychological, behavioral, smoking, pain and health information. These will include: demographics, a Tobacco Use History interview, a Brief Medical History questionnaire and Follow-up Form, a Medication Changes Questionnaire, a Health Changes Questionnaire, a Drug Use History questionnaire, a Motivation to Quit Smoking questionnaire, the Alcohol Use Disorders Identification Test (AUDIT), the Fagerstrom Test of Cigarette Dependence (FTCD), the Wisconsin Inventory of Smoking Dependence Motives (WISDM), the Minnesota Tobacco Withdrawal Scale (MTWS), the Questionnaire of Smoking Urges-Brief (QSU-B), the Brief Pain Inventory-Short Form (BPI-SF), the Graded Chronic Pain Scale (GCPS), the Pain and Smoking Inventory (PSI), the Smoking Self-Efficacy Questionnaire (SEQ-12), the Center for Epidemiological Studies-Depression scale (CES-D), and a follow-up Quitting Behaviors questionnaire. Additional questionnaires may also be used, including: the Pain Catastrophizing Scale (PCS), a Smoking Cessation Therapy Use questionnaire, the Life Events Checklist (LEC), a measure of Adverse Childhood Events (ACES), Composite Morningness Scale (CMS), PROMIS Sleep Questionnaire, the Distress Tolerance Scale (DTS), and Profile of Mood States (POMS), State-Trait Anxiety Inventory (STAI), Snaith-Hamilton Pleasure Scale (SHAPS), and the Positive and Negative Affect Schedule (PANAS), the Chronic Pain Self-Efficacy Scale (CPSS), the Cigarette Evaluation Scale (CES), PATH Dependence Scale, Cigarette Expectancies (Study Cigarette & Usual Brand) Scale, Study Cigarette Purchase Task; Perceived Health Risk (Study Cigarettes & Usual Brand), Coping Strategies Questionnaire-short form, CSQ-7 item, Chronic Pain Coping Inventory (CPCI), Pain Anxiety Symptom Scale (PASS-20), and the CHOIR body map.

Standardized Tests of Psychiatric and Cognitive Functioning. The M.I.N.I. is a structured interview of psychiatric functioning, and will be administered by trained research staff under the supervision of the PI. In addition, the Wide Range Achievement Test (WRAT-4) word reading test is a standardized measure that requires approximately a minute to administer. Participants are asked to read aloud from a page of increasingly difficult words, and to say the words as smoothly as possible. A standardized score can be calculated and provides an approximate index of current reading level/cognitive ability. This measure will allow us to set a minimum threshold necessary to ensure that participants can read and understand all study-related procedures.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Inclusion Criteria

- diagnosis of non-cancer chronic (>3 months) back pain (confirmed in medical record or by provider);
- Pain duration of ≥ 3 months with **EITHER** an average intensity of ≥ 4/10 **OR** worst pain average of ≥ 6/10 as assessed by the Graded Chronic Pain Scale (GCPS);
- 21-70 years of age;
- daily smoking at least > 2 years lifetime;
- smoking at least 7 cigs/day for the past 6 months, with no continuous periods of abstinence > 2 weeks;
- expired breath CO concentration > 10 ppm to confirm reported smoking status;
- intact intellectual functioning as indicated by score of ≥ 80 on the WRAT-4 word reading subtest;
- have an iPhone or Android smartphone capable of running the EMA software;

Exclusion criteria

- actively taking steps to quit smoking;
- inability to attend all required experimental sessions;
- report of significant health problems including but not restricted to untreated chronic hypertension, emphysema, seizure disorder, history of significant heart problems;
- systolic blood pressure > 160 or diastolic blood pressure > 100 (participants failing for blood pressure will be allowed to rescreen once);
- resting heart rate > 100 (participants failing for heart rate will be allowed to rescreen once);
- breath alcohol level > 0.000 (participants failing for BAL will be allowed to rescreen once);
- current use of prescription opioid pain relievers;
- lifetime history of bipolar or psychotic disorder;
- current *unstable* psychiatric disorder as assessed by the MINI;

- suicidal ideation with plan or intent; potential subjects who endorse items 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) and/or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia Suicide Severity Rating Scale will be excluded from study participation, and referred to appropriate psychiatric treatment;
- use of non-cigarette tobacco products or electronic cigarettes > 8 times in past 30 days;
- current use of nicotine replacement therapy (NRT) or other smoking cessation strategy;
- use of Spectrum investigational cigarettes or low nicotine content cigarettes in the past year;
- quit attempt in the past 30 days resulting in greater than 3 days abstinence;
- past year alcohol or substance use disorder;
- use of illegal drugs as measured by urine drug screen (other than marijuana);
- daily or near-daily use of cannabis;
- primary pain complaint was due to specific medical conditions (e.g., cancer, rheumatoid arthritis, or complex regional pain syndrome);
- spine surgery within the past year or planned surgery within the timeframe of the study;
- positive pregnancy test among women

Changes to inclusion criteria made to reflect changes in criteria surrounding pain rating, now incorporating worst pain rating.

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Subjects will be recruited through responses to advertisements, invitations within the Duke patient EHR portal, or by being contacted by study staff because they previously participated in an experiment within the lab and indicated they were willing to be contacted again in the future.

Duke MyChart: Potential participants will be recruited through referrals through the patient EHR portal (Duke MyChart). Patients with recent medical visits meeting pre-specified eligibility criteria will receive an invitation for study participation through MyChart or by email. Importantly, data from the Duke EHR indicates that over 1,500 smokers sought treatment for non-cancer chronic pain within the Duke Health system within the past year. As in previous studies in our lab, patients responding to the invitation will be contacted by study staff to complete a phone screen or will be invited to complete the initial online web screener.

Working with DOCR Maestro Care Analysts (MCAs), we will develop a computable phenotype that will allow us to identify potentially eligible patients. The DOCR MCAs will send us a list of potentially eligible patients. We will then verify the potential eligibility of those patients with manual chart reviews. We will then return an updated list of potentially eligible patients to the MCAs so they can send the MyChart Research Message out to those patients we have verified may be eligible. For those recipients of the MyChart Recruitment Message who do not open/view the message, we will send reminder emails, texts, or calls up to 2 times based on the patient's preferred method of contact. We may decide to remove the initial MyChart Recruitment Message and exclusively use direct-to-patient phone calls, texts, or emails to potentially eligible patients if the MyChart Message is unsuccessful in gaining participant interest. We confirm that we are checking against the "banner" in MaestroCare to verify whether or not the patient has opted out for being contacted.

Advertisements: We will advertise in local print media, on the internet (e.g., banner ads, craigslist), social media (e.g., Facebook, snapchat, twitter), and posted flyers. Participants responding to advertisements will be provided with a study phone number to contact the lab to learn more about the study and complete an initial phone screen. Advertisements will also include a link to a secure online REDCap survey if they prefer to compete preliminary screening questions online.

Contact Repositories: Participants may also be recruited through their involvement in the "CfAST Study Contact Repository" (Pro00088653). This secure REDCap database includes contact information for individuals who have previously participated in CfAST studies and have agreed to be contacted for future research.

When we receive calls from potential subjects we will return their call and ask information including name, address, age, smoking history, and questions about pain. They will be given a brief description of our studies and will be asked questions to determine interest and eligibility. Individuals will be asked if they

would like their screening information stored in a database for future studies for which they may be potentially eligible or destroyed after completion of the study. If they do qualify we will schedule a screening session where we will follow all IRB protocols of informed consent.

Compensation:
Participants are compensated for the time and effort they dedicate to the study procedures. They will receive $30 for the initial screening visit, $50 for completing the initial abstinence/training session, $30 for each of the weekly visits, and $50 for the second abstinence session. In addition, participants can earn a $100 completion bonus for attending all sessions, up to $255 for completing EMA, and up to $600 bonus for biochemical verification of adherence to study cigarettes ($1235 total). Thus, compensation is provided not only for repeated laboratory visits, but also for use of study cigarettes and completion of EMA. EMA requires multiple responses throughout the day, for a period of 3 weeks, and compensation greatly improves participants' willingness to complete these repeated assessments. In addition, study cigarette use requires committed ongoing effort from participants for a period of several weeks. As such, the compensation is commensurate with the time and effort involved. The $100 completion incentive is included because high attrition will reduce the statistical power of the study. In addition, the $600 adherence bonus (or $200 if participants truthfully disclose non-study cigarette use) is included to maximize compliance with study product because non-study cigarette use will compromise the ability to evaluate group differences. Compensation will be provided at each visit and weekly for EMA. Participants are free to discontinue at any time and will receive compensation for the sessions that they complete at the same rate as participants who complete the study.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

We do not include participants who cannot read/write/understand English or those who do not have the capacity to give legal consent.

Study Interventions

- If not already presented in the Design & Procedures section, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i. e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

After completing the screening session, abstinence/training session, and 1 week of baseline EMA while smoking usual brand cigarettes, participants will return to the lab for weekly visit 1 (V1). At this session participants will be randomly assigned by the PI (implemented in REDCap) to 4 weeks of normal nicotine content (NNC) or very low nicotine content (VLNC) SPECTRUM investigational cigarettes. SPECTRUM cigarettes will be ordered through NIDA (NOT-DA-14-004) and will have the following nicotine content and yield: *NNC cigarette condition*. NRC600/601 (non-menthol/menthol) has a nicotine content of approximately 15.8 mg/g tobacco with reported nicotine yield (ISO) of 0.8 ± 0.15 mg and a tar yield of 10.5 ± 1.5. This NNC dose was chosen because it is similar to full flavor cigarettes and is associated with similar rates of smoking, nicotine levels and dependence as the usual brand cigarettes. *VLNC cigarette condition*. NRC102/103 (non-menthol/menthol) has a nicotine content of approximately 0.4 mg/g tobacco with reported nicotine yield (ISO) of 0.03 ± 0.01 mg and a tar yield of 9 ± 1.5. This dose was chosen because prior studies have shown that the VLNC dose relative to NNC showed significant reductions in cigarettes smoked per day, nicotine exposure and cigarette dependence. These cigarettes have been used previously in our lab in several studies (R01 DA042532; R01 DA048454; U54 DA031659).

A supply of study cigarettes will be provided at each weekly visit (V1 through V4) according to daily cigarette consumption reported during the past week's timeline follow-back. Study staff and participants will be blinded to cigarette condition. Used and unused cigarette packaging will be collected at each return visit (V2 through V5) and will be carefully documented. Compliance with study cigarettes will be incentivized as described above.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Potential Risks: Continuing to smoke carries significant health risks. Participants enrolling in this study are not attempting to quit smoking, and will not be provided with smoking cessation treatment. However, participants will be provided with referral information for smoking cessation at the conclusion of the study. Use of VLNCs provided during the study does not pose any reduced risk relative to typical combustible cigarettes. There is a risk that participants in the VLNC condition could increase their smoking to compensate for lack of nicotine. Although infrequent, use of study cigarettes may also contribute to other adverse effects, including throat irritation, coughing, or nausea. There is also the risk that smokers assigned to the VLNC condition will experience increased withdrawal symptoms, including increased pain or negative affect due to decreased nicotine intake. All participants will be advised of potential symptoms and provided with coping strategies and support as necessary. Subjects may also experience withdrawal symptoms during 24-hr abstinence period. Finally, there is a risk attendant to the confidentiality of psychological data and self-report data.

There are no direct benefits to participants, but the study will increase knowledge of the role of nicotine and non-nicotine factors in the comorbidity between smoking and pain, and the effects of VLNCs on clinically-relevant outcomes among smokers with chronic pain. This information will aid in the development and evaluation of new and more effective treatments for smokers with pain. Given minimal risks of participation, we consider the risk/benefit ratio acceptable and representing an appropriate level of risk for human participation. Steps taken to minimize risks to participants are described below.

Breach of Confidentiality. Participants will be assigned a unique subject ID that will be used on all research materials. The only link between the assigned unique ID and identifiable information will be stored in the enrollment log on a Duke School of Medicine password-protected server. All forms with identifiable information including the study consent forms will be stored in a locked file cabinet in a separate location from the study data. De-identified study materials will be maintained in participant binders in a locked suite of the CfAST lab space, or for electronic data, on a secure password-protected Duke School of Medicine server. All information collected as part of this study will be accessible only to research staff. Interviews with participants will be conducted in private rooms. Biological samples for drug and pregnancy tests will only be labeled with the participant's ID. Many subjective measures will be administered via a secure Redcap surveys. EMA assessments will be administered via a secure platform (MetricWire). These will also be identified by participant ID, which will be entered into the computer prior to subject data entry. Biological markers of nicotine exposure will be marked with participant ID, date and session number and stored in a -80 freezer that is locked within the laboratory suite. No information will be shared with participants' clinicians unless the participant requests this in writing. All investigators and staff have undergone (and any new staff will undergo) human subjects' ethics training and are fully conversant with ethical principles around confidentiality. Assessments, consenting and study procedures will be closely supervised by the PI.

Nicotine Withdrawal/Treatment Referral. Participants will be fully informed at the start of the study about potential risks, including symptoms of nicotine withdrawal and risks of continued tobacco use. Participants who are seeking treatment for smoking cessation are not eligible to participate. Information regarding smoking cessation treatment resources and appropriate referrals will be provided to all participants who consent but do not pass screening for any reason. In addition, smoking cessation treatment information will be provided at the conclusion of the study for any individuals interested in quitting at that time.

Increased Smoking of Study Cigarettes. Past two-week timeline follow-back assessed at V1 will be used to establish a baseline average of usual brand cigarettes smoked per day. Past-week timeline follow-back will be reassessed at each subsequent weekly visit, and changes in total cigarettes smoked per day relative to

baseline will be calculated. As with our prior studies utilizing investigational cigarettes, participants exhibiting ≥ 200% increase in smoking rate will be removed from the study to prevent increased toxicant exposure.

Protection of pregnant women and fetuses. Sexually active females who are not pregnant must agree to use appropriate contraception during the course of the study, and to notify the study physician if they become pregnant during the study. A urine pregnancy test will be conducted during screening and must be negative for participants to continue with the study. A second urine pregnancy test will be conducted at visit 1, prior to dispensing any study cigarettes. As such, two sequential negative pregnancy tests are required before any study cigarette administration.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

If the participant does not have an unlimited data plan, additional phone costs may incur. All other study costs, including any procedures related directly to the study, will be paid for by the study.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Hypothesis testing will be conducted using generalized mixed models, which are well-equipped to handle missing data, even when data is missing not completely at random.[75] Multiple imputation will also be used to further address potential bias resulting from missing data.

Specific Aim 1 will examine the effects of NNCs versus VLNCs on: a) changes in cigarettes smoked per day, nicotine dependence, withdrawal symptoms and pain across the 5 weekly visits (V1 through V5), and b) pre-post intervention changes in withdrawal and pain following 24hr abstinence. For both sets of models, Group will be entered as a between-subjects factor with 2 levels (NNC or VLNC), and Session will be included as a within-subjects factor with 5 (week) or 2 (pre- vs post-intervention) levels. Baseline pain and FTCD scores, assessed at screening, will be included along with sex as covariates. We predict that the VLNC group will exhibit decreasing nicotine dependence and smoking frequency across the 4 weeks of study cigarette use, with no change for the NNC group (i.e., Group x Week interactions). Based on our prior work,[42] we predict only a minimal increase in withdrawal during the first week of VLNC use, with no group differences in withdrawal or pain during remaining weekly visits. During 24-hr abstinence, we predict a Group x Session interaction, such that the VLNC group will exhibit pre- to post-intervention *decre ases* in withdrawal and pain, with no change for the NNC group. *Secondary analyses* will evaluate effects of abstinence, controlling for weekly changes during *ad lib* smoking, by including withdrawal and pain assessed at V1 (pre-intervention) and V5 (post-intervention) as time-varying covariates.

Specific Aim 2 will be to examine the effects of NNCs versus VLNCs on the bidirectional, within-person associations between momentary reports (assessed with EMA) of pain, negative affect, and smoking urge and behavior. Longitudinal associations between smoking/smoking urge and a) pain intensity, b) pain interference, and c) negative affect will be evaluated in separate models. The first set of models will examine each pain measure as a predictor of smoking urge/intent to smoke at each time point. The second set of models will examine recent smoking (i.e., having smoked within the past 15 minutes) as a predictor of each pain measure. Models will include repeated assessments (Level 1) nested within participants (Level 2), nested within weeks (Level 3), with random intercepts. Cigarette condition (NNC or VLNC) and its interaction with week will then be entered to examine the moderating effects of study cigarette use on these within-person associations.

Exploratory Aim 3 will examine the effects of NNCs versus VLNCs on pre- to-post-intervention changes in smoking for pain-related cognitions, assessed at V1 and V5, including smoking to cope with pain, interest in quitting smoking, quit self-efficacy, pain catastrophizing, and pain self-efficacy. For each model, Group will be entered as a between-subjects factor, and Session will be entered as a within-subjects factor.

Sensitivity Analyses will examine the potential impact of a) VLNC compliance (described above) and b) non-opioid analgesic use on the results of primary analyses. Analgesic use will be coded as yes/no at screening and at each weekly visit for the following medication classes: NSAIDS, anticonvulsants, antidepressants, other CNS depressants, muscle relaxants, migraine medications, and corticosteroids. Sensitivity analyses will then examine the impact of weekly use of each medication class as time-varying covariates in primary models.

Sample size determination. Sample size was estimated using G*Power 3.1, assuming 85% power at alpha=0.05 for detecting group by session interactions in Aim 1 (see Statistical Design and Power for additional details). For effect sizes corresponding to Cohen's d = 0.4 to 0.6, assuming a conservative estimate of the correlation between repeated measurements of 0.4, our proposed sample size of 48 will provide 90% to 99% power for detecting group by weekly session interactions (5 measurement occasions per group), and 70% to 96% power for detecting group by abstinence session interactions (2 measurement occasions per group). Importantly, power for detecting abstinence session interactions is improved (ranging from 77% to 98%) if repeated measures correlation is higher, as suggested by our preliminary data. These calculations also do not take into account the inclusion of baseline covariates that are likely to improve power.[57] Moreover, a loss of 33% of the sample due to VLNC non-compliance during sensitivity analyses will still yield statistical power of 96% and 78% for analyses with 5 measurement occasions or 2 measurement occasions, respectively, under a moderate scenario in which Cohen's d = 0.5 and the correlation between repeated measures = 0.5. Given the increase in statistical power associated with EMA due to a) decreasing error variance,[58] and b) increasing the number of repeated assessments,[59] it is expected that sample sizes estimates determined for Aims 1 and 3 will provide ample power for detecting group differences in reciprocal smoking-pain associations in Aim 2.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Data quality will be maintained by entering most measures directly into Redcap, minimizing errors in data entry and allowing for a recorded audit trail of all data entered. Surveys and other records will be checked for accuracy and completeness by the clinical research specialist during the session in which they are collected to allow for immediate correction if possible. Any deviations from the protocol will be carefully documented. Completion of EMA data will be checked after the first 24 hours of data collection, and participants not responding to prompts will be contacted by phone to trouble-shoot difficulties. Thereafter, enrolled participants' EMA data will be checked regularly and reviewed with participants at weekly visits to address any new or ongoing concerns with non-adherence. On a regular basis (minimum once per month), the PI will review the database for accuracy of the data. When data quality issues arise, they will be immediately addressed and communicated to study staff and appropriate solutions will be identified and documented. Data quality will also be reviewed at biweekly meetings between the PI and clinical research specialist, including inspection of participant binders. In addition, IRB applications, progress reports and research participant recruitment strategies will also be regularly reviewed; this will include maintenance of adequate gender and minority participation in the proposed studies, and attempts to equate, to the extent possible, gender, age and other criteria to facilitate comparisons between groups.