AN EXAMINATION OF DIFFERENCES IN
ACUTE NICOTINE WITHDRAWAL SYMPTOMS BETWEEN
ELECTRONIC NICOTINE DELIVERY SYSTEM
AND COMBUSTIBLE CIGARETTE USE

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ABSTRACT OF THE DISSERTATION

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Acute nicotine withdrawal symptoms have been identified as a barrier to cessation among combustible cigarette smokers. Despite its clinical relevance, work examining acute withdrawal manifestation in electronic nicotine delivery systems (ENDs) users has been sparse. Of the few investigations that have examined withdrawal from ENDs broadly, findings indicate that its symptom intensity is less than withdrawal from combustible cigarettes. The current study aimed to examine multimodal differences in acute nicotine withdrawal symptoms between ENDs users and combustible cigarette smokers. Users of ENDs (n=24) or combustible cigarettes (n=10) completed assessments of autonomic reactivity when using nicotine ad-libitum, and after 24-hour abstention. Users also self-reported withdrawal intensity during abstention via ecological momentary assessment. ENDs and combustible cigarette users evinced differences in self-reported withdrawal symptom trajectory. ENDs users reported a more rapid decrease in positive affect than combustible cigarette users, and combustible cigarette users displaying trending effects suggesting a more rapid increase in sadness withdrawal symptoms than ENDs users.
during 24-hour abstention. No differences in autonomic reactivity were observed between groups. Generalization of findings is limited due to the small and unbalanced sample. However, this study suggests that ENDs and combustible cigarette users perceive differences in their withdrawal experiences, which merits continued investigation.
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Introduction

Electronic nicotine delivery systems (ENDs), battery powered devices that deliver nicotine via inhaled aerosol, have seen a precipitous increase in use in the past decade (King et al., 2014). Since ENDS’ introduction to US consumers in 2006, lifetime (‘ever’) use among US adults has risen from 1.8% of the population in 2010 to 16.3% in 2016 (Bao et al., 2018; El-Shahawy et al., 2019), with 4.5% of adults reporting current use (Mirbolouk et al., 2018). Despite the increasing prevalence of ENDS use and the documented association between combustible nicotine use and morbidity and mortality (National Center for Chronic Disease, 2014), there continues to be major gaps in understanding the relative abuse liability of ENDS. One area of inquiry that may inform this question of long-term ENDS use outcomes is the extent to which ENDS use withdrawal symptoms are similar or dissimilar to that of combustible cigarette smoking (Ponzoni et al., 2015; Hughes & Callas, 2019). Given that nicotine withdrawal symptom intensity is negatively associated with successful smoking cessation among combustible cigarette smokers (Hughes et al., 1994; Piper et al., 2011; Piasecki et al., 1998; Shiffman et al., 2007), understanding ENDS’ relative effect on nicotine withdrawal intensity would inform how long-term use impacts later likelihood of nicotine cessation.

Nicotine Withdrawal Symptoms

In combustible cigarette smoking, nicotine withdrawal symptoms may persist for several weeks (Hughes et al., 1994; Hughes, 2007), but can manifest as early as 30 minutes post cigarette use (Baker et al., 2004; Hendricks et al., 2006). Contextualizing the experience of acute nicotine withdrawal symptoms is especially important to consider, as the rapid onset of nicotine withdrawal, even in the absence of a cessation
attempt (i.e., withdrawal experienced after waking), may enhance the salience of nicotine withdrawal symptoms and shape nicotine users’ perceptions of negative cessation expectancies. In fact, during acute nicotine withdrawal, combustible cigarette smokers begin to experience a number of clinically significant withdrawal symptoms, including changes in their subjective experience (e.g., increased craving for nicotine and greater negative affect, Leventhal et al., 2007; Hendricks et al., 2006) and behavioral changes (e.g., deficits in attention, sleep disturbances, Shiffman et al., 2006).

Importantly, nicotine is a vasoconstrictive substance whose acute use, either via ENDS or combustible cigarette inhalation, activates the sympathetic nervous system, leading to autonomic changes such as increased heart rate and blood pressure (Benowitz & Gourlay, 1997, Haass & Kubler, 1997; Garcia et al., 2020; Moheimani et al., 2017). Of note, work has found that relative to smoking combustible cigarettes, ENDS use is associated with a lesser increase in these autonomic parameters, and specifically sympathetic nervous system activation, although it is unclear whether this is due to differences in constituent content, pharmacokinetic differences in nicotine delivery, or variance in smoking and vaping puff topography (Garcia et al., 2020). Sympathetic activation as elicited by nicotine use is linked to poorer cardiovascular functioning such as the development of arrhythmia, ischemia, and atherosclerosis (Benowitz, 2003; Libby et al., 2016; Middlekauff et al., 2014), as well as an increased risk of cardiovascular disease (Benowitz, 2003). With regard to the experience of acute withdrawal, work has shown that when combustible cigarette smokers abstain from nicotine use for 12 to 24 hours they display a number of physiological changes, including decreases in heart rate
and systolic and diastolic blood pressure, relative to smoking ad-libitum (Leventhal et al., 2007; Hendricks et al., 2006).

**Nicotine Withdrawal Among ENDS Users**

The experience of nicotine withdrawal among ENDS users, especially acute nicotine withdrawal (e.g., first 24-hours), is a notably underexplored area in the emergent ENDS literature. Extant research has documented evidence that ENDS use aerosol elicits withdrawal among rodents (Kallupi et al., 2019) and humans (Dawkins et al., 2012; Dawkins & Corcoran, 2014). Hughes and colleagues (2020) examined withdrawal profiles in current daily ENDS users with no history of prior combustible cigarette use who abstained from ENDS use for one week. Participants exhibited significant increases in withdrawal over the course of their abstention period, including increased craving and irritability, and decreased positive affect and heart rate. Among current daily ENDS users who reported former combustible cigarette use (past year use, but less than 5 cigarettes in the past month) who abstained for one week, they also exhibited increases in all Diagnostic and Statistical Manual-5 (DSM-5) withdrawal symptoms and decreased heart rate, with withdrawal symptoms peaking in the first two days (Hughes & Callas, 2019). While neither investigation examined withdrawal among combustible cigarette-only smokers, the authors noted that withdrawal severity was less intense than has previously been observed among daily combustible cigarette-only smokers (Hughes et al., 2020; Hughes & Callas, 2019).

**Observed Differences between ENDS and Combustible Cigarette Use Withdrawal**

Initial work has begun to directly compare acute and prolonged withdrawal intensity of ENDS and combustible cigarette use (Ponzoni et al., 2016; Hughes & Callas,
Differences in withdrawal symptom presentation between ENDS and combustible cigarettes were first examined in a sample of mice, who were either exposed to ENDS aerosol, nicotine smoke, or uncontaminated air for three 30-minute sessions per day, over the course of seven weeks (Ponzoni et al., 2016). Rodents’ urinary cotinine levels were assessed at baseline, as well as after weeks 4 and 7 of the exposure period. Immediately after final exposure, a subset of mice were sacrificed to examine neural cotinine concentrations and changes in nicotinic receptors after the administration period. The remaining mice were administered mecamylamine hydrochloride, a nicotine antagonist to induce immediate withdrawal, immediately after final nicotine exposure as a means of observing acute withdrawal symptoms. The mice also completed behavioral assessments of nicotine withdrawal 24 hours, 15 days, and 30 days after their last exposure. At the end of the exposure period, both aerosol and smoke exposed mice exhibited elevated cotinine levels and an upregulation of nicotinic receptors relative to controls; the nicotine exposed mice did not differ from one another in these indices. However, other differences in withdrawal effects emerged. Smoke-exposed mice exhibited significantly greater increases in both behavioral (e.g., increased scratching and sniffing) and physiological (e.g., teeth chattering, body tremors) indices of withdrawal relative to aerosol exposed mice during acute withdrawal; both groups displayed greater withdrawal symptoms than air-exposed mice. Furthermore, smoke exposed mice displayed more behavioral and physiological symptoms of withdrawal after prolonged withdrawal periods (24 hours, 15 days, 30 days) than aerosol exposed mice; the exception to this was that aerosol exposed mice exhibited a more perseverative profile (i.e., significantly greater spontaneous digging) at 15- and 30-days post-exposure than did smoke exposed mice. These findings
suggest that among mice, both ENDS vapor and combustible cigarette smoke exposure leads to acute and prolonged withdrawal, but withdrawal from combustible cigarette smoke is more severe.

Just one published human study to date has directly compared withdrawal symptoms during a recent quit attempt in ENDS-only and combustible cigarette-only users (Hughes & Callas, 2019). Data were drawn from participants in the US Population Assessment of Tobacco and Health (PATH) survey who made a combustible or ENDS cessation attempt and were queried regarding their retrospective recall (yes/no responding) of subjective (e.g., feeling angry, anxious, depressed) and behavioral (e.g., difficulty concentrating, eating more, insomnia, restlessness) nicotine withdrawal symptoms. Individuals who attempted to cease from ENDS-only use were less likely to retrospectively report the presence of any nicotine withdrawal symptoms compared to individuals who attempted to cease from only combustible cigarette smoking (40% vs. 71%). Moreover, among successful quitters, ENDS-only users reported fewer nicotine withdrawal symptoms than combustible cigarette users.

Early emerging evidence of differences in subjective, behavioral, and physiological withdrawal symptoms between combustible cigarette and ENDS use may be accounted for, at least in part, by differences between smoke and aerosol chemistry. As one example, nicotyrine, which forms in ENDS via oxidation in e-liquid that has been exposed to air (Martinez et al., 2015; Abramovitz et al., 2015), inhibits cytochrome CYP2A6 (Kramlinger et al., 2012), an enzyme involved with the metabolism (clearance) of nicotine (Nakajima et al., 1996; Liu et al., 2013). Relevant animal work has indeed shown that the presence of nicotyrine inhibits nicotine metabolism. Among mice who
were administered nicotine intravenously, those mice who were pre-treated with nicotyrine exhibited significantly greater nicotine concentrations in their blood, brain, and liver 60 minutes after nicotine administration than mice who received no nicotyrine (Stålhandske & Slanina, 1982). Although this work was conducted before the advent of ENDS, extant data has found that ENDs aerosol generates anywhere between 2-63 times more nicotyrine per unit of nicotine than in combustible cigarettes (Son et al., 2018).

While no work has directly examined this in humans, the previous evidence suggests that long-term inhalation of ENDS aerosol containing nicotyrine may delay nicotine clearance and in turn, attenuate acute nicotine withdrawal symptom intensity due to the more gradual decline of nicotine in the bloodstream.

There is some also evidence to suggest that carbon monoxide (CO), which is present in combustible cigarette smoke but not ENDS aerosol, plays a role in nicotine dependence and withdrawal (Milne et al., 2012). To examine this possibility, daily heavy (20+CPD) cigarette smokers who were asked to quit for 24-hours were brought to a laboratory, wherein they were assigned to one of four conditions: (1) administration of inhaled CO and nicotine via nasal spray, (2) inhaled air and a nicotine nasal spray, (3) inhaled CO and a placebo nasal spray, or (4) inhaled air and placebo spray. Before and after administration, participants completed an assessment of nicotine craving. Results showed that those smokers who received inhaled CO and nicotine via nasal spray displayed significantly greater reductions in craving than those participants receiving either CO or nicotine alone. The authors suggest that since CO influences learning and memory processes (Cutajar & Edwards, 2007), the presence of CO may maintain nicotine dependence by serving as an additional associated signaling molecule for withdrawal-
related relief. This finding suggests that CO in combustible cigarettes may have a secondary effect of increasing the perceived intensity of nicotine withdrawal among smokers, as the absence of carbon monoxide in the bloodstream during withdrawal periods may serve as an additional withdrawal relevant signal, heightening smokers’ awareness of their withdrawal state.

**Gaps in Existing Literature**

While initial evidence suggests that ENDS and combustible cigarette nicotine withdrawal symptom intensity may differ, there are a number of limitations within the existing literature that render potential conclusions premature. First, no studies have prospectively evaluated the nicotine withdrawal experiences of ENDS users compared to combustible cigarette smokers throughout an acute withdrawal period. In Hughes & Callas’ (2019) investigation, self-reported withdrawal intensity was assessed retrospectively. Previous work has found that relative to in-vivo reporting of withdrawal intensity, retrospective assessment is associated with participants reporting more intense withdrawal symptoms (Shiffman et al., 1997). Second, while Hughes & Callas (2019) captured both subjective and behavioral withdrawal symptoms, they were assessed solely via self-report. Indeed, no studies have evaluated subjective, behavioral, and physiological symptoms of acute ENDS withdrawal symptoms among humans in a laboratory setting; while Ponzoni and colleagues (2016) captured physiological and behavioral indices of withdrawal, preclinical animal studies are limited in their generalizability to human physiology. These limitations impede firm conclusions from being drawn as to the nature and course of acute nicotine withdrawal symptoms among
ENDs users and suggests that further laboratory work is necessary to better understand the nuances of nicotine withdrawal presentation among ENDs users.

**The Role of Nicotine Withdrawal in Nicotine Dependence and Cessation**

The lack of clarity with regard to how withdrawal symptoms manifest in ENDs use also impedes our understanding of the comparative effects of ENDs use more broadly, including the course of nicotine dependence and potential cessation outcomes. Indeed, among combustible cigarette smokers, withdrawal severity has important clinical implications in both domains. Nicotine dependence and withdrawal intensity are positively associated among current combustible cigarette smokers (Rios-Bedoya et al., 2008; Payne et al., 1994; Shiffman et al., 2004). Furthermore, among daily combustible cigarette smokers elevated subjective nicotine withdrawal symptoms (greater nicotine craving and negative affect) are positively associated with nicotine intake and likelihood of smoking in response to internal and external smoking cues, an index of greater nicotine dependence (Baker et al., 2012). The authors explain these findings by suggesting a causal pathway whereby smokers who are more sensitive to falling levels of nicotine in their bloodstream experience more intense subjective withdrawal symptoms, which promotes corrective action (e.g., smoking) to bring them back into a homeostatic nicotine balance. Over time nicotine withdrawal may progressively maintain and intensify nicotine dependence, due to the negatively reinforcing experiences of using nicotine in the context of withdrawal (Baker et al., 2004).

Utilization of smoking to relieve withdrawal-related negative affect can further lead to generalized learning that smoking can be used as a strategy for broader negative affect reduction, leading to an increase scope and frequency of nicotine use behavior.
Indeed, this progression can be observed in the subjective reports of combustible cigarette smokers’ changing motivations to use over the duration of their time as a smoker; in accord with the opponent process theory of drug use, smokers have been found to initially report smoking to receive positive reinforcement and later, become increasingly likely to report smoking to relieve withdrawal related effects (Kassel et al., 2003). More frequent and pervasive nicotine use, spurred on by this generalization of nicotine use behavior driven by negative reinforcement, leads to greater dependence on the substance over repeated learning trials. This progression of worsening dependence has previously been observed, as there is a positive association between nicotine dependence and years spent smoking (Donny et al., 2016).

Likewise, greater nicotine withdrawal symptom intensity during a quit attempt has been implicated in a lower likelihood of successful nicotine cessation. Among a sample of combustible cigarette smokers who intended to cease within the next three months, self-reported behavioral (i.e., greater sleep disturbance) and subjective (i.e., greater anxiety and depression) nicotine withdrawal intensity during their cessation attempt was associated with a greater likelihood of relapse (Zhou et al., 2009). Moreover, Piasecki and colleagues (2003) examined whether the time course of nicotine withdrawal symptom intensity during a quit attempt was associated with successful cessation among a sample of combustible cigarette smokers who were randomly assigned to pill and patch placebo, nicotine patch and pill placebo, patch placebo and bupropion, or bupropion and nicotine patch. Results revealed that a positive linear increase in withdrawal symptom intensity, withdrawal symptom volatility over the course of smokers’ quit attempt, as well as greater mean withdrawal symptom intensity over the course of the cessation attempt
each predicted lower likelihood of continuous abstinence at 6-month follow-up regardless of assigned condition.

In addition, acute withdrawal symptom intensity appears to be negatively associated with cessation failure. Greater acute nicotine withdrawal intensity in combustible cigarette smoking is associated with an increased likelihood of early relapse after a cessation attempt (al’Absi et al., 2004). Furthermore, among a population-based sample of current and former smokers, retrospective recall of greater subjective (craving, restlessness, anxiety, irritability, depression) and behavioral (difficulty concentrating, shakiness, drowsiness) withdrawal symptoms 24-48 hours after a cessation attempt was associated with increased odds of overall cessation failure (Xian et al., 2003). In addition, Hendricks and colleagues (2014) found that among treatment seeking combustible cigarette smokers, elevated self-reported negative affect and challenges concentrating, as well as greater decreases in heart rate, during the first four hours of withdrawal were associated with a lower likelihood of successful cessation 12-weeks post-quit attempt. These findings from combustible cigarette literature suggest that understanding acute withdrawal intensity profiles can provide additive predictive value in understanding the likelihood of successful cessation, and further highlight the benefit of examining acute withdrawal intensity from ENDS use. Taken together, the reviewed findings suggest that to better understand the role of withdrawal symptom intensity in nicotine cessation it is important to consider both the timing and course of withdrawal, as both are important predictors of combustible cigarette cessation success.

**Potential Implications of Differential Withdrawal between ENDS and Combustible Cigarettes**
Understanding whether ENDs users exhibit less intense acute nicotine withdrawal symptoms than combustible cigarette smokers will fill a considerable knowledge gap and has a number of important clinical implications to understanding the long-term outcomes of ENDs use. Specifically, understanding the experience of withdrawal from ENDs use is of particular importance in the context of its categorization as potentially harm-reducing, and/or whether these devices may effectively promote combustible cigarette cessation (Grana & Ling, 2014; Yao et al., 2016). If ENDs use does indeed elicit less intense withdrawal symptoms, it would support the implementation of ENDs as harm-reducing for combustible cigarette smokers. However, if ENDs use elicits equivalent or greater intensity withdrawal symptoms as compared to combustible cigarette smoking, it would suggest that these products may have a deleterious effect on public health due to an immediate negative impact on the user as well as their potentiating greater nicotine use.

**ENDs Withdrawal and Nicotine Dependence**

Characterizing the withdrawal intensity of ENDs use can directly inform our understanding of the abuse liability of these devices relative to combustible cigarettes, and in turn, speaks to the broader public health implications of ENDs’ growing prominence. Understanding the abuse liability of these products can speak to whether the emergence of ENDs as a prominent nicotine-use modality may lead to greater overall nicotine use, whereby ENDs could serve as a nicotine “gateway” for some non-users. Of note, ENDs serving as a “gateway” to combustible cigarette smoking would not assume that all, or even the majority, of non-combustible cigarette smokers who vape would eventually smoke. Instead, ENDs would be appropriately considered a “gateway” to combustible cigarette smoking if their use increased the likelihood of later combustible
cigarette smoking for a number of individuals greater than what would be assumed by common nicotine addiction liability (Vanyukov et al., 2012). This potential “gateway” effect can be observed most acutely among adolescents, for whom ENDSs are already the preferred nicotine-use modality (McCabe et al., 2017), with 24.7% reporting past 30-day ENDS use as of 2017 (Miech et al., 2019). Indeed, evidence suggests that adolescent ENDS use is associated with later combustible cigarette smoking (Barrington-Trimis et al., 2016), and moreover, this effect is unidirectional, as combustible cigarette smoking has not been linked to later ENDS use (Bold et al., 2018). Research in this area has also found that ENDS use is a stronger predictor of combustible use for adolescents who, based on sociodemographic factors (e.g., greater parental support, lower rebelliousness), are thought to be at a lower risk for nicotine use (Wills et al., 2017). This further suggests that ENDS may serve to broaden the potential population of nicotine users. This “gateway” effect is even more pronounced in users of flavored ENDSs, as flavored ENDS use further increases the risk of later combustible cigarette use (Dai & Hao, 2016).

Gaining a better understanding of acute nicotine withdrawal intensity from ENDS use may speak to a potential mechanism underlying this “gateway” effect. Specifically, the intensity of nicotine withdrawal symptoms among ENDS users will influence how negatively reinforcing nicotine use, broadly, is to ENDS users. If, for example, ENDS users experience similarly intense withdrawal symptoms as combustible cigarette smokers it may indicate that they would be more motivated to experiment with alternative nicotine delivery modalities such as combustible cigarettes to more effectively relieve withdrawal symptoms. In short, understanding withdrawal intensity in ENDS
users will speak to the degree to which ENDS use sensitizes further nicotine experimentation, and account for potential mechanisms underlying this sensitization.

Withdrawal and Nicotine Cessation

Understanding comparative acute nicotine withdrawal symptom severity between ENDS use and combustible cigarette smoking also will inform whether transitioning from combustible cigarettes to ENDS is beneficial or iatrogenic to long-term cessation. Before exploring this idea, it is important to note that while there is user enthusiasm for utilizing ENDS as a direct cessation aid, evidence suggests that the utility of ENDS in this domain has been equivocal (Bullen et al., 2013; Brown et al., 2014; Vickerman et al., 2013). There is evidence that ENDS use is associated with greater odds of making a nicotine cessation attempt (Zhu et al., 2017; Brose et al., 2015) and >50% combustible cigarette reduction (Berry et al., 2018). Moreover, a recent longitudinal population-based examination of ENDS use in the UK found that the odds of a successful cessation attempt increased as ENDS use became more prevalent (Beard et al., 2019). However, a recent meta-analysis of clinical and observational studies examining the use of ENDS as a cessation aid found that the odds of successful cessation are 28% lower for combustible cigarette smokers using ENDS as a cessation aid relative to those smokers who use alternative cessation aids (Kalkhoran & Glantz, 2016).

Indeed, if ENDS use alone would result in fewer withdrawal-related barriers to cessation than using combustible cigarettes alone, then ENDS may be beneficial to combustible cigarette cessation as a nicotine step-down approach. This may be especially beneficial for individuals who are in the precontemplation stage of smoking cessation. Specifically, demonstrating lower intensity acute withdrawal symptoms from ENDS
would suggest that combustible cigarette smokers who transition to ENDS use may, regardless of their current motivation to quit, experience lower distal barriers to cessation. Moreover, existing evidence supports this hypothesized pathway, as naturalistic differences in withdrawal intensity among combustible cigarette smokers has been shown to be predictive of cessation success. Combustible cigarette smokers who display lower CYP2A6 activity (and thus slower nicotine metabolism) are more likely to successfully quit when using NRT, due in part to a more gradual onset of nicotine withdrawal symptoms (Ho et al., 2009; Lerman et al. 2006; Schnoll et al., 2009). This suggests that a transition from combustible cigarettes to ENDS, if doing so results in lesser intensity and more gradual-onset withdrawal symptoms, can increase the odds of long-term nicotine cessation relative to the continued use of combustible cigarettes.

**Aims**

The current project aimed to conduct a novel, prospective, human laboratory study that utilizes multi-method assessments to evaluate the subjective and physiological aspects of withdrawal symptoms among ENDS-only users and combustible cigarette-only smokers. Single users from each product category were examined to isolate withdrawal effects from individual product classes. This investigation is the first laboratory test examining acute nicotine withdrawal among ENDS users that captures subjective and physiological aspects of withdrawal concurrently, and the first to compare their acute nicotine withdrawal symptom profiles to combustible cigarette smokers. Two significant outcomes from this research are expected: (1) To determine the differential time course of acute nicotine withdrawal symptoms (e.g., self-reported mood, physical symptoms, craving) between long-term ENDS-only users and combustible cigarette-only smokers;
and (2) identify key multimodal withdrawal differences (e.g., changes in sympathetic and parasympathetic reactivity) between ENDS-only users and combustible cigarette-only smokers after an acute withdrawal period. Specifically, it was hypothesized that combustible cigarette-only smokers would exhibit a more rapid linear increase in self-reported negative affect, craving, and physical withdrawal symptoms, and greater decrease in positive affect, during a 24-hour acute withdrawal period relative to ENDS-only users. Furthermore, consistent with previous literature that has found that use of ENDS results in less change in autonomic parameters than combustible cigarettes (Garcia et al., 2020), as well as differences in constituent content between devices that are linked to autonomic dysfunction (e.g., carbon monoxide; Middlekauff et al., 2014), it was hypothesized that ENDS-only and combustible cigarette-only users would display differences in autonomic reactivity during acute withdrawal. Specifically, it was hypothesized that relative to ENDS-only users, combustible cigarette-only smokers would exhibit greater changes in autonomic reactivity from ad-libitum use to acute withdrawal (i.e., greater decrease in respiratory sinus arrhythmia (RSA), greater lengthening of ventricle pre-ejection period (PEP)).
Method

Participants

Participants were daily ENDS-only or combustible cigarette-only users.

Participants met the following inclusion criteria: (1) Age 18-45; (2) ownership of a mobile device compatible with iOS or Android operating systems, including a data use plan; (3) daily use of only their preferred nicotine inhalation device for at least one year; (4) willingness to try to abstain from nicotine use for 24 hours; (5) ability to speak and read English fluently; (6) daily use of preferred nicotine inhalation device within 30 minutes of waking. Exclusion criteria included: (1) Endorsement of current (past-month) or lifetime psychotic or manic symptoms and/or current suicidal or homicidal ideation; (2) self-reported pregnancy; (3) inability to provide written informed consent; (4) current evidence of a non-nicotine substance use disorder (5) self-reported severe visual or hearing impairments; (6) medical condition (e.g., cardiac illnesses, chronic obstructive pulmonary disease, emphysema, bronchitis) or medication use (e.g., betablockers, benzodiazepines) that may impact autonomic parameters; (7) greater than 50% reduction in their nicotine intake in the past month; (8) self-reported night shift work during study enrollment, which would interfere with completion of study procedures during abstention period; (9) past-month use of both ENDS and combustible cigarettes. In addition, ENDS-only users were excluded if they reported currently using ENDS as a smoking cessation aid. Participants were also excluded at time of initial session attendance if they self-reported: (1) strenuous physical activity, lasting over an hour, occurring within the last two hours; (2) drinking a caffeinated beverage within the last four hours; (3) using any recreational substance other than nicotine, alcohol, or marijuana within the last 24 hours;
(4) using any medication that could cause drowsiness (e.g., antihistamines) in the last 24 hours.

**Measures**

**Online Questionnaire Measures**

*Smoking History Questionnaire (SHQ).* The SHQ is a 30-item self-report questionnaire that assesses combustible smoking history (Brown et al., 2002). Items capture domains such as smoking rate, years of consumption, quit attempt history, and family smoking history. The SHQ has been reliably utilized as a measure of smoking history (Zvolensky et al., 2004).

*E-Cigarette History Questionnaire (EHQ).* The EHQ is a 26-item self-report questionnaire that assesses ENDS use history. The EHQ was directly adapted from the SHQ (Brown et al., 2002), with changes to question verbiage to reflect vaping, rather than combustible cigarette use. The adapted version captures descriptive information about e-cigarette use, such as years spent vaping regularly, number of quit attempts, years of consumption, and family vaping history.

**Laboratory Visit & Ecological Momentary Assessment Measures**

*Wisconsin Smoking Withdrawal Scale (WSWS).* The WSWS is a 28-item self-report questionnaire which assesses subjective and behavioral nicotine withdrawal (Welsch et al., 1999). Participants utilize a 5-point Likert-type scale (0=strongly disagree to 4=strongly agree) to indicate overall withdrawal symptom intensity, as well as domain-specific withdrawal intensity. In the current study, overall withdrawal intensity, as well as subscales capturing anger, anxiety, sadness, hunger, and nicotine craving were examined. The WSWS has exhibited good construct validity and reliability in previous
investigations (West et al., 2006). The full 28-item scale was administered during the first and second in-person appointments, while an abbreviated 10-item version was administered during EMA data collection, with items reworded so that they would assess current (rather than past 24-hour) withdrawal symptoms.

*Positive and Negative Affect Schedule-Short Form (PANAS-SF)*. The PANAS-SF is a 10-item self-report questionnaire which assesses current, state level, mood (i.e., negative and positive affect [NA; PA]) (Thompson, 2007). Participants rate items on a 5-point Likert-type scale (1 = very slightly or not at all to 5 = extremely) to indicate how they are currently feeling. The PANAS-SF has exhibited good internal consistency as well as convergent and criterion validity (Thompson, 2007). The PANAS-SF was administered during the first and second in-person appointments, as well as during EMA data collection.

*Dot Tracking Task*. The dot tracking task is a brief computerized task used to manipulate participants’ attentional demands and index participants’ autonomic functioning (Muhtadie et al., 2015). After initial instructions, participants were shown a computer screen with 12 dots, two of which were initially yellow, and 10 of which were black. The yellow dots subsequently turned black, and all the dots move at random around the screen. Participants were asked to track the initial yellow dots in their peripheral vision while focusing their gaze on a fixation cross in the center of the screen. When the dots came to a stop, participants were asked to select which dots were initially yellow. There was a total of 16 trials that progressively increased in difficulty by increasing the number of dots that were initially yellow and turned to black. During the task, heart rate, and cardiac output were continually assessed, to capture changes in sympathetic and
parasympathetic nervous system reactivity from rest as a function of increased attentional demands. The Dot Tracking Task was administered during the first and second in-person appointments.

**Procedure**

**Telephone/Online Screening.** Upon initial contact with the research laboratory, participants provided verbal consent for completion of a brief phone screening to assess for eligibility. Eligible participants were invited to participate in a study investigating the relation between nicotine inhalation modality and withdrawal symptom intensity during acute deprivation. If scheduled for a lab visit, they provided electronic consent for, and completed, an online questionnaire battery in advance (see Online Questionnaire Measures, above).

**Ad Libitum Use Visit.** Participants then attended an in-person laboratory visit. After written informed consent procedures, participants were queried as to their most recent instance of nicotine use, and if it was not within the last hour, were asked to use their nicotine delivery device of choice to standardize nicotine exposure (i.e., to ensure satiation/minimal withdrawal symptoms during the assessment); participants continued the experiment regardless of whether they opted to use nicotine. Participants then provided confirmation of ad-libitum cotinine concentration by providing a saliva sample, which were tested immediately for cotinine utilizing Nicalert cotinine test strips (Cooke et al., 2008). Nicalert salivary cotinine strips provide a semi-quantitative measure of the cotinine concentration present in the nicotine user’s saliva. Results are displayed in numerical levels, with each level corresponding to a range of cotinine concentration present in the sample (see Table 1 for cotinine equivalents at each level). Next,
participants completed a baseline assessment of self-reported nicotine withdrawal aspects, including the WSWS and PANAS-SF. Following self-report completion, participants were attached to several physiological sensors to continuously measure heart rate and respiration (via electrocardiograph) and impedance cardiography. Baseline recordings were collected for the initial five minutes, wherein participants were instructed to sit quietly, refrain from excessive movement, and were told an experimenter would return after the five-minute period elapsed. This was followed by a dot-tracking task to assess changes in sympathetic and parasympathetic activity from rest to engagement in an attentionally demanding activity (Muhtadie et al., 2015). After removal of sensors, participants were provided instructions on how to complete ecological momentary assessments (EMAs) using the Life Data smartphone application (LifeData, LLC). At the end of their laboratory visit, participants began their 24-hour nicotine abstention period.

**EMA Assessment during 24-hour Deprivation Period.** During participants’ 24-hour abstention period, they were prompted via push notifications on their mobile device to report their current withdrawal symptoms, including state mood, physical withdrawal symptoms, and craving, completing the PANAS-SF and WSWS. This study used a time-based design (Shiffman et al., 2008; Shiffman, 2009), with 8 prompts administered at fixed intervals (approximately 1.5 hours apart) during typical waking hours (8 AM – 12 PM). Prompts began approximately 1.5 hours after the conclusion of participants’ first laboratory visit. The timing of distributed prompts depended on participants’ ad-libitum lab visit time and participants’ anticipated time to sleep on the evening subsequent of their ad-libitum appointment. Each prompt took approximately three to five minutes to complete.
**Post 24-Hour Abstention Visit.** During the follow-up visit, participants first provided a salivary cotinine sample to verify abstinence, which was tested immediately for cotinine concentration using Nicalert cotinine test strips (Cooke et al., 2008). Those participants who exhibited a one level decrease in cotinine concentration were classified as abstinent, consistent with the 16-hour half-life of cotinine (Benowitz et al. 2002). Participants then completed a self-report battery of nicotine withdrawal symptoms (WSWS and PANAS-SF) and a follow-up physiological assessment, capturing heart rate and respiration (via electrocardiograph) and impedance cardiography. As in session 1, baseline recordings were collected for the initial five minutes, followed by a dot-tracking task. Participants were then disconnected from the physiological monitoring equipment, verbally debriefed, and compensated for participation.

**Data Analysis**

To examine changes in self-reported positive and negative affect, craving, and physical withdrawal symptoms during the 24-hour abstention period, linear growth curve models were conducted utilizing PROC SAS Mixed, SAS University Edition. Individual models were conducted to examine each dependent variable of interest (positive and negative affect, overall withdrawal severity, anger, anxiety, sadness, hunger, and craving withdrawal symptoms) separately. Models were conducted to examine the trajectory of withdrawal over the full 24-hour period, with assessment timepoints drawn from the ad-libitum product use (baseline) visit, eight assessments collected via ecological momentary assessment, and post 24-hour deprivation visit (with a maximum of ten total timepoints for each participants). Models specified an unstructured covariance structure and restricted maximum likelihood, incorporating data from all individuals who
completed at least two EMA reports. For participants who self-reported using nicotine during the 24-hour deprivation, that timepoint and all subsequent timepoints for that participant were coded as missing so as to have existing analyses only capture the course of withdrawal for individuals who maintained nicotine abstinence. In addition, if during the 24-hour abstinence period participants responded to the EMA prompt later than 30 minutes after the prompt was sent to their smart device, the timepoint was also coded as missing. Intercepts were permitted to vary, and all continuous baseline covariates were mean-centered. Theoretically relevant covariates (years of nicotine use, biological sex) were included as predictors of both the intercept and slope values. A linear time term was used to examine the presence of changes in withdrawal symptoms during the 24-hour abstention period. Linear time was coded as the number of minutes since abstinence began, as indicated by the amount of time from the beginning of the participant’s appointment to the time at which the EMA prompt was completed.

An intercepts-only model was first examined, including the main predictor (nicotine use group) and aforementioned covariates, to determine the presence of a significant intercept (i.e., common starting point) among participants or a random intercept (i.e., variable starting point) for withdrawal symptoms of interest. To improve model parsimony, covariates that did not trend towards significantly impacting the model at the intercept level (e.g., $p < .15$, due to the underpowered sample) were removed from subsequent models. A second model was then conducted, adding the linear time variable to examine the trajectory of change in relevant withdrawal symptoms. A third model was then conducted which included use group, relevant covariates, and the interaction between use group and linear time to examine whether use group predicts changes in
withdrawal symptoms over the 24-hour deprivation period. To examine the magnitude of
the effect of nicotine use group on the trajectory of withdrawal symptoms, effect size
estimates for the group by linear time interaction for each model were calculated based
on Feingold’s (2009) recommendation, where \[d = (\beta \times \text{time})/\text{SD of the outcome variable at baseline}\]. Interpretation of effect size values are consistent with Cohen’s (2013)
guidelines, wherein a \(d = 0.2\) was interpreted as a small effect, \(d = 0.5\) interpreted as a
medium effect, and a \(d = 0.8\) interpreted as a large effect. Each model was assessed for
goodness-of-fit against the previously derived model in the sequence by comparing AIC
(Akaike information criterion; Akaike, 1974) and BIC (Bayesian information criterion;

To examine changes in sympathetic and parasympathetic reactivity, as indexed by
ventricle pre-ejection period and respiratory sinus arrhythmia respectively, during 24-
hour abstention, stepwise linear regression models were conducted in SPSS version 27.
To do so, change scores were calculated to assess the shift in RSA and PEP within each
laboratory visit. Change scores were calculated by subtracting participants’ lowest
RSA/PEP minute score across the five-minute dot-tracking task from the mean RSA/PEP
scores across the five-minute baseline period. Separate models were then conducted to
examine the incremental predictive utility of nicotine inhalation modality on the change
in PEP or RSA during the 24-hour abstention visit, after adjusting for change scores
during the ad-libitum use visit at step 1 of the model, and years of nicotine use and
adherence to the 24-hour abstention period at step 2 of the model.
Due to the small sample size ($N=34$) in the existing study, significance levels of $p \leq .15$ in the subsequent analyses were interpreted as displaying trend-level significance. Findings were interpreted based on both this significance and their effect size.
Results

Sample Characteristics

A total of \( n = 961 \) potential participants were contacted by phone to be screened for potential participation. Of those participants, \( n = 238 \) consented to be screened for eligibility for the current study, with \( n = 77 \) determined as eligible upon initial screening. Of those participants, \( n = 76 \) opted to enroll in the study. Of the eligible and enrolled participants, \( N = 34 \) completed the study (\( n = 32 \) did not attend, \( n = 6 \) ruled ineligible upon review of their responses to in-person assessments of eligibility (e.g., using both ENDS and combustible cigarettes within the last month), \( n = 3 \) dismissed due to technical issues with study equipment, \( n = 1 \) did not attend the second laboratory session).

The final sample (\( M_{\text{age}} = 21.56 \) (\( SD = 6.25 \)) consisted of \( n = 24 \) ENDS-only users and \( n = 10 \) combustible cigarette-only users. The majority of participants reported their biological sex as female (55.9%) and their sexual orientation as heterosexual (85.3%). The plurality of participants reported their race as white (44.1%), with the next most commonly endorsed race being other or multiracial (32.4%) (see Table 2 for full demographic information). On average, participants reported using nicotine for 4.67 years (\( SD = 5.97 \)), with combustible cigarette only users reporting smoking 14.3 cigarettes per day (\( SD = 12.4 \)), and ENDS users reporting taking 50.3 puffs per day (\( SD = 47.9 \)). Significant differences between groups were observed in terms of their ethnicity, racial composition, sexual orientation, age, years of nicotine use, and body mass index (\( p \)'s <.001; see Table 2). Participants with a larger body mass index were also likely to be older (\( r = .381, p < .05 \)) and have used nicotine longer (\( r = .418, p < .05 \)) (see Table 3).

Linear Growth Curve Models Examining Course of Withdrawal Symptoms
Of the data used to examine the course of withdrawal symptom change across a 24-hour abstention period, 100% of participants completed assessments at the first laboratory visit. Across participants, 70.5% of participants (24 of 34 PPTs) completed 80% of EMA prompts and 38.3% (13 of 34 PPT) completed 100% of EMA prompts. In accounting for attrition due to incomplete or late-completed assessments, no significant difference in presence of usable data was observed between ENDS users (55% usable) and combustible cigarette users (49% usable); \( t(338) = 1.009, p = .341 \) (see Table 4 for additional details on response rate). EMA response rates were consistent with prior EMA investigations among substance using populations (Messiah et al., 2011; Courvoisier et al., 2012). Participants’ withdrawal levels at baseline, as self-reported via the WSWS, generally displayed a positive association with withdrawal levels after 24-hour abstention (see Table 3). Of note, baseline NA and PA levels did not exhibit a significant bivariate correlation with NA and PA after 24-hour abstention (see Table 3).

Details of the sequences of linear growth curve models for each of the withdrawal outcomes are displayed below. The covariate indicating years of nicotine use did not display trend-level significance (\( p < .15 \)) in any of the conducted models. Therefore, it was removed from the subsequent analyses; only biological sex (dummy coded, 0=male, 1=female) was included as a covariate in the below models.

*Course of Negative Affect (PANAS-NA) over 24-Hour Abstinence.* The intercepts only model suggested trend-level significance in participant biological sex on reports of baseline negative affect (\( b = -1.247, SE = 0.86, t(144) = -1.46, p = .147 \)), with males reporting greater negative affect at the intercept level. Nicotine use group (dummy coded, 0=ENDs Users 1=Combustible cigarette users) did not significantly predict intercept
variance in negative affect ($b = -0.13$, $SE = 0.93$, $t(144) = -0.14$, $p = .888$) (see Table 4). In the subsequent model examining the trajectory of negative affect over 24-hours of abstinence, a main effect of linear time was observed ($b = 0.0009$, $SE = 0.0004$, $t(32) = 2.4$, $p = .022$), suggesting a linear increase in negative affect over the course of 24-hour abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction term between nicotine use group and linear time to the model, a trend level linear effect of time was retained ($b = .0007$, $SE = 0.001$, $t(31) = 1.49$, $p = .147$), with negative affect increasing in a linear fashion throughout the course of the abstention period. There was not a significant main effect of use group ($b = -0.2682$, $SE = 0.9453$, $t(144) = -0.28$, $p = .777$), but biological sex retained trend-level significance at the intercept level ($b = -1.256$, $SE = 0.85$, $t(144) = -1.48$, $p = .142$), with males exhibiting greater negative affect at the intercept level. The interaction between use group and linear time was not significant ($b = .0005$, $SE = 0.0008$, $t(144) = .65$, $p = .52$), with the effect size calculation showing a small effect of the interaction ($d = .17$). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Positive Affect (PANAS-PA) over 24-Hour Abstinence.** The intercepts only model found that neither biological sex ($b = -1.374$, $SE = 1.00$, $t(144) = -1.37$, $p = .172$) nor nicotine use group (dummy coded, 0=ENDs Users 1=Combustible cigarette users; $b$ = -0.107, $SE = 1.08$, $t(144) = -0.10$, $p = .921$) predicted intercept variance in positive affect (see Table 5). Due to this, biological sex was removed from subsequent models. In the subsequent model examining the trajectory of positive affect over 24-hours of abstinence, a main effect of linear time was observed ($b = -0.002$, $SE = 0.001$, $t(32) = -
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3.35, \( p = .002 \)), suggesting a linear decrease in positive affect over the course of 24-hour abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction between nicotine use group and linear time to the model, a main effect of linear time was retained \( (b = -.002, SE = 0.001, t(31) = -4.02, p < .001) \), with positive affect decreasing in a linear fashion throughout the course of the abstention period. There was not a significant main effect of use group \( (b = -1.072, SE = 1.244, t(144) = -0.86, p = .390) \). The interaction between use group and linear time was significant \( (b = .002, SE = 0.001, t(144) = 2.00, p = .047) \), and displayed a small-to-medium effect \( (d = .45) \); over the course of the 24-hour abstention period, ENDS users displayed a steeper decrease in positive affect than combustible cigarette users (see Figure 1). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Overall Withdrawal Symptoms (WSWS-Total) over 24-Hour Abstinence.** The intercepts only model found that biological sex did not significantly predict intercept level variance \( (b = -0.036, SE = 0.21, t(144) = -0.17, p = .863) \); due to this, biological sex was removed from subsequent models. A trend level effect of nicotine use group on intercept variance in overall withdrawal symptoms was observed (dummy coded, \( 0=ENDs \) Users \( 1= \)Combustible cigarette users; \( b = 0.377, SE = 0.27, t(144) = 1.67, p = .097 \), with combustible cigarette users reporting greater overall withdrawal symptoms at the intercept level (see Table 5). In the subsequent model examining the trajectory of overall withdrawal over 24-hours of abstinence, a main effect of linear time was observed \( (b = 0.0002, SE = 0.0001, t(32) = 2.34, p = .025) \), suggesting a linear increase in overall withdrawal over the course of 24-hour abstinence. Upon adding linear time to the model,
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model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction between nicotine use group and linear time to the model, the inclusion of these predictors resulted in a loss of linear time as a significant effect ($b = 0.0001, SE = 0.0001, t(31) = 1.18, p = .247$). A trend-level significant main effect of use group emerged in the final model ($b = 0.393, SE = 0.223, t(144) = 1.77, p = .08$), with combustible cigarette users displaying greater overall withdrawal symptoms regardless of assessment point. The interaction between use group and linear time was not significant ($b = .0003, SE = 0.0002, t(144) = 1.20, p = .232$). However, despite the nonsignificant finding, the effect size of the interaction displayed a medium-to-large effect ($d = .77$), with combustible cigarette users displaying a steeper increase in overall withdrawal symptoms during 24-hour abstention than ENDS users (see Figure 2). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Anger Withdrawal Symptoms (WSWS-Anger) over 24-Hour Abstinence.** The intercepts only model found that neither biological sex ($b = -0.109, SE = 0.307, t(144) = -0.35, p = .723$) nor nicotine use group (dummy coded, 0=ENDs Users 1=Combustible cigarette users; $b = 0.444, SE = 0.334, t(144) = 1.33, p = .186$) predicted intercept variance in anger withdrawal symptoms (see Table 5). Due to this, biological sex was removed from subsequent models. In the subsequent model examining the trajectory of anger withdrawal symptoms over 24-hours of abstinence, a main effect of linear time was observed ($b = 0.0005, SE = 0.0002, t(32) = 3.56, p = .001$), suggesting a linear increase in anger withdrawal symptoms over the course of 24-hour abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when
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adding the interaction between nicotine use group and linear time to the model, the main
effect of linear time retained ($b = 0.0004$, $SE = 0.0002$, $t(31) = 2.38$, $p = .023$), with anger
withdrawal symptoms increasing over the course of 24-hour abstinence. No significant
main effect of nicotine use group was observed ($b = 0.382$, $SE = 0.334$, $t(144) = 1.15$, $p = .232$), and the interaction between use group and linear time was not significant ($b = .0003$, $SE = 0.0003$, $t(144) = 0.81$, $p = .421$). The effect size calculation showed a small-
to-medium effect of the interaction ($d = .42$), with combustible cigarette users displaying
a steeper increase in anger withdrawal symptoms during 24-hour abstention than ENDS
users (see Figure 3). The addition of the use group by linear time interaction in the model
resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

Course of Anxiety Withdrawal Symptoms (WSWS-Anxiety) over 24-Hour Abstinence.
The intercepts only model found that biological sex did not significantly predict intercept
level variance ($b = -0.150$, $SE = 0.29$, $t(144) = -0.52$, $p = .601$); due to this, biological sex
was removed from subsequent models. A significant effect of nicotine use group on
intercept variance in anxiety withdrawal symptoms was observed (dummy coded,
0=ENDs Users 1=Combustible cigarette users; $b = 0.827$, $SE = 0.31$, $t(144) = 2.67$, $p = .008$), with combustible cigarette users reporting greater overall anxiety withdrawal
symptoms at the intercept level (see Table 5). In the subsequent model examining the
trajectory of anxiety withdrawal symptoms over 24-hours of abstinence, a trend-level
main effect of linear time was observed ($b = 0.0003$, $SE = 0.0001$, $t(32) = 2.02$, $p = .052$),
suggesting a linear increase in anxiety withdrawal symptoms over the course of 24-hour
abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were
poorer (see Table 5). Next, when adding the interaction between nicotine use group and
linear time to the model, the inclusion of these predictors resulted in a loss of linear time as a significant effect \( (b = 0.0002, SE = 0.0002, t(31) = 1.17, p = .252) \). Use group remained significant model \( (b = 0.729, SE = 0.332, t(144) = 2.20, p = .03) \), with combustible cigarette users displaying greater anxiety withdrawal symptoms regardless of assessment point. The interaction between use group and linear time was not significant \( (b = .0002, SE = 0.0003, t(144) = 0.73, p = .467) \), with the effect size calculation showing a small effect of the interaction \( (d = .34) \). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Craving Withdrawal Symptoms (WSWS-Craving) over 24-Hour Abstinence.**

The intercepts only model found that biological sex did not significantly predict intercept level variance \( (b = -0.032, SE = 0.295, t(144) = -0.11, p = .913) \); due to this, biological sex was removed from subsequent models. A trend level effect of nicotine use group on intercept variance in craving withdrawal symptoms was observed (dummy coded, 0=ENDs Users 1=Combustible cigarette users; \( b = 0.627, SE = 0.321, t(144) = 1.96, p = .052 \)), with combustible cigarette users reporting greater craving withdrawal symptoms at the intercept level (see Table 5). In the subsequent model examining the trajectory of craving withdrawal symptoms over 24-hours of abstinence, a trend-level main effect of linear time was observed \( (b = 0.0002, SE = 0.0001, t(32) = 1.63, p = .113) \), suggesting a linear increase in craving withdrawal symptoms over the course of 24-hour abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction between nicotine use group and linear time to the model, the inclusion of these predictors resulted in a loss of linear time as a
significant effect \((b = 0.0001, SE = 0.0002, t(31) = 0.83, p = .413)\). Use group remained significant \((b = 0.601, SE = 0.317, t(144) = 1.90, p = .06)\), with combustible cigarette users displaying greater craving withdrawal symptoms regardless of assessment point. The interaction between use group and linear time was not significant \((b = .0002, SE = 0.0002, t(144) = 0.75, p = .453)\), with the effect size calculation showing a small effect of the interaction \((d = .36)\). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Hunger Withdrawal Symptoms (WSWS-Hunger) over 24-Hour Abstinence.**

The intercepts only model found that neither biological sex \((b = 0.219, SE = 0.272, t(144) = 0.81, p = .421)\) nor nicotine use group (dummy coded, 0=ENDs Users 1=Combustible cigarette users; \(b = 0.126, SE = 0.251, t(144) = 0.50, p = .617\) predicted intercept variance in hunger withdrawal symptoms (see Table 5); due to this, biological sex was removed from subsequent models. In the subsequent model examining the trajectory of hunger withdrawal symptoms over 24-hours of abstinence, no main effect of linear time was observed \((b = 0.0006, SE = 0.0001, t(32) = 0.37, p = .711)\). Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction between nicotine use group and linear time to the model, no significant effect of linear time was observed \((b = -.0001, SE = 0.0002, t(31) = -0.06, p = .954)\), no significant main effect of use group was observed \((b = .151, SE = 0.282, t(144) = 0.53, p = .594)\), and the interaction between use group and linear time was also not significant \((b = .0002, SE = 0.0003, t(144) = 0.58, p = .562)\), with the effect size calculation showing a small effect of the interaction \((d = .35)\). The addition of the use group by linear time
interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Course of Sadness Withdrawal Symptoms (WSWS-Sadness) over 24-Hour Abstinence.**

The intercepts only model found that neither biological sex \((b = -0.08, SE = 0.214, t(144) = -0.37, p = .710)\) nor nicotine use group (dummy coded, 0=ENDs Users 1=Combustible cigarette users; \(b = 0.104, SE = 0.233, t(144) = 0.45, p = .656\)) predicted intercept variance in sadness withdrawal symptoms (see Table 5); due to this, biological sex was removed from subsequent models. In the model examining the trajectory of craving withdrawal symptoms over 24-hour abstinence, a trend-level main effect of linear time was observed \((b = 0.0002, SE = 0.0001, t(32) = 1.88, p = .070)\), suggesting linear change in sadness withdrawal symptoms over the course of 24-hour abstinence. Upon adding linear time to the model, model fit indices (AIC, BIC) were poorer (see Table 5). Next, when adding the interaction between nicotine use group and linear time to the model, the inclusion of these predictors resulted in a loss of linear time as a significant effect \((b = .0001, SE = 0.0001, t(31) = 0.65, p = .523)\). No main effect of nicotine use group was observed \((b = .074, SE = 0.233, t(144) = 0.32, p = .751)\). The interaction between use group and linear time showed trend-level significance \((b = .0003, SE = 0.0002, t(144) = 1.55, p = .123)\), and displayed a medium effect \(d = .50\); over the course of the 24-hour abstention period, sadness displayed a steeper increase among combustible cigarette users than ENDS users (see Figure 4). The addition of the use group by linear time interaction in the model resulted in poorer model fit as indicated by both AIC and BIC (see Table 5).

**Autonomic Reactivity**

**Sample Correlations**
Bivariate correlations were conducted to examine the relation between autonomic parameters (sympathetic reactivity as indexed by ventricle pre-ejection period (PEP); parasympathetic reactivity as indexed by respiratory sinus arrhythmia (RSA)) during ad-libitum use and abstinence period, and sample characteristics (see Table 3). Greater sympathetic reactivity during ad-libitum use was positively associated with using combustible cigarettes ($r = .457$), older age ($r = .381$), higher BMI ($r = .539$), and more years using nicotine ($r = .438$). Greater sympathetic reactivity after 24-hour abstention was associated with older age ($r = .442$) and more years using nicotine ($r = .419$). No significant correlations were observed between parasympathetic reactivity and sample characteristics during either the ad-libitum use or after 24-hour abstention.

**Stepwise Linear Regression Analyses Examining Autonomic Parameters**

Stepwise linear regression models were conducted to examine whether exclusive use of ENDS or combustible cigarettes predicted changes in sympathetic and parasympathetic reactivity after 24-hour abstention (see Table 6). In the model predicting change in sympathetic reactivity, the first step of the model included baseline visit sympathetic reactivity as a predictor. A significant regression equation was not found ($F(1, 32) = 3.732, p = .063$), with the equation estimated to account for 7.9% of the variance in abstinence-visit sympathetic reactivity. Baseline sympathetic reactivity exhibited trend-level significance in predicting sympathetic reactivity after 24-hour abstention ($\beta = .328, p = .063$) at this stage of the model. When adding years of nicotine use and abstention during the study task into the model as predictors, a significant regression equation was not found ($F(3, 32) = 2.522, p = .077$), with the equation estimated to account for 12.5% of the variance in abstinence-visit sympathetic reactivity.
Baseline sympathetic reactivity ($\beta=.326, p = .302$) and abstention during the study task ($\beta=-.078, p = .652$) did not significantly predict sympathetic reactivity after 24-hour abstention at this stage of the model. Years of nicotine use exhibited trend level significance in predicting sympathetic reactivity after 24-hour abstention ($\beta=.326, p = .091$). In the final step of the model where nicotine use group was added as a predictor, a significant regression equation was not found ($F(4, 32) = 1.831, p = .151$), with the equation estimated to account for 9.4% of the variance in abstinence-visit sympathetic reactivity. In the final model, neither baseline sympathetic reactivity ($\beta=.195, p = .328$), years of nicotine use ($\beta=.310, p = .201$), abstention ($\beta=-.086, p = .650$), nor nicotine use group ($\beta=.028, p = .908$) significantly predicted sympathetic reactivity after 24-hour abstention.

In the model predicting parasympathetic reactivity, the first step of the model included baseline visit parasympathetic reactivity as a predictor. A significant regression equation was not found ($F(1, 32) = 1.936, p = .174$), with the equation estimated to account for 2.8% of the variance in abstinence-visit parasympathetic reactivity. Baseline parasympathetic reactivity did not significantly predict parasympathetic reactivity after 24-hour abstention ($\beta=.242, p = .174$) at this stage of the model. When adding years of nicotine use into the model as a predictor, a significant regression equation was also not found ($F(3, 32) = 0.856, p = .475$), with the equation estimated to account for 1.4% of the variance in abstinence-visit parasympathetic reactivity. Baseline parasympathetic reactivity ($\beta=.252, p = .176$), years of nicotine use ($\beta=-.101, p = .581$), and abstention ($\beta=.104, p = .565$) did not significantly predicted parasympathetic reactivity after 24-hour abstention at this stage of the model. In the final step of the model where nicotine
use group was added as a predictor, a significant regression equation was not found ($F(4, 32) = 0.741, p = .648$), with the equation estimated to account for 4.9% of the variance in abstinence-visit parasympathetic reactivity. In the final model, neither baseline RSA parasympathetic reactivity ($\beta=.247, p = .197$), years of nicotine use ($\beta=-.077, p = .763$), abstention ($\beta=.117, p = .570$) nor nicotine use group ($\beta=-.036, p = .890$) significantly predicted parasympathetic reactivity after 24-hour abstention.
Discussion

The current investigation examined differences in acute nicotine withdrawal presentation among individuals who report daily ENDS-only or combustible cigarette-only use. Participants were asked to abstain from nicotine use for 24 hours, during which time they completed intermittent EMA assessments of self-reported withdrawal symptoms to determine whether the course and magnitude of withdrawal differed between product class users. Results showed that ENDS users displayed a steeper decrease in positive affect over the course of 24-hour abstention than combustible cigarette users (small-to-medium effect); trending effects suggested that combustible cigarette users display a steeper increase in sadness over the course of 24-hour abstention than ENDS users (medium effect). In addition, a large but non-significant effect of use group on overall withdrawal symptoms was observed such that combustible cigarette users evidenced a steeper increase than ENDS users over the course of the 24-hour abstention period. Participants also completed laboratory assessments immediately prior to abstention, and at the conclusion of their 24-hour abstention period, to assess whether acute withdrawal from these products elicited differential changes in sympathetic and parasympathetic reactivity. Nicotine use group did not predict differences in either sympathetic or parasympathetic reactivity after 24-hour abstention. Of note, data collection for this project was prematurely terminated due to the onset of the COVID-19 pandemic, so findings should be interpreted with caution due to the small sample size.

Ecological Momentary Assessment Findings

Of the EMA findings, two exhibited at least trend level significance: combustible cigarette users showed a steeper increase in sadness, and ENDS users displaying a steeper
decrease in positive affect, over the course of 24-hour abstention. In the model examining positive affect a significant main effect of time was also observed, where regardless of users’ nicotine inhalation device they exhibited a decrease in PA over the course of the acute abstention period. These findings are notable, as state mood and affect during nicotine withdrawal has been shown to be predictive of poorer cessation outcomes (Piper et al., 2017). Piper and colleagues found that combustible cigarette smokers who display a withdrawal profile characterized in part by elevated anhedonia (as well as elevated craving) during their first 24-hours of a cessation attempt were less likely to maintain cessation 8-weeks after quitting, and relapsed sooner, relative to smokers who did not display elevated anhedonia during this period. Piper and colleagues also found that combustible cigarette smokers who displayed acute withdrawal symptoms characterized by elevated sadness, anxiety, and anger withdrawal symptoms also relapsed sooner after a cessation attempt than smokers who exhibited low-to-moderate levels of those symptoms. Affective presentations such as these have shown broader relevance to cessation-related outcomes outside of acute withdrawal presentations. Nicotine users who present with elevated depression symptoms (Weinberger et al., 2017) or a diagnosis of major depressive disorder (Hitsman et al., 2013), each of which are often characterized by elevated sadness and low positive affect, are less likely to make a cessation attempt and less likely to maintain short and long-term abstinence. When considering the current investigation’s findings in light of the aforementioned work, this suggests that acute ENDS and combustible cigarette abstinence elicits differential, but equally noteworthy, barriers to cessation in the experience of acute withdrawal. These findings, if replicated, suggest that cessation interventions targeting early cessation lapsers (e.g., Brown et al.,
2013) may show increased efficacy if these approaches are tailored to the product class the individual is attempting to cease from.

The growth curve models examining overall withdrawal symptom intensity during the 24-hour abstention period also revealed notable findings. In the final model, the interaction between use group and linear time was not significant but displayed a large effect size. Moreover, in that final model the main effect of use group was significant, with combustible cigarette users displaying greater overall withdrawal symptoms. Together this suggests that during acute abstinence combustible cigarette users experience more intense withdrawal than ENDS users, but that the trajectory of change within that 24-hour period does not significantly differ from that of ENDS users. A similar pattern of findings was also observed when examining anxiety and craving withdrawal symptoms. Alongside the aforementioned significant effect of use group on increases in sadness withdrawal symptoms over time, this suggests that the subjective experience of acute withdrawal is potentially more aversive for combustible cigarette smokers than for ENDS users. Considering that previous work has found more intense craving and anxiety during acute withdrawal is associated with a lower likelihood of maintaining cessation among combustible cigarette smokers (Hendricks et al., 2014; Piper et al., 2017; Xian et al., 2002), these findings tentatively suggest that the withdrawal profiles between use groups may be different enough to influence the likelihood of successful long-term cessation. This may be an area worthy of future investigation pending replication of these findings among a larger, more representative sample. It should be noted, however, that the observed pattern of findings may be accounted for by significant differences in demographic composition between the two
samples. While some of these differences are reflective of naturalistically occurring differences between the two use groups (e.g., ENDS users tend to be younger; Weaver et al., 2016), that in and of itself does not rule out that these demographic differences may be driving the observed effects rather than the nicotine delivery systems being used. Future investigations into self-reported acute withdrawal should control for this demographic variance to more conclusively determine whether differential product class usage is driving the observed trend-level effects.

Two additional observations within the EMA findings are worth noting. First, across outcome variables the most commonly observed significant effect in base models prior to inclusion of an interaction term was a significant or trending effect of linear time, with the exception of hunger withdrawal symptoms. Here, independent of use group, withdrawal symptoms increased in intensity over the 24-hour abstention period. This suggests that the withdrawal assessments and methodology were appropriately capturing symptoms of withdrawal, and that the pattern of findings observed are likely not explained by measurement or design flaws. In addition, despite indications of meaningful relations within many of the outcome variable of interest, as models increased in complexity model fit universally worsened. It is unclear whether this issue of model fit is driven exclusively by the small sample size in the current investigation, as the indices used (Akaike information criterion; Bayesian information criterion) are likelihood functions that are highly influenced by sample size (Akaike, 1974; Schwarz, 1978). Considering the external data collection limitations, study aims, and likelihood that our small sample size was impacting model fit, the decision was made to consistently interpret the full, more complex models across outcome variables despite the worsening
fit. However, this worsening of model fit does further call into question the 
generalizability of the present findings and supports the importance of replicating or 
expanding the current investigation to determine the most parsimonious model for the 
given variables.

**Autonomic Findings**

In the analyses examining differences between ENDS and combustible cigarette 
users in changes in sympathetic and parasympathetic reactivity after 24-hour abstention, 
no significant differences were observed. The lack of any significant findings is 
surprising, as ENDS do not contain a number of additives present in combustible 
cigarettes that are linked to autonomic dysfunction (e.g., carbon monoxide; Middlekauff 
et al., 2014). Furthermore, ENDs use is linked to a lesser magnitude increase in 
sympathetic activation than combustible cigarette use (Garcia et al., 2020), which 
regardless of underlying mechanism, one would expect to have a reciprocal influence on 
withdrawal presentation due to the magnitude of available change during this period. It is 
also especially noteworthy that these two groups did not evince differences in autonomic 
reactivity despite a significant difference in the number of years each group has used 
nicotine. Long term nicotine use impairs baroreflex function, which leads to greater 
increase in sympathetic nervous system activation during acute use (Hering et al., 2006; 
Shinozaki et al., 2008) and greater resting sympathetic activation when not inhaling 
nicotine (Dinas et al., 2013). Conversely, among shorter term smokers a decrease in 
sympathetic activation is sometimes observed after acute use, due to an intact baroreflex 
engaging in compensatory restriction of sympathetic activation in response to an acute 
increase in blood pressure upon nicotine inhalation (Grassi et al., 1991; Niedermaier et
al., 1993). Considering this, one could expect that simply by virtue of the two samples in this current investigation differing in their nicotine use duration differences in the direction and magnitude of sympathetic reactivity after 24-hour abstention would have been observed. While an absence of significant findings is not conclusive evidence for the absence of differences autonomic withdrawal parameters, it is worth exploring potential explanations as to why no significant findings emerged.

The lack of findings may be accounted for by methodological constraints. Firstly, assessments of baseline autonomic reactivity during the initial appointment occurred approximately 45-60 minutes after participants arrived at the laboratory for their first appointment. While participants were asked to use their preferred inhalation device upon arrival if they reported not smoking/vaping in the last hour, this design decision may still have resulted in some participants completing baseline autonomic assessments following up to two hours of deprivation. As noted previously, nicotine withdrawal symptoms can begin as early as 30 minutes after last using (Baker et al., 2004; Hendricks et al., 2006). While little work has assessed the course of autonomic changes during very early withdrawal, Hendricks and colleagues (2006) found that changes in heart rate occurred within 60 minutes of abstention. Perhaps some participants’ ‘baseline’ assessments of autonomic reactivity were in fact capturing very early withdrawal presentations, which may not differ significantly from autonomic functioning after abstaining for 24 hours. This conjecture is supported by supplemental analyses of the existing data that found that key autonomic parameters in the current study (PEP, RSA) did not significantly differ within-groups between laboratory visits. Future investigations would benefit from more
tightly standardizing nicotine use and capturing autonomic parameters immediately after nicotine inhalation.

Alternatively, the lack of observed findings may be due to the absence of significant differences in autonomic reactivity during acute abstinence, and instead emerge as abstinence duration lengthens. While no work has directly examined the trajectory of autonomic change during ENDS use withdrawal, it is worth briefly speculating as to why differences may emerge after 24 hours. As noted earlier, ENDS have been shown to evidence elevated levels of nicotyrine, a compound which slows nicotine metabolism, thereby maintaining nicotine in users’ bodies for a longer time (Abramovitz et al., 2015). While it was hypothesized that this differential metabolism might account for lesser change in autonomic parameters among ENDS users during acute abstinence, perhaps the degree of metabolic change is not large enough to evince autonomic discrepancies after this withdrawal duration. Future work should aim to directly examine the course of autonomic functioning among ENDS users during acute withdrawal and beyond.

It is important to note that during the ad-libitum session, greater sympathetic reactivity was associated with both combustible cigarette use and older age. Considered in concert with the nonsignificant between-group findings after acute abstinence, this may suggest that any differential pharmacokinetic effects between product classes on sympathetic activation may be observed during ongoing use rather than during withdrawal. This is consistent with the previously noted findings where acute ENDS use is associated with lesser magnitude sympathoexcitatory effects than using combustible cigarettes (Garcia et al., 2020). This finding, if able to be further replicated, has
interesting implications with regard to the picture of chronic effects of using ENDS or combustible cigarettes. Chronically elevated sympathetic activation is linked to poorer autonomic outcomes (Benowitz, 2003; Libby et al., 2016; Middlekauff et al., 2014). The finding that combustible cigarette smokers evince greater sympathetic reactivity to modest attentional demands suggests that this use group may evince pervasive excitation to normal stimuli relative to ENDS users when inhaling nicotine ad-libitum, and thus may display poorer long-term cardiovascular outcomes from chronic use. In addition, greater sympathetic reactivity among non-smokers has also been linked to psychosocial outcomes such as greater social sensitivity (Muhtadie et al., 2015), which would suggest that these groups may respond differently to the onset of emergent stressors. As the current study’s time scope is relatively narrow, and the duration of use differs significantly between groups, it is difficult to render conclusions as to whether this snapshot of differential ad-libitum reactivity is reflective of ongoing differences between use-groups after long-term use. However, further investigations are warranted to examine ad-libitum use differences in sympathetic reactivity.

Discrepancy between Self-Report and Autonomic Findings

The discrepancy in findings between self-reported and autonomic withdrawal symptoms is notable. This may suggest that any differences in withdrawal manifestation between users of ENDS or combustible cigarettes may be due to perceptual or experiential factors rather than biochemical differences between product classes. While autonomic parameters are bidirectionally influenced by psychological and behavioral experiences, they are less influenced by perceptual and experiential factors than self-report data. Because of this, if any discrepancy was observed between the two data
modalities one would expect that autonomic parameters would be impacted relatively more by the biochemical composition of the vapor/smoke inhalation, whereas questionnaire completion would show greater relative influence of cognitive factors such as abstinence related expectancies. Indeed, nicotine users’ expectancies of withdrawal have shown a relation to acute withdrawal intensity (Hendricks & Leventhal, 2013; Robinson et al., 2012). Differential user perspectives and expectancies of withdrawal manifestation could be driven by a number of different factors, such as users’ prior experience of withdrawal when using the devices or differences in how product classes are used. For example, habitual ENDS users tend to use their devices more frequently and inhale lower doses of nicotine than combustible cigarette users when doing so (Behar et al., 2015; De Jesus et al., 2013). This may lead them to experience relatively fewer periods of acute withdrawal than combustible cigarette users, who via their differing pattern of use may experience more frequent bouts of intense withdrawal and thus may develop greater aversive expectations of the experience. Furthermore, broader cultural messaging surrounding devices’ safety may influence users’ perception of withdrawal (e.g., ENDS being regarded as a ‘safer alternative’; Goniewicz et al., 2013). While both indices of self-reported and autonomic acute withdrawal have shown a relation to cessation likelihood (al’Absi et al., 2004; Hendricks et al., 2014), our discrepant findings, if borne out upon replication, suggest that any focus on differentiating treatment by product class would be more usefully focused on modifying cognitive-behavioral interventions.

It is also worth acknowledging that the analytic approaches utilized for the EMA and autonomic data led to modestly different sample compositions, which could have
impacted the relative disparity in results. For the EMA analyses, once participants reported that they used their preferred inhalation device data at that and all subsequent timepoints were coded as missing. Conversely, due to the small available sample all participants were included in the regression analyses examining sympathetic and parasympathetic reactivity, with abstention being included in the model to control for participants who were not able to refrain from nicotine use during the abstention period. Notably, supplemental analyses found the same pattern of nonsignificant findings when only including participants who successfully abstained, but with an immensely underpowered sample ($n = 16$). As one cannot conclude from the existing dataset as to whether examining only true abstainers would change the pattern of autonomic findings, this once again speaks to the utility of replicating the existing study among a larger sample.

**Limitations and Future Directions**

The current investigation does possess some major limitations with regard to sample composition and potentially unaccounted for confounding variables that require the findings to be interpreted with caution. First and foremost, the sample was both small and imbalanced, with an $n = 24$ ENDS users and an $n = 10$ combustible cigarette users recruited during a collection period truncated by the COVID-19 pandemic. Furthermore, as noted earlier the two samples differed significantly in terms of key demographic variables, including ethnicity, race, gender, age, years of nicotine use, and body mass index, variance in each of which has been linked to differences in nicotine withdrawal symptom profiles (Bello et al., 2016; Blendy et al., 2005; Falcone et al., 2014; Hughes et al., 1994). Future work should aim to replicate the current study in a more robust sample,
WHEREIN ANALYSES WOULD HAVE THE POWER TO CONTROL FOR DEMOGRAPHIC VARIABILITY BETWEEN SAMPLES.

The study recruited participants who reported at least minimum nicotine use and dependence indices (i.e., using their preferred device daily, using nicotine within 30 minutes of waking), and did not attempt to match samples or control for these parameters. In part, this was due to issues with measurement; administration of the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991; Farsalinos et al., 2014) among ENDS users was not able to be scored due to the vast majority of ENDS users failing to report nicotine concentration in their preferred administration method. This is especially important, as a nicotine user’s dependence severity is positively associated with the intensity of withdrawal symptoms they experience (Rios-Bedoya et al., 2008; Payne et al., 1994; Shiffman et al., 2004). Because of this, the current investigation cannot determine whether the observed findings are due to differences in the products used or differential dependence between samples. To more conclusively determine this, future work should replicate these findings while either recruiting samples matched on dependence indices or controlling for dependence in their analyses.

Finally, it is worth noting that the current findings may not be generalizable to the experience of acute nicotine withdrawal during a prolonged cessation attempt. As noted earlier, participants in the current investigation were not actively engaged in an attempt to cease or reduce their nicotine intake at the time of participation. This may influence participants’ behavior during the cessation attempt (e.g., their likelihood of maintaining abstinence) as well as their subjective experience of withdrawal. Indeed, low motivation to quit is associated with a lower likelihood of successfully maintaining short-term (seven day) nicotine use abstinence (Jardin & Carpenter, 2012). Furthermore, nicotine users’ motivation to quit is inversely associated with retrospectively reported withdrawal
intensity during early (first week) cessation (Zvolensky et al., 2004). Future studies should aim to assess nicotine users’ subjective assessments of their acute withdrawal experience during a prolonged cessation attempt to more conclusively determine whether the observed effects occur in a more naturalistic context.

**Conclusion**

The current investigation examined the differential presentation of acute nicotine withdrawal between ENDS and combustible cigarette users. Findings revealed that ENDS and combustible cigarette users’ intensity and trajectory of self-reported withdrawal during this period differed in certain domains (e.g., positive affect, sadness). However, no differences in sympathetic or parasympathetic reactivity were observed after 24-hour abstention. The small and imbalanced sample limits the generalizability of the present findings. Nevertheless, the results of this investigation do provide initial support for continued investigations into the differential presentation of withdrawal between users of these product classes. Further work in this area has the potential to elucidate potential differences in users’ experience of ENDS and combustible cigarettes and speak to the public health effects of increasing ENDS use.
### Tables and Figures

**Table 1**

*Nicalert Test Strip Cotinine Equivalents for each Semi-Quantitative Level*

<table>
<thead>
<tr>
<th>Level</th>
<th>Cotinine Equivalents (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-10</td>
</tr>
<tr>
<td>1</td>
<td>10-30</td>
</tr>
<tr>
<td>2</td>
<td>30-100</td>
</tr>
<tr>
<td>3</td>
<td>100-200</td>
</tr>
<tr>
<td>4</td>
<td>200-500</td>
</tr>
<tr>
<td>5</td>
<td>500-2000</td>
</tr>
<tr>
<td>6</td>
<td>2000+</td>
</tr>
</tbody>
</table>
### Table 2

**Participant Demographic Characteristics**

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Overall Sample (N=34)</th>
<th>ENDS Users (N=24)</th>
<th>Combustible Cigarette Users (N=10)</th>
<th>Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Sex (Female)</td>
<td>19 (55.9%)</td>
<td>14 (58.3%)</td>
<td>5 (50%)</td>
<td>.493</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>4 (11.8%)</td>
<td>3 (12.5%)</td>
<td>1 (10%)</td>
<td>**&lt;.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td><strong>.005</strong></td>
</tr>
<tr>
<td>White</td>
<td>15 (44.1%)</td>
<td>10 (41.7%)</td>
<td>5 (50%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (8.8%)</td>
<td>2 (8.3%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (14.7%)</td>
<td>5 (20.8%)</td>
<td>0 (0%)</td>
<td></td>
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<tr>
<td>Other/Multiracial</td>
<td>11 (32.4%)</td>
<td>7 (29.2%)</td>
<td>4 (40%)</td>
<td>**&lt;.001</td>
</tr>
<tr>
<td>Orientation (Heterosexual)</td>
<td>29 (85.3%)</td>
<td>21 (87.5%)</td>
<td>8 (80%)</td>
<td>**&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>21.56 (6.25)</td>
<td>19.0 (1.45)</td>
<td>27.7 (8.88)</td>
<td>**&lt;.001</td>
</tr>
<tr>
<td>Years of Nicotine Use</td>
<td>4.67 (5.97)</td>
<td>2.29 (1.26)</td>
<td>10.4 (8.66)</td>
<td>**&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>21.94 (2.34)</td>
<td>21.1 (1.93)</td>
<td>23.8 (2.19)</td>
<td>**.001</td>
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<tr>
<td>Nicotine Use</td>
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<tr>
<td>Cigarettes per day</td>
<td>N/A</td>
<td>N/A</td>
<td>14.3 (12.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Vape puffs per day</td>
<td>N/A</td>
<td>50.3 (47.9)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Note.** For continuous variables, between-group differences were assessed via independent-samples t-tests. For categorical variables, chi-square tests were conducted to assess for between-groups differences.

* = Significance value indicates the result of a chi-square test to determine differences in the overall distribution of racial identification between use groups.

** = p <.01
### Table 3

Zero-Order Correlations between Nicotine Use Group, Demographics, and Outcomes of Interest

<table>
<thead>
<tr>
<th>Variable</th>
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<th>24</th>
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</thead>
<tbody>
<tr>
<td>1. Nicotine Use Group (0 = ENDS)</td>
<td>-.076</td>
<td>.634*</td>
<td>.119</td>
<td>.628*</td>
<td>-.032</td>
<td>.419*</td>
<td>.081*</td>
<td>-.099</td>
<td>-.148</td>
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<td>2. Biological Sex (0 = Male)</td>
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<td>.534*</td>
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<td>3. BMI</td>
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<td>-.607</td>
<td>-.540*</td>
<td>-.076</td>
<td>-.567</td>
<td>-.076</td>
<td>-.190</td>
<td>-.249</td>
<td>-.197</td>
<td>-.222</td>
<td>-.249</td>
<td>-.209</td>
<td>-.287</td>
<td>-.313</td>
<td>-.190</td>
<td>-.519*</td>
<td>-.364*</td>
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<td>4. Years Using Nicotine</td>
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<td>5. PANAS Negative Affect - Ad Libitum</td>
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<td>6. PANAS Positive Affect - Ad Libitum</td>
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<td>7. PANAS Negative Affect – After Abstention</td>
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<td>8. PANAS Positive Effect – Ad Libitum</td>
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<td>9. PANAS Positive Effect – After Abstention</td>
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<td>10. WSWS Total – Ad Libitum</td>
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<td>11. WSWS Total – After Abstention</td>
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<td>12. WSWS Anger – Ad Libitum</td>
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</table>

*PANAS = Positive and Negative Affect Schedule; WSWS = Wisconsin Smoking Withdrawal Scale; RSA = Respiratory Sinus Arrhythmia; PEP = Ventricle Pre-ejection Period

Ad libitum indicates results on a given variable during the first laboratory visit, whereas after abstention indicates results on a given variable during the second laboratory visit.

\( *p < .05, **p < .01 \)
<table>
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<tr>
<th>Prompt Number</th>
<th>Overall Usability</th>
<th>ENDs PPT Usability</th>
<th>Combustible PPT Usability</th>
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<td>Baseline (Laboratory Visit 1)</td>
<td>34/34 (100%)</td>
<td>24/24 (100%)</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>Prompt 1</td>
<td>26/34 (76.4%)</td>
<td>19/24 (79.1%)</td>
<td>7/10 (70%)</td>
</tr>
<tr>
<td>Prompt 2</td>
<td>25/34 (73.5%)</td>
<td>17/24 (70.8%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Prompt 3</td>
<td>23/34 (67.6%)</td>
<td>17/24 (70.8%)</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>Prompt 4</td>
<td>18/34 (52.9%)</td>
<td>11/24 (45.8%)</td>
<td>7/10 (70%)</td>
</tr>
<tr>
<td>Prompt 5</td>
<td>19/34 (55.9%)</td>
<td>13/24 (54.1%)</td>
<td>6/10 (60%)</td>
</tr>
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<td>Prompt 6</td>
<td>18/34 (52.9%)</td>
<td>12/24 (50%)</td>
<td>6/10 (60%)</td>
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<td>10/24 (41.6%)</td>
<td>5/10 (50%)</td>
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<td>6/10 (60%)</td>
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<td>Laboratory Visit 2</td>
<td>15/34 (44.1%)</td>
<td>9/24 (37.5%)</td>
<td>6/10 (60%)</td>
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</table>

*Note. A datapoint is defined as usable if the participant completed the prompt within 30 minutes of being prompted, and they did not report using nicotine at any prior point during the 24-hour abstinence period.*
### Table 5: Longitudinal Growth Curve Model Results

<table>
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<tr>
<th>Outcome Variable &amp; Model</th>
<th>AIC</th>
<th>BIC</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>t (df)</th>
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<td>-1.46 (144)</td>
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WITHDRAWAL FROM ENDS OR COMBUSTIBLE CIGARETTES

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WSWS – Anger Subscale

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</table>

WSWS – Anxiety Subscale

<table>
<thead>
<tr>
<th></th>
<th>Intercept Only</th>
<th>Adding Linear Time</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.640  0.483  3.39(31)  .002</td>
<td>1.230  0.175  7.43(32)  &lt;.001</td>
<td>1.329  0.180  7.38(32)  &lt;.001</td>
</tr>
<tr>
<td>Biological Sex</td>
<td>-0.150  0.286  -0.52(144)  .601</td>
<td>0.826  0.304  2.72(144)  .007</td>
<td>0.729  0.332  2.20(144)  .030</td>
</tr>
<tr>
<td>Nicotine Use Group</td>
<td>0.827  0.309  2.67(144)  .008</td>
<td>0.826  0.304  2.72(144)  .007</td>
<td>0.729  0.332  2.20(144)  .030</td>
</tr>
<tr>
<td>Linear Time</td>
<td>0.0003  0.0001  2.02(32)  .052</td>
<td>0.0003  0.0001  2.02(32)  .052</td>
<td>0.0002  0.0002  1.17(31)  .252</td>
</tr>
<tr>
<td>Linear Time x Use Group</td>
<td>0.0003  0.0003  0.73(144)  .467</td>
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</table>

WSWS – Craving Subscale

<table>
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<th>Intercept Only</th>
<th>Adding Linear Time</th>
<th>Final Model</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>2.020  0.500  4.04(31)  &lt;.001</td>
<td>1.945  0.172  11.34(32)  &lt;.001</td>
<td>1.954  0.172  11.35(32)  &lt;.001</td>
</tr>
<tr>
<td>Biological Sex</td>
<td>-0.032  0.295  -0.11(144)  .913</td>
<td>0.627  0.321  1.96(144)  .052</td>
<td>0.601  0.317  1.90(144)  .060</td>
</tr>
<tr>
<td>Nicotine Use Group</td>
<td>0.627  0.321  1.96(144)  .052</td>
<td>0.628  0.314  2.00(144)  .047</td>
<td>0.601  0.317  1.90(144)  .060</td>
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<tr>
<td>Linear Time</td>
<td>0.0002  0.0001  1.63(32)  .113</td>
<td>0.0002  0.0001  1.63(32)  .113</td>
<td>0.0001  0.0002  0.83(31)  .413</td>
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<tr>
<td>Linear Time x Use Group</td>
<td>0.0002  0.0002  0.75(144)  .453</td>
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</table>
## WITHDRAWAL FROM ENDS OR COMBUSTIBLE CIGARETTES

### WSWS – Hunger Subscale

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<th>Adding Linear Time</th>
<th>Final Model</th>
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<tbody>
<tr>
<td><strong>Intercept Only</strong></td>
<td>625.2</td>
<td>639.9</td>
<td>653.7</td>
</tr>
<tr>
<td><strong>Adding Linear Time</strong></td>
<td>631.3</td>
<td>646.0</td>
<td>659.8</td>
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<tr>
<td><strong>Final Model</strong></td>
<td>653.7</td>
<td>659.8</td>
<td>581.5</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Biological Sex</th>
<th>Nicotine Use Group</th>
<th>Linear Time</th>
<th>Nicotine Use Group</th>
<th>Linear Time</th>
<th>Linear Time x Use Group</th>
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<tbody>
<tr>
<td><strong>Intercept Only</strong></td>
<td>1.505</td>
<td>0.219</td>
<td>0.126</td>
<td>0.006</td>
<td>0.206</td>
<td>0.0006</td>
<td>0.0002</td>
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<tr>
<td><strong>Adding Linear Time</strong></td>
<td>639.9</td>
<td>1.691</td>
<td>0.206</td>
<td>0.0006</td>
<td>1.708</td>
<td>0.151</td>
<td>0.0001</td>
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<tr>
<td><strong>Final Model</strong></td>
<td>653.7</td>
<td>1.708</td>
<td>0.151</td>
<td>0.0001</td>
<td>1.961</td>
<td>0.074</td>
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### WSWS – Sadness Subscale

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<tr>
<td><strong>Intercept Only</strong></td>
<td>557.1</td>
<td>568.9</td>
<td>581.5</td>
</tr>
<tr>
<td><strong>Adding Linear Time</strong></td>
<td>563.2</td>
<td>575.0</td>
<td>587.6</td>
</tr>
<tr>
<td><strong>Final Model</strong></td>
<td>581.5</td>
<td>587.6</td>
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<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Biological Sex</th>
<th>Nicotine Use Group</th>
<th>Linear Time</th>
<th>Nicotine Use Group</th>
<th>Linear Time</th>
<th>Linear Time x Use Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intercept Only</strong></td>
<td>1.094</td>
<td>-0.080</td>
<td>0.104</td>
<td>0.0002</td>
<td>1.094</td>
<td>0.074</td>
<td>0.0003</td>
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<tr>
<td><strong>Adding Linear Time</strong></td>
<td>557.1</td>
<td>0.945</td>
<td>0.123</td>
<td>0.0002</td>
<td>1.094</td>
<td>0.074</td>
<td>0.0003</td>
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<tr>
<td><strong>Final Model</strong></td>
<td>581.5</td>
<td>0.961</td>
<td>0.074</td>
<td>0.0001</td>
<td>1.094</td>
<td>0.074</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
Figure 1

*Interaction of Use Group and Linear Time on Positive Affect during Abstention*
Figure 2
*Interaction of Use Group and Linear Time on Overall Withdrawal Severity during Abstention*

![Graph showing the interaction of use group and linear time on overall withdrawal severity during abstinence.](image)

**WSWS Total Score**

- **ENDs Users**
- **Combustible Users**

**Minutes Since Abstention Period Began**
Figure 3

Interaction of Use Group and Linear Time on Anger during Abstention
Figure 4

Interaction of Use Group and Linear Time on Sadness during Abstention
Table 6: Stepwise Linear Regression Results Examining Change in Physiological Parameters

<table>
<thead>
<tr>
<th>Model &amp; Level of Restriction</th>
<th>$t$</th>
<th>$p$</th>
<th>β</th>
<th>F</th>
<th>$df$</th>
<th>$p$</th>
<th>adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model predicting Δ in PEP from Baseline to Dot Tracking Tasks during 24-hour Abstention Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>With Baseline Session Δ in PEP</td>
<td>3.732</td>
<td>1, 32</td>
<td>.063</td>
<td>.079</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Session Δ in PEP</td>
<td>1.932</td>
<td>.063</td>
<td>.328</td>
<td></td>
<td></td>
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<tr>
<td>Adding Years of Nicotine Use</td>
<td>2.522</td>
<td>3, 32</td>
<td>.077</td>
<td>.125</td>
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<td></td>
<td></td>
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<tr>
<td>Baseline Session Δ in PEP</td>
<td>1.052</td>
<td>.302</td>
<td>.199</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Years of Nicotine Use</td>
<td>1.747</td>
<td>.091</td>
<td>.326</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstention during 24-hour period</td>
<td>-.456</td>
<td>.652</td>
<td>-.078</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Final Model, with Nicotine Use</td>
<td>1.831</td>
<td>4,32</td>
<td>.151</td>
<td>.094</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Group | Baseline Session Δ in PEP | .995 | .328 | .195 |     |      |     |           |
|       | Years of Nicotine Use | 1.310 | .201 | .310 |     |      |     |           |
|       | Abstention during 24-hour period | -.458 | .650 | -.086 | |      |     |           |
|       | Nicotine Use Group | .117 | .908 | .028 |     |      |     |           |

| **Model predicting Δ in RSA from Baseline to Dot Tracking Tasks during 24-hour Abstention Visit** |      |     |    |     |      |     |           |
| With Baseline Δ in RSA | 1.936 | 1, 32 | .174 | .028 |
| Baseline Session Δ in RSA | 1.391 | .174 | .242 |     |      |     |           |
| Adding Years of Nicotine Use | .856 | 3, 32 | .475 | -.014 |
| Baseline Session Δ in RSA | 1.386 | .176 | .252 |     |      |     |           |
| Years of Nicotine Use | -.559 | .581 | -.101 | |      |     |           |
| Abstention during 24-hour period | .582 | .565 | .104 | |      |     |           |
| Final Model, with Nicotine Use | .625 | 4,32 | .648 | -.049 |

| Group | Baseline Session Δ in RSA | 1.322 | .197 | .247 |     |      |     |           |
|       | Years of Nicotine Use | -.304 | .763 | -.077 |     |      |     |           |
|       | Abstention during 24-hour period | .575 | .570 | .117 | |      |     |           |
|       | Nicotine Use Group | -.140 | .890 | -.036 |     |      |     |           |

RSA = Respiratory Sinus Arrhythmia; PEP = Ventricle Pre-Ejection Period
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WITHDRAWAL FROM ENDS OR COMBUSTIBLE CIGARETTES


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