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ACUTE EFFECTS OF AN ORAL NICOTINE POUCH IN PEOPLE WHO USE SMOKELESS
TOBACCO

A dissertation proposal submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy at Virginia Commonwealth University.

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List of Abbreviations

ANOVA	analysis of variance
BP	blood pressure
BPM	beats per minute
CO	carbon monoxide
CSTP	Center for the Study of Tobacco Products
DESLT	Direct Effects of Smokeless Tobacco
ENDS	electronic nicotine delivery system
FDA	Food and Drug Administration
FTC	Federal Trade Commission
gLMS	General Labeled Magnitude Scale
HR	heart rate
HzR	hazard ratio
IARC	International Agency for Research on Cancer
IRB	Institutional Review Board
LOQ	limit of quantification
min	minute(s)
mg	milligram
ng	nanogram
NRT	nicotine replacement therapy
OB	own brand
ONPs	oral nicotine pouches
OR	odds ratio
ppm	concentration in parts per million
SLT	Smokeless Tobacco
USDHHS	US Department of Health and Human Services
USST	US Smokeless Tobacco Company
VAS	visual analog scale
WHO	World Health Organization

Abstract

ACUTE EFFECTS OF AN ORAL NICOTINE POUCH IN PEOPLE WHO USE SMOKELESS TOBACCO.

By Alisha N. Eversole, M.S.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2024

Major Director: Thomas Eissenberg, Ph.D.
Professor of Psychology

Department of Psychology and Center for the Study of Tobacco Products

People who use smokeless tobacco (SLT) are exposed to a variety of carcinogenic toxicants, yet, despite health risks, nearly 6 million people in the US use SLT. SLT contains and delivers nicotine, a psychostimulant that causes dependence and hinders cessation efforts. An orally-administered nicotine pouch marketed as “tobacco-free” recently has become available for purchase in the US. However, there are very few non-industry-sponsored studies regarding the effects of these oral nicotine pouches.

The current study used clinical laboratory methods to determine the acute effects of an oral nicotine pouch in people who use SLT. Participants completed four sessions (within subjects, Latin-square ordered) that included an own brand (OB) SLT positive control and three oral nicotine pouch conditions (ONP; 2, 4, and 8 mg total nicotine content; “ON!”, Altria, Richmond VA). Outcomes included plasma nicotine concentration and subjective measures. The primary hypotheses are that plasma nicotine concentration will increase significantly as ONP total nicotine content increases, such that the 2 and 4 mg ONP condition will differ but the 8 mg ONP condition will not differ from OB SLT, and abstinence symptoms will be lowest in the OB and 8 mg ONP condition and will differ significantly from the 2 and 4 mg ONP conditions.

Results indicate the 8 mg ONP did not differ significantly from OB across physiological and subjective measures; the 4 mg ONP differed from OB and 8 mg on some measures, and the 2 mg reliably delivered less nicotine and reduced abstinence symptoms less effectively when compared to OB and the 8 mg ONP. Study results offer preliminary support for the notion that ONPs may substitute for SLT in people who use SLT regularly. Results also are consistent with the idea that lower nicotine content ONPs may mimic “starter” SLT products of the past by being more palatable to nicotine-naïve users; historically, starter products were designed to facilitate nicotine use and initiate a “graduation” to higher nicotine content ONPs or other products that deliver nicotine more effectively. One policy-related implication of these results is that regulating ONP pH (and SLT pH) such that there is an upper limit on the pH of these products may help reduce the likelihood that nicotine-naïve individuals who begin using these products will continue that use over the long-term.

Acute Effects of an Oral Nicotine Pouch in People Who Use Smokeless Tobacco

Introduction

Smokeless tobacco (SLT) is defined by the US Food and Drug Administration (FDA) as “a noncombustible tobacco product” made from tobacco leaves (FDA, 2010). The most popular form of SLT in the US is moist snuff (or “dip”; IARC, 2007). During use, SLT is placed between the cheek and gum for 10-30 minutes (IARC, 2007), and users almost always spit out saliva during use. SLT use has been increasing in the US (Delnevo et al., 2014). In 2018, 5.9 million US adults and ~1 million US middle and high school students reported current SLT use (Creamer et al., 2019; Gentzke et al., 2019). The majority of people who use SLT in the US are white men who live in rural, underserved areas (Elias et al., 2018; Hu et al., 2019). SLT use causes cancer and other fatal diseases (NCI, 2014; Rostron et al., 2018; Timberlake et al., 2017; Tomar et al., 2019), and there are no medications approved by the FDA for SLT cessation. The harms of SLT and lack of effective SLT cessation aids highlight the need for new approaches for helping people who use SLT reduce their health risks.

While most US people who use combustible tobacco products are subject to restrictions on where and how often they smoke, SLT can be used throughout the day in almost any environment. Additionally, relative to combustible cigarettes, SLT use involves a longer use episode with similar peak plasma nicotine concentrations that increase more slowly and decline less rapidly (Benowitz et al., 1988; Fant et al., 1999). Thus, in general, in each tobacco use episode, people who use SLT are exposed to as much or more nicotine than people who use combustible tobacco products.

Nicotine is a psychomotor stimulant that supports dependence in the majority of people who use tobacco regularly (Benowitz, 2008). Nicotine dependence results in aversive symptoms

during periods of abstinence (e.g., craving, irritability, insomnia), and these aversive symptoms make quitting difficult (Hughes & Hatsukami, 1986). With regard to SLT, measures of dependence and abstinence symptoms that appear upon abrupt SLT cessation have been established (Ebbert et al., 2012). Severity of nicotine dependence is similar in people who use SLT and people who smoke cigarettes, yet people who use SLT make fewer quit attempts (Kypriotakis et al., 2018; Strong et al., 2017).

Fewer attempts at SLT cessation are puzzling given that 45% of people who use SLT report interest in quitting/cutting down (suppl. table A of Strong et al., 2015). Despite evidence of nicotine dependence among people who use SLT, the majority of FDA-approved tobacco/nicotine cessation aids are intended for use by cigarette smokers and are not effective for SLT cessation (Severson et al., 2020). SLT products have been proposed as a reduced harm alternative to conventional cigarettes (Clarke et al., 2019; Fagerström & Ramström, 1998; Gartner et al., 2007). More relevant to the present study, novel oral tobacco products that may expose the user to fewer tobacco toxicants have been characterized as a possible reduced harm product and/or cessation aid for people who use SLT (Hatsukami & Carroll, 2020; Kostygina et al., 2016).

Recently, novel oral tobacco products that are marketed as containing no tobacco but instead consist of a small pouch filled with nicotine powder and non-tobacco additives (e.g., flavorants, pH adjusters) have become available for purchase to anyone over the age of 21 in the US. The absence of tobacco leaf in these products suggests less exposure to tobacco toxicants and a potential innovative treatment/reduced harm option for people who use SLT. However, there are very little non-industry-sponsored data regarding the effects of these oral nicotine pouches (ONPs) in people who use SLT. The sections below provide an overview of SLT

(including the acute and long-term effects of SLT use), the clinical laboratory methods established for understanding the acute effects of novel tobacco products, and available information (including industry-sponsored data) on the acute effects of ONPs. The aim of this study was to apply clinical laboratory methods in an independent evaluation of the acute effects of ONPs.

Smokeless Tobacco

An array of tobacco products exist within the category of “smokeless tobacco,” including those that are administered orally and nasally. Globally, the prevalence of SLT use and typical product characteristics differ considerably across countries and regions (NCI, 2020; Siddiqi et al., 2020). The heterogeneity of SLT products makes broad characterization of the acute and long-term effects of SLT difficult. Instead, SLT products may be grouped based on composition similarity and/or regional popularity in order to represent accurately the effects of products of interest. In the US, the vast majority of SLT products consumed are moist snuff, or “dip,” that consists of cut tobacco leaves, loose or pouched, that are placed between the cheek or lip and gum during use (Center for Tobacco Products, 2023). The focus of this dissertation is on SLT use in the US; therefore, the following sections focus on moist snuff.

Who uses smokeless tobacco?

History of Smokeless Tobacco Use. Global awareness of tobacco and the subsequent proliferation of tobacco use occurred as a result of the colonization of the Americas in the late 15th and 16th centuries. Prior to colonization, tobacco was used medicinally within many indigenous nations located in North and South America, and sacred tobacco use has been documented in over 300 indigenous nations in North America (Winter, 2000). The recent discovery of tobacco seeds in the Great Basin, located in the North American Desert West,

provide evidence of human tobacco use approximately 12,000 years ago (Duke et al., 2021). Traditional tobacco use within indigenous nations includes the offering of tobacco leaves as gifts or sacred offerings (Struthers & Hodge, 2004), medicinal application (e.g., chewing tobacco leaves as a treatment for tooth pain; Pego et al., 1995), as well as ceremonial inhalation via pipe smoking (Winter, 2000; Struthers & Hodge, 2004). Additionally, many indigenous nations' creation stories include descriptions of the tobacco plant (Winter, 2000; Struthers & Hodge, 2004), providing evidence that the tobacco plant and tobacco use are fundamental elements of the history and culture of the Americas. Tobacco continues to be an important and sacred aspect of the culture of many indigenous nations (Nadeau et al., 2012; Struthers & Hodge, 2004).

Within one century of the “discovery” of the Americas by Christopher Columbus, tobacco was being cultivated and used worldwide, becoming an important element of the economy of the American colonies (Christen et al., 1982). Tobacco consumption via oral administration was common in indigenous nations prior to colonization, and post-colonialization American tobacco use included both nasal (e.g., dry snuff) and oral administration (e.g., chewing tobacco; Goodman, 1994). Smokeless tobacco was the most popular form of tobacco used in the US from the American Revolution until the industrialization of cigarette production in the late 19th century (Ravenholt, 1990; Young et al., 1988).

The modern cigarette quickly became the most popular tobacco product in the US, in part due to the industrialization of cigarette production (i.e., the invention of the Bonsack cigarette rolling machine), the discovery and use of flue-cured tobacco, and innovative national advertising campaigns (Giovino, 2002; Goodman, 1994; Hannah, 2006; Slade, 1989). As the cigarette grew in popularity, SLT use declined throughout the US (Giovino, 2002; Goodman, 1994). In 1908, combustible tobacco sales (i.e., cigarettes, cigars) by weight exceeded sales of

smokeless tobacco for the first time in the US; by 1918, cigarette consumption was greater than consumption of all other forms of tobacco (Fiore et al., 1993; Hannah, 2006). Estimates of per capita tobacco consumption in the first half of the 20th century allow insight into the dramatic shift in product use. In 1900, smokeless tobacco consumption per capita was 5.68 lbs. and cigarette consumption was 1.27 lbs.; by 1950, smokeless tobacco consumption per capita was 1.20 lbs. and cigarette consumption was 9.54 lbs. (Psoter & Morse, 2001).

Modern Smokeless Tobacco Use. In response to the steady decline in SLT use during the first half of the 20th century, tobacco corporations began an aggressive marketing campaign of SLT products aimed at youth and young adults (Glover et al., 1982), as well as manipulation to product pH to elicit tobacco use initiation (via more palatable “starter” products) and graduation to dependence (via products with comparably greater nicotine delivery). In particular, white boys and young men were targeted with advertisements and campaigns aimed at constructing an image of white masculinity that included SLT use (Bender, 1984; Glover et al., 1982), and the SLT products marketed to young men were often designed to contain less freebase nicotine and thus be more palatable to first time users. Advertisements constructed an image of SLT as a signal of hegemonic masculinity via “rugged,” outdoors imagery and endorsement by “macho” sports stars and musicians (Glover et al., 1982). Adolescents and adults continue to associate SLT with hegemonic masculinity, describing the images on SLT cans as “manly” and “tough” (Liu et al., 2014). Additionally, white men continue to make up the majority of people who use SLT in the US, and the cultural significance of SLT as a marker of masculinity remains an important factor influencing SLT use initiation and maintenance (Helme et al., 2012, 2020).

Tobacco companies have a long history of pursuing tobacco use initiation in young people via product design and targeted marketing (Anderson, 2011; Kostygina & Ling, 2016;

Qian et al., 2021; Wayne & Connolly, 2002), and in 1972, the US Smokeless Tobacco Company (USST) worked with the Swedish Tobacco Company to create a “starter” smokeless tobacco product that was more mild (i.e., less nicotine delivered) and flavored than other SLT products, aimed at “mainly young consumers” (Hendlin et al., 2017; O’Grady, 1973). In fact, early advertisements characterized flavored SLT products as “just right for new users,” with instructions to the “new user, [to] be careful not to swallow the juices,” and assertions that a brand “continues to please all ages” (US Smokeless Tobacco, n.d.). These starter products were flavored and contained less freebase nicotine than other SLT products, and therefore were considered the “start” of what one company designated the “graduation process,” with an eventual “graduation” to use of an SLT product that contained a high amount of freebase nicotine (e.g., Copenhagen; (US Smokeless Tobacco, 1972). By the late 1970s, USST actively targeted college students via on-campus marketing programs (Qian et al., 2021). These programs employed student representatives to approach, demonstrate, and sample SLT products with other students. Representatives were instructed to conduct sampling sessions at campus functions, including sporting events. Initiation of SLT use continues to occur at sporting events for many users (Helme et al., 2012).

Student representatives often provided samples of these “starter” products during these sampling events, and program requirements included the distribution of at least 180 samples per month (Qian et al., 2021). By 1983, the USST College Marketing Program was active within 175 colleges and universities in the US, and student representatives were compensated \$120 per month. From 1978 to 1982, sales of SLT increased by 55% (USDHHS, 1986). By 1987, approximately 9% of 18-24 year old men reported current SLT use (Nelson et al., 2006). Additionally, approximately 19% of high school boys reported current use of SLT products in

1991 (Nelson et al., 2006). By the early 21st century, the prevalence of SLT use declined to 5% among 18–24-year-old men in 2000 and to 11% among high school boys in 2003 (Nelson et al., 2006).

More recently, prevalence of SLT use has increased (Creamer et al., 2019), and the most popular form of SLT in the US is moist snuff (or “dip”) that represents approximately 90% of SLT sales (FTC, 2021). From 2002 to 2012, SLT use increased from 6.7% to 7.1% among adult men (Agaku & Alpert, 2016). In 2018, 5.9 million US adults and ~1 million US middle and high school students reported current SLT use (Creamer et al., 2019; Gentzke et al., 2019). Prevalence of SLT use is substantially greater among men in occupations with a high degree of sex-segregation (e.g., construction, mining; Syamlal et al., 2016) as well as occupations that maintain a particularly salient masculinization (e.g., soldier/military personnel, firefighter; Bray et al., 2009; Jitnarin et al., 2015). Sales of SLT increased by 65% between 2005 and 2011 (Delnevo et al., 2014), and in 2019 sales of moist snuff in the US were more than \$4 billion (FTC, 2021).

SLT use is more prevalent in the southern and midwestern states, and most people who use SLT live in non-metropolitan/rural areas (Hu et al., 2019; Wiggins et al., 2020). The states with the highest prevalence of SLT use are among the most economically disadvantaged (Elias et al., 2018; Hu et al., 2019). For example, the five states with the highest rates of SLT use in 2016 were Wyoming (9.8%), West Virginia (8.5%), Arkansas (7.8%), Montana (7.7%), and Kentucky (7.4%). The average percentage of people living in poverty is higher than the 11.2 % national average in three of these states (West Virginia, 14.6%; Arkansas, 14.7%; and Kentucky, 14.4%; US Census Bureau, 2021b). Additionally, rural areas have a higher proportion of uninsured residents (US Census Bureau, 2021a), which may make options for tobacco cessation treatment inaccessible. As mentioned previously, there are no medications approved for SLT cessation by

the FDA; nonetheless, treatments that include behavioral interventions often administered in healthcare settings (e.g., counseling sessions with a therapist, health professional, or dental professional) have been shown to increase SLT quit rates (Hatsukami et al., 1996; Severson et al., 2009; Walsh et al., 2010). The convergence of economic disadvantage, absence of FDA-approved SLT cessation medications, and lack of healthcare may explain why 45% of people who use SLT report interest in quitting/cutting down their SLT use, yet they are less likely to have made cessation attempts when compared to people who smoke cigarettes (suppl. table A, Strong et al., 2015; Kypriotakis et al., 2018).

As detailed above, SLT use in North America was common pre- and post-colonization, though product characteristics and administration routes differed. A decline in the use of SLT products in the early and mid-20th century was met with product changes (i.e., pH manipulation) and aggressive marketing tactics by tobacco corporations intended to construct an image of SLT as an indicator of white masculinity. Many of these marketing efforts targeted youth and college-aged men. Additionally, “starter” products were designed, marketed, and distributed to young men (Mejia & Ling, 2010). These products were intended to deliver nicotine less effectively than other commercially available SLT products in order to facilitate SLT use initiation in nicotine naïve individuals. As a result of the emphasis on reinforcing SLT’s masculine image and aggressive promotion of “starter” products by the tobacco industry, SLT experienced a “reemergence,” and use increased among young white men throughout the 1970s and 1980s (Connolly et al., 1986). The demonstrated ability of the tobacco industry to construct and shape public consciousness regarding tobacco products highlights the need for independent (i.e., not industry-sponsored) research on tobacco products. In order to understand accurately the

individual and public health consequences of initiation and habituation of SLT use, the acute and long-term effects of these products must be examined independently and systematically.

What are the acute effects of smokeless tobacco products?

Clinical laboratory studies have established the acute effects (including the nicotine delivery profile and subjective effects) of SLT products. In general, people who use SLT are exposed to as much or more nicotine per use episode than people who use combustible tobacco products (Benowitz et al., 1988; Cheng et al., 2020), but nicotine delivery can vary based on product brand (Fant et al., 1999). Nicotine delivery is an important predictor of the acute subjective effects of tobacco products (e.g., reported product strength, suppression of aversive nicotine/tobacco abstinence symptoms; Fant et al., 1999), but often nicotine delivery alone does not account entirely for the subjective effects reported during use (Gire & Eissenberg, 2000; McChargue et al., 2002; Pickworth, 2014). Several factors have been identified that influence the acute effects of SLT products, including length of use and product characteristics (e.g., nicotine content, pH).

Nicotine Delivery of Smokeless Tobacco. During use, SLT is placed between the cheek or lip and gum for 10 - 30 minutes (IARC, 2007), and this extended use period (compared to many other tobacco products, including combustible cigarettes) influences the amount of nicotine exposure for the user. For example, in a study of 10 male people who smoke, the nicotine delivery of four tobacco products was characterized and compared (Benowitz et al., 1988). Participants used one tobacco product during each of four study conditions: two SLT products (moist snuff and chewing tobacco), combustible cigarettes, or nicotine gum (Benowitz et al., 1988). Participants used all oral products (moist snuff, chewing tobacco, nicotine gum) for 30 minutes, and took 12 puffs of their own brand of cigarette over 9 minutes. Participants were

able to choose from among the most popular brands of moist snuff (Copenhagen or Hawken-Wintergreen) and chewing tobacco (Redman, Days Work, or Brown Mule), and all participants used Nicorette brand nicotine gum (two 2 mg pieces). Mean peak plasma nicotine concentration did not differ significantly between SLT products (moist snuff, chewing tobacco) and cigarettes. Peak plasma nicotine concentration was significantly less during use of nicotine gum. The rise and decline of plasma nicotine was less rapid in SLT products when compared to cigarettes, resulting in greater total nicotine exposure during SLT use. Specifically, estimated total nicotine absorption from moist snuff was 3.6 mg; from chewing tobacco, 4.5 mg; from a cigarette, 1.8 mg; and from nicotine gum, 1.9 mg. The extended use period of SLT, coupled with the comparable peak nicotine concentration, resulted in nicotine exposure levels double the amount observed during cigarette use (Benowitz et al., 1988).

Comparing brands of SLT products, a study of 10 people who use SLT examined the nicotine delivery and subjective effects of 4 different brands of moist snuff and 1 brand of tobacco-free mint snuff (Fant et al., 1999). The moist snuff brands used in this study were Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits. These brands are popular, commercially available products. Nicotine content was similar for all brands (11.4, 11.4, and 10.5 mg/g, respectively) with the exception of Skoal Bandits (7.5 mg/g; Henningfield et al., 1995). Participants used 2 g of each product for 30 minutes, and the nicotine delivery observed varied according to product used. Specifically, the greatest plasma nicotine concentration increase was observed for Copenhagen, with a mean maximum increase of 19.5 ng/ml ($SEM = 4.1$). Mean plasma nicotine concentration increase was 14.9 mg/ml for Skoal Long Cut Cherry ($SEM = 3.0$) and was 14.9 mg/ml for Skoal Original Wintergreen ($SEM = 2.4$) as well. Additionally, plasma nicotine concentration increased most rapidly in Copenhagen, with

plasma nicotine concentration reaching an average of 15 ng/ml within six minutes of administration. In comparison, plasma nicotine concentration reached an average of 15 ng/ml for Skoal Long Cut Cherry at 20 minutes and for Skoal Original Wintergreen at 25 minutes following product administration. The lowest plasma nicotine concentration increase was observed during Skoal Bandit use, with a mean maximum increase of 4.2 ng/ml ($SEM = 1.4$). Importantly, Skoal Bandits were created as a “starter” product; the nicotine delivery observed in this study bolsters the argument that these products were intended to be “milder” (i.e., deliver less nicotine) than other SLT products in order to increase palatability in nicotine-naïve consumers (Hendlin et al., 2017). Overall, the nicotine delivery of SLT varies considerably based on the brand of product used, with plasma nicotine concentration increases during SLT use comparable to (Copenhagen, Skoal Long Cut Cherry and Skoal Original Wintergreen) or significantly less than (Skoal Bandits) plasma nicotine increases observed during combustible cigarette use (Fant et al., 1999; Benowitz et al., 1988). The differences observed in nicotine delivery among brands with similar nicotine content may be related to product pH, as described next.

pH Influences Nicotine Delivery. Nicotine is weakly basic, and at a pH of 8.0 consists of 50% protonated nicotine and 50% freebase nicotine. As the pH of nicotine becomes more alkaline (i.e., > 8.0), the proportion of freebase nicotine increases. Freebase nicotine more readily crosses lipid membranes, making it more bioavailable than nicotine in protonated form. Nicotine products with higher pH (i.e., > 8.0), and thus containing a higher proportion of freebase nicotine, may expose the user to greater amounts of nicotine more rapidly when compared to products with a lower pH (and thus, a lower proportion of freebase nicotine). Because nicotine delivery may be influenced by pH, instructions for oral nicotine cessation aids (i.e., nicotine

gum, lozenge) often include directions to avoid eating or drinking for 15 minutes prior to use. These directions are aimed at preventing disruptions to nicotine delivery via changes in oral pH as a result of recent consumption of acidic food or drink (CDC, 2021; US Department of Veteran Affairs, 2013). Comparing across popular SLT brands (including Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits), a study examined the relationship of nicotine content, pH and available (freebase) nicotine content (Henningfield et al., 1995). As mentioned previously, mean nicotine content of these brands ranged from 10.3 - 11.4 mg/g, with the exception of Skoal Bandits at 7.5 mg/g. Mean pH values varied according to product brand. Specifically, the highest mean pH was observed for Copenhagen, with a pH of 8.6 ($SD = 0.5$). Mean pH values observed for Skoal Long Cut Cherry were 7.5 ($SD = 0.12$), for Skoal Original Wintergreen were 7.6 ($SD = 0.14$), and the lowest mean pH value was observed in Skoal Bandits, with a pH of 6.9 ($SD = 0.27$; Henningfield et al., 1995). Total freebase nicotine of each product was calculated, and was greatest for Copenhagen at 9.0 mg/g; values for Skoal Long Cut Cherry and Skoal Original Wintergreen were lower at 2.6 mg/g and 2.9 mg/g, and the lowest freebase nicotine content was observed for Skoal Bandits at 0.5 mg/g. These freebase nicotine values parallel the nicotine delivery results observed in clinical examination of these brands (Fant et al., 1999).

The nicotine delivery of SLT is influenced by pH, yet pH is not the only factor influencing the acute effects of SLT products. Importantly, the examination of different SLT brands does not control for product characteristics such as tobacco blend and/or nicotine content. In order to understand accurately the factors that influence the acute effects of SLT, product characteristics must be controlled and examined individually to determine the extent of their influence on subjective effects ratings.

In a study examining the effect of pH on nicotine delivery, a commercially available brand of SLT (Copenhagen Original Long Cut) was manipulated to differ in pH in order to control for other product characteristics (e.g., nicotine content; Wilhelm et al., 2021). All product used had a nicotine content of 9 mg/g, consistent with previous research examining Copenhagen SLT (see above). Modifications to product pH were accomplished by the addition of an acid (citric acid) to decrease pH or a base (calcium carbonate) to increase pH. These additions to the SLT product produced four conditions: a low pH condition (pH = 5.0), the original product pH (pH = 7.7), and two high pH conditions (pH = 8.2 and pH = 8.4). Differences in nicotine delivery based on product pH were observed, and these differences support earlier research that established pH as an important factor in the determination of SLT nicotine delivery (e.g., Henningfield et al., 1995; Fant et al., 1999). Specifically, greater pH resulted in greater maximum nicotine concentration (C_{\max}), with a mean C_{\max} of 16.7 ng/ml ($SEM = 0.9$) in the 8.4 (highest) pH condition, 14.8 ng/ml ($SEM = 0.7$) in the 8.2 pH condition, 8.7 ng/ml ($SEM = 0.6$) in the 7.7 pH condition, and 3.9 ng/ml ($SEM = 0.4$) in the 5.0 (lowest) pH condition. The results observed in these and other studies (Henningfield et al., 1995; Fant et al., 1999) suggest that other factors in addition to nicotine content may influence the acute effects of SLT products, including their subjective effects.

Subjective Effects of Smokeless Tobacco. For all tobacco products, use is perpetuated via acute drug effects (e.g., stimulating effects of nicotine; (Glautier, 2004) as well as negative reinforcement via suppression of nicotine/tobacco abstinence symptoms (Eissenberg, 2004; Pomerleau et al., 2003). Habitual exposure to nicotine-containing tobacco products results in neuroadaptive changes, and these changes are at least partly responsible for the aversive symptoms typically experienced following abrupt tobacco cessation (e.g., irritability, craving

nicotine/tobacco products, insomnia; Hughes & Hatsukami, 1986). Upon subsequent use of nicotine-containing product(s), these aversive symptoms are reduced and/or eliminated. Importantly, some of these aversive symptoms are also reduced when placebo tobacco products are administered following a period of abstinence (e.g., denicotinized cigarettes; Buchhalter et al., 2005; Gire & Eissenberg, 2000; Gross et al., 1997; Pickworth et al., 1999), suggesting that nicotine dependence alone does not account for the presence and severity of all nicotine/tobacco abstinence symptoms. Many tobacco users report relief from abstinence symptoms as a motivation for maintained use of tobacco products as well as relapse during quit attempts (Piasecki et al., 2007; Piper et al., 2004; Shiffman et al., 1996). For this reason, examinations of the acute effects of tobacco products, including SLT, often include measures of nicotine/tobacco abstinence symptoms.

In a study examining nicotine/tobacco abstinence symptoms in people who use SLT, participants used their own brand of SLT (Copenhagen) for 3 days, followed by 3 days of tobacco/nicotine deprivation (Hatsukami et al., 1987). All participants were people who use SLT daily, and abstinence was verified via saliva cotinine. During tobacco abstinence, participants reported increased aversive abstinence symptoms (e.g., craving, irritability) relative to pre-abstinence baseline. For example, mean ratings of “craving for tobacco” significantly increased by 17.5 ($SD = 3.9$) during abstinence when compared to mean craving ratings at baseline. Additionally, mean total scores on a withdrawal symptom checklist (Hughes & Hatsukami, 1986) significantly increased by 2.5 ($SD = 0.9$) during abstinence when compared to baseline. The results from this study establish that aversive symptoms occur during SLT abstinence, and these symptoms are similar to those observed experienced in cigarette smokers during abstinence (Hughes & Hatsukami, 1986). While many abstinence symptoms may be similar between people

who use SLT and people who smoke cigarettes, symptom severity may differ based on the typical tobacco product used, with more severe abstinence symptoms reported by people who smoke when compared to people who use SLT during tobacco abstinence in this study.

Limitations of this study include potential confounding factors of biological sex and amount of SLT use (Allain et al., 2015; Carpenter et al., 2006; Weinberger et al., 2015). In order to understand the specific factors that may influence SLT abstinence symptoms, the suppression/reduction of abstinence symptoms based on nicotine-specific and non-nicotine factors must be examined.

In a study examining the efficacy of NRT for SLT cessation, 60 people who use SLT were assigned randomly to one of three nicotine gum conditions: 0 mg, 2 mg, or 4 mg (Hatsukami et al., 1992). All participants were asked to abstain from SLT for 5 days and were required to use at least 6 pieces of gum per day. No significant differences in nicotine/tobacco abstinence symptoms were observed among groups. However, when participants were divided into two categories of “high” and “low” cotinine at baseline (based on median cotinine at baseline, 250 ng/ml), significant differences in craving ratings were observed between conditions in the high cotinine group. Specifically, changes in craving ratings were significantly greater in the 0 mg condition ($M = 0.82$) when compared to the 2 mg condition ($M = -0.11$) and approached significance when compared to the 4 mg condition ($M = -0.04$; standard deviations not provided by Hatsukami et al., 1992). No significant differences were observed between the 2 mg and 4 mg condition. These results suggest that non-tobacco nicotine may reduce abstinence symptoms in people who use SLT. This effect may only be present in people who use SLT heavily and/or frequently, and nicotine gum may be less effective at reducing nicotine/tobacco abstinence symptoms in people who use SLT when compared to people who smoke cigarettes (Fagerström

et al., 1993; Shiffman et al., 2003). Similar studies examining the effects of the transdermal nicotine patch on nicotine/tobacco abstinence symptoms in people who use SLT have found short-term reductions in active patch conditions when compared to placebo, yet both the nicotine gum and the nicotine patch have been shown to have no effect on SLT quit rates at long-term follow-up when compared to placebo (Boyle, 1992; Hatsukami et al., 1996, 2000; Howard-Pitney et al., 1999).

As discussed, peak plasma nicotine concentrations can be similar in people who use SLT and people who smoke cigarettes, but the prolonged use period results in significantly greater total nicotine exposure in people who use SLT when compared to people who smoke (Benowitz et al., 1988). For this reason, standard doses of NRT that have been established based on efficacy in people who smoke may not be high enough to be effective in people who use SLT (Lindson et al., 2019; USDHHS et al., 2020). In a study examining the effects of high-dose NRT on SLT abstinence symptoms, 42 people who use SLT were randomized to four conditions: 21, 42, 63 mg/day or placebo nicotine patch (Ebbert et al., 2007). Participants were instructed to wear three patches simultaneously every day for 8 weeks. The number of active patches was double-blind and dependent on condition (i.e., one patch was active in the 21 mg condition, two patches were active in the 42 mg condition, three patches were active in the 63 mg condition, and zero patches were active in the placebo condition) for 8 weeks. During the first week, a dose-dependent relationship was observed such that the higher doses of the nicotine patch were associated with greater decreases in arousal, negative affect, and restlessness. At week 2, the higher patch doses were associated with greater decreases in arousal, and no significant relationship between patch dose and abstinence symptoms were observed in the remaining 6 weeks. In a subsequent clinical trial, 52 people who use SLT were assigned randomly to a high nicotine patch (42 mg; $n = 25$) or

placebo patch (0 mg; $n = 27$) condition. Total abstinence scores were observed to be higher in the placebo group when compared to the active group during the first week of abstinence, but this difference was not significant. Additionally, the high dose nicotine patch significantly increased abstinence rates (40%) when compared to placebo (19%) at 3 months, but this effect was not significant at 6 months (32% vs 19%). These results establish that high (i.e., 42 mg) nicotine patch treatment may reduce tobacco/nicotine abstinence symptoms effectively in people who use SLT, but may not increase long-term quit rates. Overall, various amounts of nicotine delivered via gum or nicotine do not have a significant effect on long-term SLT abstinence rates, suggesting that there may be other factors influencing the nicotine/tobacco abstinence symptoms experienced by people who use SLT.

In a placebo-controlled study of the influence of non-nicotine factors on the subjective effects of SLT, 14 people who use SLT completed three sessions based on study condition: their own brand of SLT (active), nicotine-free SLT (placebo), or no SLT (abstinence condition; Gire & Eissenberg, 2000). Participants used 2 g of the active and placebo products for 30 minutes, 4 times per session (with 30 minutes between each administration) for a total session length of 4.5 hours. Suppression of abstinence symptoms did not differ significantly in the active or placebo conditions, when compared to the abstinence condition. For example, ratings of “Urge to use SLT” were not significantly different at baseline between conditions, and changes over time differed by condition, with increased ratings in the abstinence (no SLT) condition and decreased ratings in the active and placebo conditions. Specifically, mean baseline ratings of urge to use SLT for the abstinence condition were 48.3 ($SD = 34.9$) and increased to a mean of 63.2 ($SD = 32.7$) by the end of the session. For the active and placebo conditions, mean baseline urge ratings did not differ significantly, with a mean of 60.4 ($SD = 32.5$) in the active condition and 41.4 (SD

= 33.5) in the placebo condition. By the end of the session, mean urge ratings were decreased in the active and placebo conditions, with mean urge ratings of 26.5 ($SD = 28.5$) in the active condition and 19.1 ($SD = 24.1$) in the placebo condition. Additionally, significant differences were observed on items measuring the direct/sensory effects of SLT. When collapsed across time, mean ratings of product strength were significantly higher in the active condition ($M = 29.8$, $SD = 32.0$) when compared to the placebo condition ($M = 15.2$, $SD = 21.3$). The differences in the subjective effects of placebo vs. active SLT observed in this study are similar to those observed in studies of non-nicotine or low-nicotine cigarettes (Butschky et al., 1995; Gross et al., 1997; Pickworth et al., 1999), suggesting that non-nicotine factors influence nicotine/tobacco abstinence symptoms and severity. Additionally, these results suggest that the influence of non-nicotine factors are important considerations in the measurement and treatment of nicotine/tobacco abstinence symptoms.

Overall, the acute effects of SLT vary considerably based on product characteristics, including nicotine content, pH, and non-nicotine factors (e.g., sensory effects). During SLT use, peak plasma nicotine concentration values can be similar to those observed during cigarette smoking, but SLT use involves a longer use episode. Thus, people who use SLT may be exposed to as much or more nicotine than cigarette smokers. Importantly, the nicotine delivery of SLT depends on both nicotine content and product pH, with increases in pH resulting in more freebase nicotine and thus greater amounts of nicotine delivered to the user. Nicotine delivery influences the subjective effects of SLT products, such that ratings of strength are greater during use of SLT with high freebase nicotine content (Fant et al., 1999). Additionally, when non-tobacco nicotine is administered following acute SLT abstinence (i.e., via pharmaceutical products like nicotine gum or patch), ratings of nicotine/tobacco abstinence symptoms are

reduced. Non-nicotine factors, such as the sensorimotor effects associated SLT use, also contribute to reductions in ratings of abstinence symptom severity; products that mimic the sensory experience of tobacco use but do not deliver nicotine reduce some abstinence symptoms relative to complete abstinence (Gire & Eissenberg, 2000; Gross et al., 1997; Pickworth et al., 1999). Importantly, tobacco users report relief from abstinence symptoms as a motivation for continued use (McEwen et al., 2008; Piasecki et al., 2007; Piper et al., 2004). Aversive nicotine/tobacco abstinence symptoms also make cessation difficult, even when users experience the long-term negative health effects of SLT use such as oral leukoplakic lesions, cardiovascular disease, and cancer.

What are the long-term effects of smokeless tobacco use?

Regular SLT use leads to aversive nicotine/tobacco abstinence symptoms upon abrupt cessation (Hatsukami et al., 1987). These aversive symptoms make quitting difficult, even when people who use SLT experience the negative physiological/health consequences associated with SLT use. The relatively swift onset of some of the negative health effects of SLT use (i.e., pre-cancerous leukoplakic lesions) compared to smoking provide an early indicator to people who use SLT of the negative health consequences of SLT use. For this reason, many SLT interventions are designed to be administered by dental professionals, and these interventions are among the most effective available (Carr & Ebbert, 2012; Gordon et al., 2006). Other negative health consequences of SLT use exhibit a similar time course to those caused by smoking, including oral cancer and coronary heart disease (Lee & Hamling, 2009; Timberlake et al., 2017). Despite similarities in the long-term effects of cigarette smoking and SLT use, people who use SLT who are interested in quitting are at a particular disadvantage due to the lack of

FDA-approved SLT cessation aids as well as the large portion of users who experience poverty and/or are un- or under-insured.

Leukoplakic lesions are the most common pre-cancerous oral lesions and estimates of the percentage that develop into malignancy vary widely from 1% - 30% (Arduino et al., 2013). Characterized as a white patch or plaque, initial diagnosis of these oral lesions is made by exclusion (i.e., after excluding other diseases; van der Waal, 2015). Though the exact cause of leukoplakic lesions is unknown, their high prevalence in people who use SLT and people who smoke cigarettes and typical resolution following tobacco cessation is considered sufficient evidence to identify tobacco use as a cause of these lesions (Bánóczy et al., 2001).

Leukoplakic lesions are considered by WHO as a “potentially malignant disorder” (Lodi & Porter, 2008). In a longitudinal observational study of 320 patients with oral leukoplasia, 17.8% developed oral carcinoma in a mean of 4.5 years (Liu et al., 2012). Similarly, in a study of 257 patients with oral leukoplakia, 17.5% developed carcinoma in a mean of 8.1 years (Silverman et al., 1984). The gold standard treatment for leukoplakia is surgical removal of the lesion, despite a lack of scientific evidence of the effectiveness and high rates of lesion reoccurrence following removal (Holmstrup & Dabelsteen, 2016; Sundberg et al., 2019). Additionally, there is insufficient evidence that any complementary treatments (e.g., retinoids, non-steroidal anti-inflammatory drugs) are effective at preventing leukoplakic lesions from developing into oral cancer (Lodi et al., 2017). Tobacco use has been shown to increase the risk of leukoplakic lesions, and these lesions develop in a large portion of people who use SLT (Fisher et al., 2005; Reichart, 2001). Leukoplakic lesions often appear within the first years of SLT use, with lesions observed in up to 33% of 12- to 17-year-old people who use SLT (Tomar et al., 1997).

In a study that examined the prevalence of leukoplakic lesions, basic military training provided an environment of mandatory tobacco cessation (Martin et al., 1999). Participants ($N = 3,015$) were US Air Force military trainees who completed examinations of the oral cavity before and after six weeks of tobacco cessation (during basic military training). Participants also answered questionnaires regarding their SLT use prior to their military training. Among the 3,051 male participants, 302 were identified as people who use SLT (Martin et al., 1999). Leukoplakia was present in 39.4% of people who use SLT, compared to 1.2% of non-users. Importantly, the average age of participants in this study was 19.5 years, demonstrating that the development of leukoplakia can occur within the first years of SLT use. In fact, length of use was associated significantly with risk of leukoplakia, with leukoplakic lesions present in 71% of participants who reported using SLT for more than 4 years, compared to 15% of participants who reported using SLT for 1 year or less. Following six weeks of mandatory tobacco cessation, 97.5% of leukoplakic lesions were completely resolved (Martin et al., 1999). While length of SLT use increased the risk of developing leukoplakia, the results from this study establish that six weeks of tobacco cessation can resolve nearly all leukoplakic lesions present in young adult male people who use SLT.

SLT was first designated as hazardous to human health in a Surgeon's General report released in 1986 (USDHHS, 1986), and expert panels continue to assert there is sufficient evidence that SLT use leads to an increased risk of cancers of the oral cavity, esophagus, and pancreas (IARC, 2007; NCI et al., 2014). Despite these assertions, results from population-level studies have been mixed, leading some scientists to argue that evidence is insufficient to designate SLT as hazardous to human health (Rodu & Jansson, 2004; Waterbor et al., 2004). Many population studies are not powered sufficiently to examine the effects of SLT use, due to

the relatively small numbers of people who use SLT that result from the low use prevalence in the US, and this limitation may impact the consistency of results. In fact, the frequency of critical limitations in studies of the long-term health effects of SLT use is perhaps one reason why evidence evaluated in recent expert reports include data that are more than 50 years old, despite changes in prevalence and product type of SLT (IARC, 2007; NCI, 2014). More recent evidence of the detrimental health effects of SLT is mixed; some large, industry-funded or -affiliated studies have found few differences in tobacco-related disease and mortality in people who use SLT when compared to never tobacco users (Fisher et al., 2019; Rodu & Plurphanswat, 2019), while other, independent examinations have found increased risk of diseases of the heart (Rostron et al., 2018; Timberlake et al., 2017) and all-cause mortality (Salazar et al., 2021), consistent with the conclusions reached in previous expert panel reports. Importantly, the tobacco industry's documented history of manipulating academic and scientific inquiry raises concerns regarding the ethical standard and validity of industry-sponsored conclusions.

In a study examining National Longitudinal Mortality Study participants between the years 1985 and 2011, mortality risks were compared in people who use SLT currently ($n = 4,919$) as compared to people who had never used tobacco ($n = 340,622$; Timberlake et al., 2017). The maximum participant follow-up time was 26.3 years, with a median follow-up time of 8.8 years, and participants reported their current tobacco use one time. People who use SLT currently did not have a significantly greater risk of all-cause or cancer mortality compared to people who never used tobacco but were at increased risk of coronary heart disease (H_zR : 1.24, 95% CI: 1.05, 1.46). The increase in risk of mortality from coronary heart disease was associated with moist snuff use (H_zR : 1.30, 95% CI: 1.03, 1.63), the most popular form of SLT used in the US. The authors acknowledge the use of a single measurement of SLT use was not capable of

capturing potential changes in tobacco use, including cessation or transition to other, more harmful tobacco products. Additionally, the relationship between SLT use and mortality from coronary heart disease could be confounded by lifestyle factors that were not measured in this study (e.g., alcohol use, BMI).

In a study examining National Health Interview Survey between the years 1987 and 2014, mortality risks in people who use SLT currently ($n = 3,324$) aged 35 and older were compared to people who had never used tobacco ($n = 126,788$) aged 35 years and over (Salazar et al., 2021). A significantly greater risk of all-cause mortality was observed in adult people who use SLT (women and men combined) aged 35–44 (H_zR : 3.14, 95% CI: 1.44, 6.87), and aged 75–84 (H_zR : 1.34, 95% CI: 1, 1.81) compared to people who had never used tobacco in the same age groups. Additionally, male who use SLT exclusively (i.e., men who use SLT who did not switch from cigarettes to SLT) aged 35-64 had a significantly greater risk of all-cause mortality (H_zR : 2.04, 95% CI: 1.27, 3.27) compared to males who had never used tobacco. This study did not assess disease-specific mortality risk in people who use SLT, but such an analysis likely would be hindered due to the small sample of people who use SLT. Additionally, demographic (e.g., insurance status, urban/rural residence) and lifestyle factors (e.g., alcohol use, physical activity) were not controlled for in this study, potentially confounding the observed effects. As detailed previously, people who use SLT may be more likely to be under-insured (US Census Bureau, 2021a), and SLT is more prevalent in rural areas (Hu et al., 2019; Wiggins et al., 2020); these factors may make people who use SLT more vulnerable to the detrimental health effects of SLT.

In a 2019 study examining data from the National Longitudinal Mortality Study as well as from the National Health Interview Study, the authors did not detect a significantly increased risk of all-cause mortality, all cancer mortality, or diseases of the heart in people who use SLT

(Fisher et al., 2019). The results of this study contrast with those observed in other studies examining data from NLMS (Timberlake et al., 2017) and NHIS (Salazar et al., 2021). Specifically, the authors of this study did not find a significantly increased risk of CVD in the NLMS dataset nor of significantly increased mortality risk in the NHIS dataset. First focusing on the NLMS discord, the dataset used in this study was a public use file in contrast to the larger restricted access dataset used in Timberlake et al., 2017. Specifically, the dataset used in Timberlake et al., 2017 was larger in sample size ($n = 4919$) and temporal range (1986-2011) compared to that used in this analysis ($n = 1863$; 1993-2005). Shifting focus to the NHIS discord, the group of people who use SLT used in this study included all participants (males and females combined) over the age of 18 who reported SLT use in contrast to the age and sex group stratifications used in Salazar et al., 2021. The inclusion of younger people who use SLT may have prevented the detection of mortality risk that increases with age and duration of tobacco use. Additionally, this analysis was funded by Altria, a tobacco corporation, and the results of this study are similar to those observed in other industry-sponsored studies of the long-term health effects of SLT use (Accortt et al., 2002; Rodu & Plurphanswat, 2019). The tobacco industry, including Altria/Phillip Morris, has an extensive history of using unethical practices to influence public perception of tobacco products. As detailed previously, tobacco corporations have used advertisements and the recruitment of peer representatives to construct and reinforce SLT use as an indicator of hegemonic masculinity (Glover et al., 1982; Mejia & Ling, 2010; Qian et al., 2021). In addition, the tobacco industry has attempted to influence public as well as academic perception of the risks of tobacco use via direct manipulation of scientific investigation and publication (Bero, 2005; Brandt, 2012; Hendlin et al., 2019; Muggli et al., 2003; Proctor, 2012). For these reasons, independent (i.e., not industry funded) studies of nicotine and tobacco

products must be prioritized when considering available evidence and attempting to draw meaningful conclusions from the scientific literature.

Scientific panels have designated SLT as carcinogenic and hazardous to human health since 1986 (IARC, 2007; NCI, 2014; USDHHS, 1986). More recent evidence to support this designation is mixed. The low prevalence of SLT use in the US makes population-level investigation challenging, and often SLT user groups are considerably smaller than the study sample (e.g., 3,492 people who use SLT vs. 210,090 study sample; Fisher et al., 2019). Another, perhaps more pertinent, reason for conflicting evidence regarding the long-term health effects of SLT use is the role of the tobacco industry within the field of science. Recent, independent work supports the conclusion that SLT use is hazardous to human health, but evidence suggests that the negative health consequences of SLT use may be of a lesser magnitude than the risks associated with cigarette smoking (Gupta et al., 2004; Inoue-Choi et al., 2019). For this reason, SLT products have been posited as potentially reduced harm alternatives to other tobacco product use, in particular cigarette smoking, by independent scientists (Clarke et al., 2019; Gartner et al., 2007; Pindborg & Axelsen, 1980) as well as tobacco industry-affiliated scientists (Colilla, 2010; Rodu & Godshall, 2006; Savitz et al., 2006). More relevant to the present study, novel oral tobacco products that may expose the user to fewer tobacco toxicants have been characterized as a possible reduced harm product and/or cessation aid for people who use SLT by independent scientists (Hatsukami & Carroll, 2020; Kostygina et al., 2016) and the tobacco industry (Azzopardi et al., 2021; Lee et al., 2021).

Novel Tobacco Products Marketed by the Tobacco Industry

The tobacco industry's response to steady reductions in conventional cigarette smoking over time includes the marketing of a variety of novel tobacco products as smoking alternatives

(Jacob, 2019), including electronic nicotine delivery systems (ENDS; Breland et al., 2018) and, now, orally-administered nicotine pouches (ONPs) such as Swedish Match's "Zyn" (Plurphanswat et al., 2020) and Altria's "ON!" (Robichaud et al., 2019). While these products are often marketed as reduced harm products, the demonstrably dishonest history of the tobacco industry's practices to influence public opinion (Malone, 2013) require independent evaluations of these products to determine their intended use, actual use, and potential as reduced harm/cessation aid products. In particular, the documented practices of product design and deceptive marketing aimed at recruitment of nicotine-naïve users (Glover et al., 1982; Hendlin et al., 2017; Qian et al., 2021), as well as efforts made to disrupt scientific consensus on the harms of tobacco use (Bero, 2005; Brandt, 2012; Drope & Chapman, 2001; Hendlin et al., 2019; Muggli et al., 2003; Proctor, 2012) engender mistrust in any statements or conclusions made by the tobacco industry regarding novel tobacco products.

As established previously, the tobacco industry has a history of targeting young, nicotine-naïve consumers via the addition of flavors to "starter" products that were marketed as "just right for new users" (US Smokeless Tobacco, n.d.). In addition to vulturine product design and marketing tactics, the tobacco industry has engaged in various tactics with the sole intent of manipulating and influencing tobacco science, including (but not limited to) funding scientific research (Brandt, 2012; Drope & Chapman, 2001; Finder, 2008) and publications (Hendlin et al., 2019) with the goal of introducing bias and eroding scientific consensus to advance corporate interests (Bramoullé & Orset, 2018; WHO, 2009). Oftentimes, the role of the tobacco industry has been concealed to present pro-tobacco evidence that appears to be funded independently.

In addition to funding scientific research, the tobacco industry has also infiltrated scientific journals/publications to "manufacture doubt" (Bramoullé & Orset, 2018). A systematic

review examining peer-reviewed articles on tobacco harm reduction published between 1992 and 2016 found a significant relationship between tobacco industry funding and support for tobacco harm reduction via product substitution (Hendlin et al., 2019). A total of 826 (326 empirical and 500 nonempirical) articles addressing substitution with a potentially less lethal tobacco product (e.g., SLT, ENDS) as a harm reduction strategy were included in the analysis. Funding by the tobacco, ENDS, or pharmaceutical industry was reported in nearly a quarter (23.9%; $n = 197$) of articles and was associated significantly with support for tobacco harm reduction. Articles funded by the tobacco industry (7%; $n = 59$) were over 50 times more likely to support tobacco harm reduction ($OR: 59.4, 95\% CI: 10.1, +infinity$). Specifically, 88% of tobacco industry funded articles were pro-harm reduction, compared to 41% of non-industry funded articles.

Additionally, all empirical studies funded by the tobacco industry ($n = 32$) were pro-harm reduction. Importantly, industry funding/support was identified based on author disclosures and conflict of interest statements and does not address undisclosed funding sources. For this reason, the authors acknowledge that industry influence likely is greater than what was observed in this study. Similar studies have found further evidence of an increased likelihood of pro-industry conclusions in tobacco-funded research and publications (Barnes & Bero, 1996; Pisinger et al., 2019).

Familiarity with the unethical conduct of the tobacco industry is critical when evaluating the evidence and conclusions presented regarding novel tobacco products. A recent example of the intersection of routine industry practices regarding a novel tobacco product can be found in ENDS. Early marketing often portrayed ENDS products as a harm reduction tool for smokers (Richardson et al., 2014), and publications authored by individuals associated with the tobacco industry attempted to legitimize this image (Nitzkin, 2014; Polosa et al., 2013). Independent

studies of early ENDS found they delivered little to no nicotine (Bullen et al., 2010; Vansickel et al., 2010), and adult use of ENDS increased from 1.3% in 2013 (Agaku et al., 2014) to 3.7% in 2020 (Cornelius et al., 2022).

In 2015, JUUL, a pod-based ENDS, was introduced to the ENDS market. While industry funded studies report the nicotine delivery of JUUL as significantly less than that of cigarettes (Goldenson et al., 2020, 2021), independent studies revealed these devices were able to deliver as much or more nicotine than a combustible cigarette (Hajek et al., 2020; Yingst et al., 2019). Increases in ENDS use by youth directly correspond with the introduction of JUUL; prevalence in high schoolers increased from 1.5% in 2011 to 16% in 2015 and subsequently grew to a peak of 20.8% in 2018 (Gentzke et al., 2019). In 2018, the FDA declared an epidemic of youth ENDS use (FDA, 2018), and in 2019, congressional hearings were conducted to investigate the marketing practices of JUUL (House Committee on Oversight and Reform, 2019).

Congressional and scientific investigations have established that JUUL engaged in marketing practices specifically aimed at young, nicotine-naïve users (House Committee on Oversight and Reform, 2019; Jackler, Chau, et al., 2019; Jackler, Li, et al., 2019), similar to industry practices detailed above. JUUL pods originally were available in a variety of sweet flavors, a well-established product characteristic designed to appeal to youth (Cummings et al., 2002; King, 2020; Villanti et al., 2019). A federal ban on flavored pod-based liquids was enacted in 2019 in direct response to the epidemic of youth ENDS use (FDA, 2020). Perhaps unsurprisingly, the tobacco industry owned shares in JUUL or its parent company from 2010 - 2023 (27% owned by Japan Tobacco International 2010-2015, Japan Tobacco International, 2011; 35% owned by Altria, 2018-2023, Altria Group, Inc., 2023). Additionally, JUUL has conducted, presented, and sponsored research that has been criticized as a threat to scientific

integrity and public health (Ault, 2019; Briggs & Vallone, 2022; Tan et al., 2019), including the purchase of a complete issue of a scientific journal in order to present company-funded research (Shiffman & Augustson, 2021). In a letter urging the FDA to “carefully scrutinize [...] industry funded research”, US Senators Warren and Blumenthal characterized JUUL’s purchase of a scientific journal as “abhorrent behavior” and drew comparisons to strategies historically employed by the tobacco industry (Warren & Blumenthal, 2021). Further, studies that disclose ENDS industry funding (or industry-related financial conflicts of interest) are over 20 times more likely to support tobacco harm reduction via product substitution, and industry sponsored studies report findings of no harmful substances or effects of ENDS significantly more often when compared to independent (i.e., non-industry funded) research (Hendlin et al., 2019; Pisinger et al., 2019).

A convincing case can be made for the tobacco industry’s reliance on tried-and-true tactics to manipulate public and scientific perception of ENDS unethically. For this reason, independent evaluations are critical to any conclusions with regard to novel tobacco products. Clinical laboratory methods have been used to examine the acute effects of various drugs for decades, including tobacco products. More recently, independent evaluations of ENDS have included studies using clinical laboratory methods to examine the acute effects of these products.

The sections below describe clinical laboratory methods as well-established, powerful tools for understanding the nicotine delivery profile and physiological and subjective effects of novel tobacco products (e.g., ENDS). Further, an overview of ONPs, including industry-sponsored data on the effects of these products, is provided. Importantly, virtually no independent research has examined the effects of ONPs in people who use smokeless tobacco, and only one independent study published in 2024 is currently available on the effects of ONPs

in people who smoke cigarettes (Keller-Hamilton et al., 2024a). In order to study these products and consider the potential for application as a reduced harm product and/or cessation aid, the nicotine delivery and subjective effects profile of ONPs must be determined in a manner that is independent of the tobacco industry and its funding sources that have been proven to influence results published in the peer-reviewed scientific literature (Bero, 2005; Brandt, 2012; Hendlin et al., 2019; Muggli et al., 2003; Proctor, 2012).

How Have Clinical Lab Methods Been Used to Evaluate Tobacco Products?

Clinical laboratory methods are well-established as powerful tools used to evaluate acute drug effects. These methods have been used to evaluate the physiological and subjective effects of several tobacco products, including SLT (Benowitz et al., 1988; Fant et al., 1999; Gire & Eissenberg, 2000; Hatsukami et al., 1987; Wilhelm et al., 2021) as well as novel tobacco products (e.g., ENDS).

Nicotine delivery profile and other physiological effects

Changes in plasma nicotine concentration and other physiological effects (e.g., heart rate increase) following the administration of nicotine and/or tobacco products are outcomes that have been used for decades in clinical lab research to evaluate a variety of tobacco products including combustible cigarettes (Benowitz et al., 1988; Malson et al., 2002), heated tobacco products (Breland et al., 2002; Maloney et al., 2020), ENDS (Hajek et al., 2020; Vansickel et al., 2010), and orally-administered SLT products (Gritz et al., 1981; Kotlyar et al., 2011).

In an early study examining the abuse liability of nicotine, eight male smokers completed eight experimental sessions based on different doses and dose order of intravenous nicotine (4 doses, including placebo; 4 sessions) or inhaled nicotine (4 doses, including placebo; 4 sessions; Henningfield et al., 1985). In this repeated-measures study, experimental sessions differed by

dose order, determined by randomly assigned Latin square sequences, and sessions alternated based on route of administration. Each session included administration of all 4 doses of either intravenous (0.75, 1.5 and 3.0 mg/10-sec infusion and placebo) or inhaled nicotine (0.4, 1.4 and 2.9 mg and placebo) at 1-hour intervals. A dose-dependent relationship was observed such that ratings of drug strength and liking were significantly increased as a function of nicotine dose. Additionally, ratings of “desire to smoke cigarettes” were inversely related to IV doses of and inhaled exposure to nicotine. Overall, this study established nicotine as a reinforcing, psychoactive substance similar to other drugs of abuse. The similarity of effects observed between IV and inhaled administration established nicotine as critical to the physiological and subjective effects of cigarettes.

The vast majority of studies evaluating the physiological effects of novel tobacco products examine inhaled tobacco products. For example, in an early lab study of ENDS, 32 cigarette smokers participated in four independent lab sessions in which they puffed from an ENDS with a 16 mg/ml nicotine liquid, an ENDS with an 18 mg/ml nicotine liquid, their own brand (OB) of cigarette that was lit (as a positive control for the effects participants usually experienced from tobacco smoke/nicotine self-administration), or an unlit OB cigarette (as a negative control for puffing behavior without smoke or nicotine; Vansickel et al., 2010). Blood was sampled and heart rate recorded before and after puffing. The two ENDS failed to deliver nicotine or increase heart rate reliably, as did the unlit cigarette; OB cigarettes delivered nicotine and increased heart rate reliably (Vansickel et al., 2010). As ENDS have evolved, subsequent lab studies using very similar methods have demonstrated that these products have become more effective at nicotine delivery (e.g., Dawkins et al., 2016; Hiler et al., 2017; Wagener et al., 2017). Indeed, nearly identical clinical lab methods have been used to compare the nicotine delivery and

other effects of a popular ENDS (JUUL) to those of novel heated tobacco product (IQOS) relative to OB cigarettes (Maloney et al., 2020). With regard to SLT, clinical lab methods have been used to establish the large amount of nicotine delivered to the user (Fant et al., 1999), twice as much as that observed in cigarette smokers due to the duration of SLT use (Benowitz et al., 1988). In a lab study of potential reduced harm SLT products, 13 people who use SLT participated in 4 independent lab sessions in which they used Stonewall (a compressed tobacco tablet), General snus (a tobacco product marketed in Sweden), OB SLT, or a non-tobacco placebo smokeless product (Gray et al., 2008). Each session consisted of four 30-minute use periods and physiological measures were measured similar to Vansickel et al., 2010. The placebo SLT product and Stonewall failed to deliver nicotine or increase heart rate reliably, OB SLT and General snus delivered nicotine and increased heart rate reliably (Gray et al., 2008). Very recently, one independent (i.e., not industry-funded) study has used clinical lab methods to evaluate the effects of ONPs (Zyn brand) in people who smoke cigarettes; results suggest nicotine content influences the nicotine delivery of ONPs, with higher nicotine content associated with greater plasma nicotine concentration following ONP use (Keller-Hamilton et al., 2024a). In sum, well-established, valid, and reliable clinical lab methods can be used to evaluate the nicotine delivery and physiological effects of a variety of tobacco products, including ONPs, but no non-industry investigators have used these methods to examine these effects in people who use SLT to date.

Subjective effects

A mainstay of novel tobacco product evaluation in the clinical lab is measuring the effect of tobacco product administration on subjective experience, particularly abstinence symptom suppression (e.g., Buchhalter & Eissenberg, 2000; Butschky et al., 1995; Harvanko et al., 2017;

Vansickel et al., 2010). Similar to clinical lab evaluations of physiological effects, the vast majority of studies evaluating subjective effects examine inhaled tobacco products. Abstinence symptom suppression is a key subjective effect outcome, as a novel product that exposes users to fewer tobacco toxicants (e.g., ENDS) and that suppresses abstinence effectively may substitute for the normally marketed product that is associated with greater tobacco toxicant exposure (e.g., combustible cigarette). Indeed, measures of subjective effects have been used in clinical lab evaluations of heated tobacco products (Buchhalter & Eissenberg, 2000; Maloney et al., 2020), ENDS (Farsalinos et al., 2014; Hiler et al., 2019) and SLT products (Gire & Eissenberg, 2000; Gray et al., 2008). For example, in a study of ENDS and heated tobacco products, abstinence symptom suppression was measured in 18 people who smoke cigarettes in separate sessions before and after participants puffed from a novel ENDS (JUUL), a novel heated tobacco product (IQOS), or an OB cigarette (Maloney et al., 2020). Abstinence symptoms (e.g., “impatient,” “irritable,” “craving”) were significantly lower following use of OB compared to either JUUL or IQOS, suggesting incomplete substitution by the novel products (Maloney et al., 2020).

Subjective measures used to evaluate the effects of ENDS and heated tobacco products have been adapted to measure the effects of SLT use (Gire & Eissenberg 2000; Gray et al., 2008). Results reveal that people who use SLT experience aversive effects when they abstain from SLT, that OB SLT suppresses these aversive effects effectively, and that novel products can also suppress aversive abstinence effects, though to a lesser degree (Gire & Eissenberg, 2000; Gray et al., 2008). Importantly, while abstinence suppression is a key indicator and is often used in clinical lab evaluations of pharmaceutical products (e.g., Molander et al., 2000), these measures have not been used in any independently published study to examine the effects of ONPs in people who use SLT.

In sum, clinical lab methods reveal the nicotine delivery profile and subjective effects of novel tobacco products (see also Lopez et al., 2016). Strengths of clinical lab methods include rigorous control over product administration and participant safety as well as sensitive repeated measures designs that provide statistical power with sample sizes ≤ 32 (Guo et al., 2013; Machin et al., 2018). Crucially, ONPs are currently marketed and available to anyone over the age of 21 in the US, despite the lack of knowledge available on their effects.

Oral Nicotine Pouches

The tobacco industry sometimes expresses keen interest in reducing their customers' exposure to lethal tobacco toxicants. Recently, this interest has resulted in the marketing of orally-administered products that contain no tobacco but instead consist of a small pouch filled with nicotine powder and non-tobacco additives (e.g., flavorants). ONPs are intended to be used in the same manner as SLT (i.e., placed between the cheek or lip and gum for 20 - 30 minutes), though users are not required to spit during use (Robichaud et al., 2019). ONPs (such as Zyn and ON!) have been marketed as "tobacco-free," and differ from SLT in that they lack tobacco leaf and instead contain a nicotine powder, pH adjusters (e.g., sodium carbonate), fillers, and flavorants (Plurphanswat et al., 2020; Robichaud et al., 2019). The absence of tobacco leaf in these products suggests less exposure to tobacco toxicants and a potential innovative treatment/reduced harm option for people who use SLT. Importantly, while there has been a great deal of independent research investigating ENDS (e.g., Breland et al., 2018) and heated tobacco products (e.g., Simonavicius et al., 2019), virtually no independent research has examined the effects of ONPs. The information available on ONPs is nearly entirely tobacco

industry-funded or -affiliated, a portion of which is detailed below. Research conducted, funded by, or affiliated with the tobacco industry is designated as such.

ONPs were introduced to the US marketplace in 2016 and are often advertised as “tobacco-free” products that can be used anywhere (Marynak et al., 2021; Robichaud et al., 2019). At least 5 tobacco corporations currently sell these products at or below the typical price of a pack of cigarettes. Sales of ONPs increased from \$709,635 in 2016 to \$216,886,819 in the first half of 2020 (Marynak et al., 2021). Tobacco companies have engaged in cross-promotion of these products (e.g., advertising ON! brand ONPs on the Marlboro website; Talbot et al., 2021), and one corporation reported a 52% increase in ONP shipment volume from 2020 to 2021 in the US (Swedish Match, 2021). In 2021, 29.2% of adult smokers ($N = 1018$) reported being aware of ONPs, and awareness was significantly higher among smokers who had ever used SLT ($AOR: 3.38$; Hrywna et al., 2022). A portion of this sample had ever used ONPs (5.6%); however, 18–44-year-old smokers were nearly 3 times more likely to report having tried ONPs when compared to smokers over the age of 44. Additionally, 16.8% of participants reported interest in using ONPs within the next six months (Hrywna et al., 2022).

ONPs are available in various strengths (i.e., amount of total nicotine contained in each pouch) and flavors. The second most popular brand of nicotine pouch in the US, “ON!”, (Marynak et al., 2021), is available in five strengths (1, 2, 3.5, 4, and 8 mg nicotine) and seven flavors (mint, wintergreen, cinnamon, citrus, coffee, berry, and original/unflavored). The range of nicotine content available in these ONPs lends itself to a study addressing the extent to which the nicotine delivery is dependent on the nicotine content/“strength” of the product.

In a study published by Altria, the nicotine delivery and subjective effects of a 4 mg ON! ONP were examined in adults who smoke cigarettes (Rensch et al., 2021). Forty-one participants

completed the randomized, crossover design study consisting of seven sessions based on study condition: six 4-mg ONPs that differed based on flavor (wintergreen, cinnamon, citrus, coffee, berry, and unflavored/original) and participants' own brand cigarette. Following 12-hour overnight nicotine/tobacco abstinence, participants completed a controlled administration period (30-minute ONP use or 10 puffs of a cigarette, 30-sec inter-puff interval, 5 minutes total). Maximum nicotine concentration (C_{\max}) of the ONPs ranged from 9.0 to 11.5 ng/ml and did not differ significantly based on flavor. The C_{\max} of the own brand cigarette was 16.3 ng/ml, and was significantly greater than all flavors of the ONPs. Median time to maximum plasma nicotine concentration (t_{\max}) of the ONPs ranged from 30.1 to 34.9 min, and the t_{\max} of the own brand cigarette was 7.5 min. ONPs reduced participants' urge to smoke, though not to the same degree as their own brand cigarette. The t_{\max} and subjective effects results observed in this study are similar to other industry studies of different ONP brands (Lunell et al., 2020; McEwan et al., 2022). Differences in nicotine delivery between studies may be due to differences in the total and/or freebase nicotine contained in the pouches used.

In a study published by British American Tobacco, the nicotine delivery and subjective effects (product liking) of five brands of ONPs were examined in adults who smoke cigarettes (McEwan et al., 2022). Thirty-five participants completed the randomized, crossover study consisting of six sessions based on study condition: five different ONP brands and a combustible cigarette (Pall Mall Red). The ONPs used in this study varied based on brand and labelled nicotine content. Specifically, this study examined Lyft mint 10 mg, Zyn spearmint 10 mg, Nordic Spirit mint 9 mg, Skurf Super White Fresh Stark mint 8 mg, and ON! mint 6 mg. Following 12-hour overnight nicotine/tobacco abstinence, participants completed a controlled administration period (60-minute ONP use or 5-minute, *ad libitum* cigarette smoking). Mean

maximum nicotine concentration (C_{\max}) of the ONPs ranged from 11.9 to 18.4 ng/ml and the C_{\max} of the cigarette was 13.9 ng/ml. Specifically, C_{\max} of Lyft 10 mg ONP was 17.1 ng/ml, Zyn 10 mg was 11.9 ng/ml, Nordic Spirit 9 mg was 18.4 ng/ml, Skurf 8 mg was 13.0 ng/ml, and ON! 6 mg was 17.5 ng/ml. The C_{\max} of Lyft 10 mg ONP was significantly greater compared to the combustible cigarette. For all other C_{\max} comparisons, the Lyft 10 mg ONP was used as the reference product and was significantly greater than the C_{\max} of Zyn 10 mg and Skurf 8 mg ONPs. No significant differences in C_{\max} were observed between Lyft 10 mg and Nordic Spirit 9 mg or between Lyft 10 mg and ON! 6 mg ONPs. Median time to maximum plasma nicotine concentration (t_{\max}) of the ONPs (ranged from 60-65 min) was higher than the t_{\max} of the combustible cigarette (7 min).

In a study funded by Swedish Match, the nicotine delivery of an ONP, snus, and SLT were examined in people who use SLT (Lunell et al., 2020). In Study 1, 17 participants completed the randomized, crossover study consisting of 3 sessions based on study condition: Zyn 3 mg ONP, Zyn 6 mg ONP, and General snus 8 mg pouches. Following overnight abstinence, participants completed a controlled administration period (60-minute ONP or SLT use). Mean maximum nicotine concentration (C_{\max}) of the General snus 8 mg condition (10.6 ng/ml) was significantly greater compared to the C_{\max} of Zyn 3 mg (7.7 ng/ml) and significantly lower compared to the C_{\max} of Zyn 6 mg (14.7 ng/ml). Median time to maximum plasma nicotine concentration (t_{\max}) did not differ significantly between conditions and ranged from 61 (Zyn, 3 mg) to 69 (General snus) minutes. In Study 2, 29 participants completed the randomized, crossover study consisting of 3 sessions based on study condition: Zyn 8 mg ONP, American Longhorn moist snuff (18 mg), and General snus 8 mg (participants used two snus pouches simultaneously during use; 16 mg total). Other study procedures were identical to Study 1

(overnight abstinence, 60-minute ONP or SLT use period). Mean maximum nicotine concentration (C_{\max}) of two General snus 2 x 8 mg pouches (21.2 ng/ml) was significantly greater compared to the C_{\max} of Zyn 8 mg (18.5 ng/ml). No significant differences in C_{\max} were observed between the Zyn 8 mg ONP and American Longhorn 18 mg moist snuff (16.9 ng/ml). Median time to maximum plasma nicotine concentration (t_{\max}) did not differ significantly between conditions and ranged from 59 (Zyn) to 65 (Longhorn) minutes. The results of this industry-sponsored study suggest that the nicotine content of ONPs influences the nicotine delivery of these products, and high nicotine content ONPs (i.e., 6 mg) may deliver similar amounts of nicotine to the user as more popular SLT products.

In the only independent (i.e., non-industry-affiliated) study available at this time, the nicotine delivery and product appeal of ONPs were examined in people who smoke cigarettes (Keller-Hamilton et al., 2024a). 30 participants completed the randomized, crossover study consisting of 3 sessions based on study condition: Zyn nicotine pouch 3 mg (wintergreen), Zyn nicotine pouch 6 mg (wintergreen), and OB cigarette. Following 12-hour abstinence, participants completed a controlled administration period (30-min pouch use period or 10 puff, 30-sec IPI cigarette use period). At 30 minutes, mean plasma nicotine concentration was significantly greater in the 6 mg ONP condition ($M = 17.5$ ng/ml, $SD = 9.8$) when compared to the 3 mg ONP ($M = 9.5$ ng/ml, $SD = 5.6$) and the OB cigarette ($M = 11.4$ ng/ml, $SD = 5.7$). However, at 5 minutes, mean plasma nicotine concentration in the OB cigarette condition reached 27.8 ng/ml ($SD = 17.6$), and this value was greater than the maximum plasma nicotine concentration values observed in both ONP conditions (at 30 minutes). Also at 5 minutes, mean reduction in craving ratings was significantly greater in the OB cigarette condition when compared to the 3 mg and 6 mg ONP conditions, but craving ratings did not differ significantly across conditions at any other

timepoint. Participants rated both ONP conditions as less appealing than their OB cigarette. The results of this study suggest that nicotine content influences the nicotine delivery of ONPs. Specifically, higher nicotine content ONPs (i.e., 6 mg) can deliver significantly more nicotine than ONPs with lower nicotine content (i.e., 3 mg). Additionally, results indicate that differences in ONP nicotine content may not influence abstinence symptom reduction and/or product appeal in a similar manner when used by people who smoke cigarettes. Abstinence symptom and product appeal are important considerations, along with nicotine delivery, when considering ONPs as potential reduced harm alternatives for people who use more harmful tobacco products (e.g., cigarettes).

The influence of ONP nicotine content on the nicotine delivery of ONPs observed in Keller-Hamilton et al., (2024a) is consistent with the effect observed in Study 1 of Lunell et al., (2020). Yet, when the nicotine delivery values (e.g., maximum plasma nicotine concentration) are compared, the results from these two studies diverge despite using the same nicotine content and brand of ONPs (3 mg and 6 mg, Zyn). In the independent study, mean nicotine plasma concentration at 30 minutes was 9.5 ng/ml ($SD = 5.6$) in the 3 mg condition and 17.5 ng/ml ($SD = 9.8$) in the 6 mg condition; in the industry-sponsored study, mean plasma nicotine concentration at the same time point was 5.4 mg/ml ($SD = 1.6$) in the 3 mg condition and 10.1 ng/ml ($SD = 3.1$) in the 6 mg condition (plasma nicotine results at 30 minutes were not reported in the Lunell et al., 2020 publication, but can be found at <https://doi.org/10.1186/ISRCTN14866695>; see Swedish Match, 2024). The differences observed between these two studies may be due to product design changes over time and/or differences in the population sampled; Keller-Hamilton et al., 2024a was conducted in 2022 in the US and Lunell et al., 2020 was conducted in 2017 in Sweden. Also, random variability may have been a

contributing factor to the differences observed between these two studies. Additionally, as reported by Swedish Match (2024) in the Clinical Study Report for Lunell et al., (2020), four different Zyn pouches were used: Zyn 3 mg, Zyn 6 mg, and Zyn 3 mg “alternative manufacturing process”, and Zyn 6 mg “alternative manufacturing process”. Interestingly, the “alternative manufacturing process” is not detailed, but examination of nicotine delivery results across all four conditions do not reveal substantial differences between pouch conditions with the same nicotine content. For example, at 30 minutes, mean plasma nicotine concentration for both Zyn 3 mg ONPs was 5.4 - 5.5 ng/ml (*SDs* = 1.6 - 2.8) and for both Zyn 6 mg ONPs was 8.9 - 10.1 ng/ml (both *SDs* = 3.1). Finally, pouch pH is a potential design change that could explain the divergent results observed between these two studies; product pH is reported generally as 8.3 in Lunell et al., (2020) and specific information on pH (i.e., the pH of Zyn at different nicotine contents) is not included in the 180-page Clinical Study Report (Swedish Match, 2024). In a 2021 independent examination of ONP product characteristics, the pH of Zyn ranged from 8.44 (*SEM* = 0.12) for the 6 mg pouches to 8.59 (*SEM* = 0.09) for the 3 mg pouches (Stanfill et al., 2021).

In order for ONPs to be viable as a reduced harm product, they must expose the user to fewer toxicants when compared to other tobacco products. In an industry-sponsored study, the toxicant profiles of ONPs, snus, and NRT products (lozenge and gum) were compared (Azzopardi et al., 2021). Products were tested for 24-26 toxicants, including compounds identified by the FDA as harmful and potentially harmful constituents in smokeless tobacco products and combustible cigarettes. Among the products, ≤ 5 toxicants were detected in nicotine lozenges (3 of 25), ONPs (4 of 25), and nicotine gum (5 of 25). Eleven of 24 toxicants were detected in snus products. Importantly, snus products have been characterized as reduced harm

tobacco products, and eight Swedish Match snus products are currently FDA-authorized modified risk tobacco products (FDA, 2019). These results suggest the toxicant profile of ONPs is comparable to NRT products, and use of ONPs may expose users to fewer toxicants than snus products. The authors conclude that ONPs should be characterized as similar to NRT in terms of toxicant delivery.

ONPs may be a less lethal substitute for more popular SLT products, yet research on the effects of these products is nearly exclusively industry-funded or affiliated. The tobacco industry has an established history of scientific manipulation and deception intended to influence public opinion. For this reason, industry-funded research does not provide sufficient evidence to draw meaningful conclusions regarding the effects of ONPs. In order to study these products and consider the potential for application as a reduced harm product and/or cessation aid, the nicotine delivery and subjective effects profile of ONPs must be determined independently. Clinical laboratory methods are well-established as powerful tools used to evaluate acute drug effects, and have been used to evaluate the nicotine delivery and subjective effects of several tobacco products, including SLT and novel tobacco products.

Statement of the Problem

SLT is used by ~6 million US adults, despite harmful health consequences. Like other tobacco products, SLT contains nicotine, a psychomotor stimulant that supports dependence and results in aversive symptoms upon abrupt abstinence, making cessation difficult. Novel tobacco products have been developed and marketed by the tobacco industry, including ONPs (Robichaud et al., 2019), which are intended to be used in a similar manner to SLT. No independent clinical lab studies examining ONPs in people who use SLT have been conducted.

The Present Study

This study used clinical laboratory methods to examine nicotine delivery and subjective effects of ONPs in people who use SLT. Specifically, this within-subject study examined the nicotine delivery profile and physiological and subjective effects of three strengths (i.e., total nicotine content) of an ONP (Altria's "ON!"; 2, 4, and 8 mg, administered double-blind; see Appendix A) compared to participants' OB SLT as a positive control.

Statement of Hypothesis

The primary hypotheses of this study were that plasma nicotine concentration would increase significantly as ONP total nicotine content increases, such that the 2 and 4 mg pouch condition would be significantly different than OB SLT, but the 8 mg ONP condition would not differ significantly from OB SLT, and abstinence symptoms would be lowest in the OB and 8 mg ONP condition and would differ significantly from the 2 and 4 mg ONP conditions. This study is the first objective evaluation of the nicotine delivery and subjective effect profile of ONPs in people who use SLT.

Method

Participant Selection

Participants were recruited via word-of-mouth and community and/or internet advertisements approved by the VCU Institutional Review Board (IRB). Internet advertisements included social media ads (e.g., posts on Facebook, Instagram, and Craigslist), as well as the use of BuildClinical. BuildClinical is a platform designed to assist academic researchers with study recruitment via social media, software, and machine learning; all screening data collected via BuildClinical were encrypted and stored on secure data servers in the US. The use of BuildClinical was approved by the VCU IRB in this study. All screening and experimental

sessions took place at the VCU Center for the Study of Tobacco Products (CSTP). Individuals were considered eligible for the study if they were healthy, aged 18 - 55, reported using SLT products, and were willing to abstain from tobacco/nicotine as required. Specifically, participants were required to report daily use of SLT and use of ≥ 2 cans of SLT per week, and no use of other tobacco products (including ONPs) on more than 15 of the past 30 days. Regular ONP users were excluded from this study to ensure the population sampled was consistent (i.e., traditional SLT users) to maintain internal validity. Urine cotinine was measured for all participants at screening, and a positive test was required to verify nicotine use.

Participants were excluded if they reported a current, diagnosed chronic illness or psychiatric condition, or psychotropic medication use. Additionally, participants were excluded if they reported current alcohol use > 25 days, cannabis use > 15 days, or any other illicit drug use (cocaine, opioids, benzodiazepines, and methamphetamine) in the past 30 days. Biologically female participants were excluded if they reported current breast-feeding or if they tested positive for pregnancy (by urinalysis) at screening. Participants that reported any intention to quit tobacco/nicotine in the next 30 days were excluded and referred to cessation treatment. Individuals who reported using any other tobacco products (other than what is permitted per the inclusion criteria) on a weekly or more frequent basis were excluded.

Informed Consent and Screening

All participants completed the screening process in two parts. Interested participants made initial contact via telephone or website (both provided on advertisements) and answered questions about their health and current tobacco product use. Based on their answers to these initial questions, eligible participants were invited to the CSTP to complete an in-person screening visit where they provided informed consent to participate in the screening and the

study. After completing the informed consent procedures, participants completed additional screening questionnaires covering demographics, health status, and tobacco product use. All participants provided a urine sample that was tested for cotinine and tested for pregnancy in biologically female participants.

Participant Safety

The methods and procedures used in this study involved minimal risk. Similar methods and procedures have been used numerous times at the CSTP over the course of 20 years. Abstinence from nicotine/tobacco products for twelve hours could result in mild discomfort, but this discomfort is not medically dangerous. Blood drawing procedures involve minimal risk of bruising and/or infection at the catheter site; these risks were minimized by trained nursing staff, sterile equipment, and aseptic procedures. Potential risks and/or side effects of using oral nicotine pouches are routine for the target population (users of smokeless tobacco products).

All CSTP staff were trained on good clinical practices, including the protection of participants' safety and rights. Heart rate (HR) and blood pressure (BP) was monitored during each session. Research personnel were trained to alert the research nurse if HR continually exceeded 120 beats per minute, if systolic BP continually exceeded 150 mm Hg, or if diastolic BP continually exceeded 100 mm Hg. Individuals whose HR and/or BP levels remained elevated were monitored by the nurse, and if necessary, emergency responders would be notified at the research nurses' discretion. Data are not identified by name or initials; only an alphanumeric code is used as identification. All data is stored in locked cabinets that can be opened by CSTP staff only.

Materials

The ONP brand used in this study (“ON!”) was chosen because it is available in unflavored “original” that minimized confounds associated with taste preference and in five nicotine strengths that differ by total nicotine content (1.5, 2, 3.5, 4, and 8 mg), that allowed exploration of a full range of effects related to ONP nicotine content. As with previous work with OB cigarettes (e.g., Maloney et al., 2020), OB SLT products were purchased by study staff from retail venues in Richmond, VA and were provided (unblinded) in the OB session.

Procedures

After screening and obtaining informed consent, participants completed four Latin-square ordered conditions that differed only by product used: OB SLT (un-blinded because these tobacco leaf products are dissimilar in every way to “ON!”) and 2, 4, or 8 mg original flavor “ON!” ONP (these three conditions were administered under double-blind conditions; the 2, 4, and 8 mg ONPs are indistinguishable in appearance). The pH of ON! is particularly high among ONP brands (~ 9.5), indicating a correspondingly high percentage of freebase nicotine (>90%; Stanfill et al., 2021). Prior to each session, staff with no participant contact selected the appropriate product and delivered it to the staff member conducting the session. During the OB condition, participants were provided with an entire can and instructed to use their typical amount; each can was weighed before and after product use to determine the amount of OB SLT used. Each session was approximately 4 hours in length and was separated by at least 48 hours to prevent carryover effects as in previous work (e.g., Eversole et al., 2022). Prior to each session, participants were instructed to abstain from all tobacco/nicotine-containing products for ≥ 12 hours and provided an expired air CO sample to verify abstinence from combustible tobacco products (i.e., ≤ 10 ppm). Baseline plasma nicotine concentration was used to exclude

participants who did not abstain from non-combustible tobacco products, as in previous work (e.g., > 5.0 ng/ml at baseline; Hiler et al., 2017). Participants were instructed not to drink anything except water within one hour of session start and were instructed to drink at least 12 ounces of water or rinse their mouth out with water before product use (to neutralize oral pH, as in Gire & Eissenberg, 2000). HR and BP were monitored throughout the session and a nurse inserted an intravenous catheter into participants' forearm vein for blood sampling. After a 1 hour observed waiting period (to ensure no nicotine/tobacco use; Hiler et al., 2019), participants completed baseline subjective measures and 7 ml blood was sampled. Participants then completed a 30-min use period in which they placed the product in their mouth and held it between their cheek and gum. During this use period, 7 ml blood was sampled at 15-min and participants completed subjective measures. Immediately following this use period, 7 ml blood was sampled and participants completed subjective measures again. After 60 minutes rest, a second use period commenced with subjective measures and blood sampling occurring before and immediately after product use. Thus, a total of 5 blood samples (total = 35 ml) were taken in each session for a total of 140 ml for the entire study (in contrast, donating a pint of blood in a single sitting in a blood drive is 473 ml). As with previous work, participants were compensated for time and inconvenience: \$15 for the initial screening visit, \$75 for the 1st session, \$100 for the 2nd, \$150 for the 3rd, and \$200 for the 4th, for a total of \$540 for the entire study.

Outcome Measures

Physiological measures

All blood samples were centrifuged and stored at -80°C. Analysis of plasma nicotine concentration took place at VCU's Bioanalytical Analysis Core Laboratories using a limit of quantitation (LOQ) of 0.1 ng/ml. Participants' HR was measured via pulse oximeter (Criticare

systems), and expired air CO was measured with a BreathCO monitor (Vitalograph, Lenexa, KS).

Subjective effect measures

To measure the subjective effects of ONP use, three questionnaires were administered via computer using the Visual Analog Scale (VAS) format; for each item, a word or phrase was centered on a horizontal line with “not at all” on the left of the line and “extremely” on the right. Participants clicked on any point of the line with a mouse/cursor and response scores reflected the percentage of the total line length measured from the left anchor, resulting in a score range of 0-100. The Hughes-Hatsukami Withdrawal Scale and Direct Effects of Nicotine Scale were administered during the first administration period (at 15 minutes), and before and after both administration periods, for a total of five times each session. The Direct Effects of Smokeless Tobacco Scale (DESLT) was administered during (at 15 minutes) and immediately after the two administration periods, for a total of 3 times each session. The General Labeled Magnitude Scale (gLMS) and the Single Product and Cross Product Smokeless Tobacco Purchase Tasks (CPT) were administered via paper and pen once per session following the second administration period. Subjective measures were adapted for use with SLT when appropriate (e.g., “cigarette” is changed to “tobacco”).

Hughes-Hatsukami Withdrawal Scale. Severity of nicotine withdrawal and suppression of nicotine abstinence symptom(s) were assessed by the Hughes-Hatsukami withdrawal scale, which consists of 11 items: “Anxious,” “Craving a dip/nicotine,” “Depression,” “Difficulty concentrating,” “Drowsy,” “Hunger,” “Impatient,” “Irritable,” “Restlessness,” “Desire for sweets,” and “Urge to dip” (Hughes & Hatsukami, 1986; see Appendix A).

Direct Effects of Nicotine. The direct effects and side effects of nicotine were assessed by the direct effects of nicotine scale, which consists of 11 items: “Confused,” “Dizzy,” “Headache,” “Heart Pound,” “Lightheaded,” “Nauseous,” “Nervous,” “Salivation,” “Sweaty,” and “Weak” (Evans et al., 2006; see Appendix B).

Direct Effects of Smokeless Tobacco. The subjective effects of SLT use were assessed by the Direct Effects of Smokeless Tobacco scale (DESLT), which consists of 12 items: “Overall, how strong is the product?,” “What amount of product have you swallowed?,” “Has your salivation increased?,” “Does the product produce any burning sensations?,” “Do you feel any tingling in your mouth?,” “Do you feel any nausea?,” “Is your heart racing?,” “Do you feel a head rush?,” “Are you relaxed?,” “Do you like the way the product makes you feel?,” “Do you like the way the product tastes?,” and “How alert does the product make you feel?” (Fant et al., 1999; see Appendix C).

General Labeled Magnitude Scale. The General Labeled Magnitude Scale (gLMS) was used to measure specific sensations associated with product use. Participants were instructed to draw a horizontal line indicating their level of sensation, and then write the corresponding number in a box (see Appendix D). The following SLT-specific sensations were measured via paper and pen: “Flavor” and “Harshness” (Green et al., 1993). This measure used a scale of 0-100 and sensation level descriptions at the following numbers: 0 (“No Sensation at All”, 1 (“Barely Detectable”), 6 (“Weak”), 16 (“Moderate”), 35 (“Strong”), 53 (“Very Strong”), and the highest possible rating of 100 (“Strongest Imaginable Sensation of Any Kind”).

Single Product/Cross Product Smokeless Tobacco Purchasing Tasks. The Single and Cross Product Smokeless Tobacco Purchasing Tasks were adapted from previous work (Mackillop et al., 2008; Bono et al., 2022). These behavioral economic-based tasks allow for

comparisons of abuse liability and demand for different drugs (Bickel et al., 2017; Jacobs & Bickel, 1999). In this study, these tasks were administered via a pen and paper. Participants were instructed to imagine a typical day, and to indicate how much of the session product (“ON!” nicotine pouch or OB SLT) they would purchase at various prices (see Appendix E).

Additionally, participants were instructed to assume that their economic condition had not changed and that no other sources of tobacco products were available to them. The amount of product purchased as the lowest price (intensity) and changes to consumption as a result of increasing price (sensitivity to price, or elasticity) were measured.

Participant characteristics.

A total of 40 participants provided informed consent, and 9 of these were determined ineligible for study participation at the screening visit for failure to meet study criteria (e.g., use of other tobacco products on more than 15 of the last 30 days). Five participants were eligible at the screening visit but voluntarily withdrew before their first session due to scheduling conflicts. Two participants voluntarily withdrew from the study before completing the first session: 1 due to failure to adhere to study protocol (i.e., unable to remain abstinent for 12 hours prior to each study session as evidenced by expired air CO concentration > 7 PPM upon arrival) and 1 due to inability to complete the entire session due to a lack of transportation.

Twenty-four participants completed all study sessions. Among these 24, two participants were determined (via plasma nicotine concentration) to be noncompliant (e.g., did not abstain from nicotine/tobacco products for 12 hours prior to at least one session). However, preliminary results of plasma nicotine concentration and abstinence measures did not change when data from these participants were excluded; therefore, data from these two participants are included in the final sample. One participant’s data were excluded due to repeated noncompliance (e.g., failing

to inform study staff when ending product use before 30 minutes had elapsed). Thus, data from a total of 23 participants (22 male, 1 female) are included in the final analyses.

The mean age (*SD*) of the final sample was 34.7 (8.9) years. Twenty-two participants reported their race as white, and one reported their race as African American. Seventeen participants reported being currently employed, 3 reported being unemployed, 2 reported their employment as “student”, and 1 reported being permanently or temporarily disabled. Mean (*SD*) expired air CO at screening was 2.0 (1.2) ppm.

Participants reported using smokeless tobacco a mean (*SD*) of 5.0 (1.6) times daily, and 3.6 (1.6) cans of SLT per week. Participants scored a mean (*SD*) of 3.2 (1.9) on the Fagerström Test for Nicotine Dependence - Smokeless Tobacco, indicating a low to moderate level of dependence (Ebbert et al., 2006; Heatherton et al., 1991). Most participants reported using mint or wintergreen flavor SLT ($n = 18$), and Copenhagen and Grizzly were the most popular brands among this sample ($n = 18$).

Table 1. Demographics Information for the 23 Participants Included in the Final Analysis.

Participant Demographics	Mean (SD) or N (%), N = 23
Age	34.7 (8.9)
Gender	
Male	22 (96%)
Female	1 (4%)
Race	
White	22 (96%)
Black/African American	1 (4%)
Education (years)	14.5 (1.8)
Employment	
Part or full time	17 (74%)
Unemployed	3 (13%)
Student	2 (9%)
Disabled	1 (4%)
SLT use	
Dips/day	5.0 (1.6)
Cans/week	3.6 (1.6)
FTND-SLT	3.2 (1.9)

Note: SLT = Smokeless Tobacco; FTND = Fagerström Test for Nicotine Dependence.

Data Analysis

For plasma nicotine, values < LOQ were replaced with 0.1 ng/ml (LOQ). Two-factor (condition x time) repeated measures ANOVA was used to examine each measure. Huynh-Feldt corrections were used for sphericity violations and Tukey's Honestly Significant Difference tests were used for post-hoc testing (Keppel, 1991). In order to maximize statistical sensitivity, this

study was designed to recruit 32 participants. Thirty-two completers were needed for power > 0.80 on the primary outcome measure (plasma nicotine). Sample size was determined based on a power analysis using G*Power software (Faul et al., 2007) conducted for a repeated measures analysis of variance (ANOVA) and assuming a moderate effect size for a main effect of condition and small/moderate correlation between repeated measures (as in Eversole et al., 2020). However, due to difficulties with recruitment and retention, data collection was terminated after 24 participants completed the study. Smokeless tobacco users are a relatively small subset of tobacco users (making recruitment challenging), and many participants who screened for the study and were eligible were unable to participate due to scheduling conflicts (i.e., they were unable to attend sessions during regular business hours due to their work schedules).

All data were analyzed using repeated measures ANOVA. Specifically, for physiological measures (i.e., plasma nicotine concentration and HR) and subjective questionnaires administered pre-, during, and post-product administration, ANOVAs were used, with two within-subjects factors: condition (OB SLT, and the ON! oral nicotine pouch in 2 mg, 4 mg, and 8 mg total nicotine content; four levels), and time (before, during, and after product use for the first use period, and before and after the second use period; five levels). The factor of time was adjusted for the DESLT questionnaire for the first use period only, because it was administered during (at 15 minutes) and following the first use period (two levels). Analyses of subjective measures administered once per session did not include the factor of time (gLMS, Purchase Tasks). All VAS subjective questionnaire items were analyzed individually. In order to analyze across and within factors (condition and time), Tukey's Honestly Significant Difference (HSD) was used.

Results

For outcomes administered pre- and post-product use, the results of particular interest are those that involve changes from baseline that occurred after use that may have varied by condition. For this reason, the Condition x Time interactions are most relevant and are detailed below. Table 2 displays ANOVA results for the main effects of Condition and Time and the Condition x Time interaction.

For outcomes not involving time as a factor (i.e., those administered only after product use), each use period was analyzed separately (where applicable) and Tables 3 and 4 display these ANOVA results.

Missing data occurred in the physiological measures (i.e., plasma nicotine concentration and heart rate), as well as in the DESLT subjective measure. One participant's data was not included in the plasma nicotine concentration analysis due to missing blood samples (the research nurse was unable to draw blood for two timepoints; final $N = 22$), and two participants' data were not included in the heart rate (HR) analysis due to missing data (HR data was not collected at one timepoint for each participant; final $N = 21$). One participant failed to complete all questions of the DESLT, and one participant partially completed the DESLT following the second use period. Specifically, data were missing for one participant during the first and second use period for the item "Strong" ($n = 22$), and for two participants during the second use period for the item "Relaxed" ($n = 21$). For all other DESLT items, data were missing for one participant ($n = 22$). Once these missing data were observed, study procedures were amended and all questions were coded as mandatory to prevent future participant oversight during sessions.

Table 2. Statistical Analysis Results for Two-Factor Analysis of Variance.

Outcome Measure	Condition			Time			Condition*Time		
	F	<i>p</i>	η_p^2	F	<i>p</i>	η_p^2	F	<i>p</i>	η_p^2
Plasma Nicotine^a	13.375	<.001	.389	74.217	<.001	.779	7.192	<.001	.255
HR^b	4.603	.006	.187	43.728	<.001	.686	2.258	.013	.101
HH^c									
Anxious	.694	.544	.031	15.201	<.001	.409	.425	.888	.019
Craving	9.738	<.001	.307	36.902	<.001	.626	3.730	<.001	.145
Depression	.335	.711	.015	6.829	.002	.237	.333	.899	.015
Difficulty Concentrating	3.795	.025	.147	12.115	<.001	.355	1.295	.252	.056
Drowsy	2.957	.039	.118	8.347	<.001	.275	1.458	.163	.062
Hunger	1.951	.135	.081	11.165	<.001	.337	2.278	.022	.094
Impatient	2.118	.130	.088	16.829	<.001	.433	.762	.622	.033
Irritable	3.924	.026	.151	15.210	<.001	.409	.581	.812	.026
Restless	1.604	.207	.068	11.071	<.001	.335	.962	.472	.042
Sweets	1.603	.205	.068	7.778	.004	.261	.758	.614	.033
Urge	5.056	.005	.187	38.546	<.001	.637	4.555	<.001	.172
DE Nicotine^d									
Confused	.510	.575	.023	.970	.410	.042	.799	.547	.035
Dizzy	1.435	.248	.061	1.353	.268	.058	1.229	.306	.053
Headache	1.405	.249	.060	2.375	.116	.097	2.085	.074	.087
Heart Pounding	.930	.399	.041	2.354	.108	.097	1.523	.195	.065
Lightheaded	1.592	.217	.067	4.030	.023	.155	2.532	.040	.103
Nauseous	1.995	.149	.083	3.045	.054	.122	1.595	.194	.068
Nervous	.213	.798	.010	2.688	.081	.109	.662	.651	.029
Salivation	1.610	.195	.068	6.175	.009	.219	1.131	.344	.049
Sweaty	.510	.672	.023	.337	.755	.015	1.720	.158	.073
Weak	.196	.890	.009	.774	.470	.034	.749	.586	.033

^a $df C = (3, 63)$; $df T = (4, 84)$; $df C*T = (12, 252)$

^b $df C = (3, 60)$; $df T = (4, 80)$; $df C*T = (12, 240)$

^c $df C = (3, 66)$; $df T = (4, 88)$; $df C*T = (12, 264)$

^d $df C = (3, 66)$; $df T = (3, 66)$; $df C*T = (9, 198)$

Note: HR = Heart Rate; HH = Hughes-Hatsukami; DE = Direct Effects

Physiological Measures

Plasma Nicotine Concentration

For plasma nicotine, a significant condition by time interaction was observed, $F(12, 252) = 7.2, p < .05$, as well as a significant main effect of condition, $F(3, 63) = 13.4, p < .05$, and a significant main effect of time, $F(4, 84) = 74.2, p < .05$. The means ($\pm SEM$) for all conditions across time are depicted in Figure 1. As the figure shows, baseline plasma nicotine concentration means were low and did not differ significantly by condition. However, mean plasma nicotine concentration increased significantly over time for the 4 mg, 8 mg, and OB conditions after the first and second use period, ($ps < .05$, Tukey's HSD). For example, for the 4 mg condition, baseline mean plasma nicotine concentration was 1.6 ($SD = 2.2$) ng/ml and increased to 8.4 ($SD = 4.6, p < .05$) ng/ml following the first use period; for the 8 mg condition, baseline mean plasma nicotine concentration was 1.1 ($SD = 1.2$) ng/ml and increased to 12.5 ($SD = 6.6, p < .05$) ng/ml; for the OB condition, baseline mean plasma nicotine concentration was 1.2 ($SD = 1.6$) ng/ml and increased to 10.0 ($SD = 7.9, p < .05$; See Figure 1) ng/ml.

Following the first use period, mean plasma nicotine concentration was significantly lower in the 2 mg condition ($M = 4.3$ ng/ml, $SD = 3.5$) when compared to 8 mg ($M = 12.5$ ng/ml, $SD = 6.6$) and OB ($M = 10.0$ ng/ml, $SD = 7.9, ps < .05$).

For the second use period, mean plasma nicotine concentration increased significantly following product use for the 4 mg, 8 mg, and OB conditions ($ps < .05$). For example, for the 4 mg condition, pre-use mean plasma nicotine concentration was 4.7 ($SD = 2.6$) ng/ml and increased to 10.4 ($SD = 4.4, p < .05$) ng/ml following the second use period; for the 8 mg condition, pre-use mean plasma nicotine concentration was 7.3 ($SD = 3.9$) ng/ml and increased to 14.3 ($SD = 7.3, p < .05$) ng/ml; for the OB condition, pre-use mean plasma nicotine

concentration was 6.0 ($SD = 3.6$) ng/ml and increased to 13.0 ($SD = 9.4$, $p < .05$; See Figure 1) ng/ml.

Following the second use period, mean plasma nicotine concentration was significantly lower in the 2 mg condition ($M = 4.8$ ng/ml, $SD = 2.9$) when compared to 4 mg ($M = 10.4$ ng/ml, $SD = 4.4$), 8 mg ($M = 14.3$ ng/ml, $SD = 7.3$), and OB ($M = 13.0$ ng/ml, $SD = 9.4$; $ps < .05$).

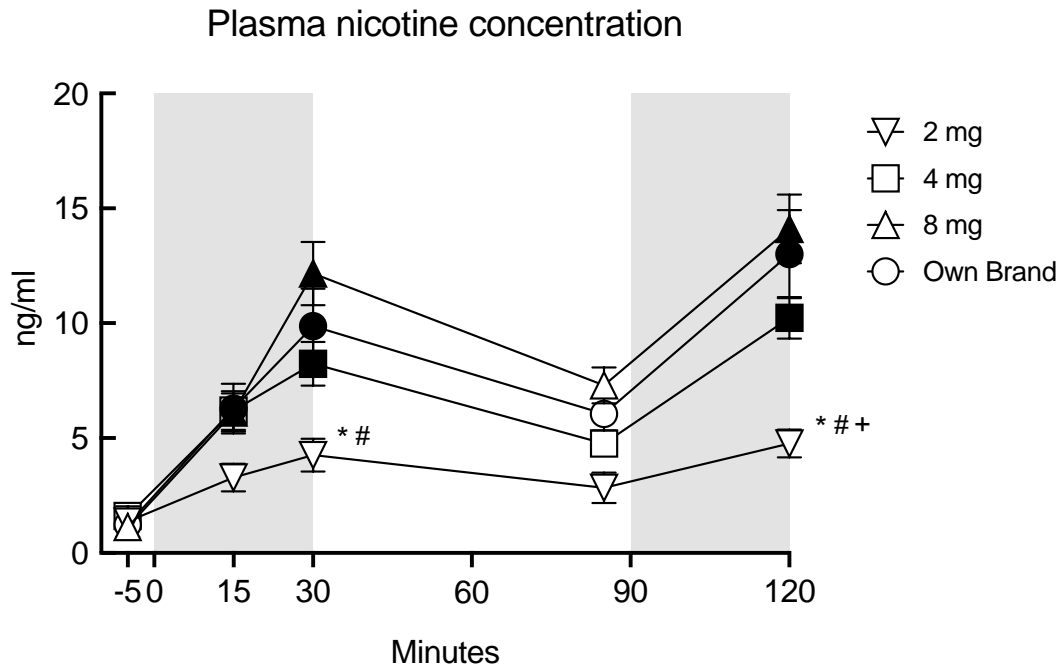


Figure 1. Mean data (\pm SEM) for plasma nicotine concentration across conditions ($N = 22$). Participants completed two, 30-minute use periods (use periods shaded gray) in four conditions (2 mg, upside-down triangle symbol; 4 mg, square symbol; 8 mg, right-side-up triangle symbol; OB, circle symbol). Filled symbols indicate a significant difference from pre-use plasma nicotine concentration (same condition). Asterisk (*) indicates significant difference from OB at same time point. Pound sign (#) indicates significant difference from 8 mg at same time point. Plus sign (+) indicates significant difference from 4 mg at same time point. All $ps < .05$; Tukey's HSD.

Heart Rate

For HR, a significant condition by time interaction was observed, $F(12, 240) = 2.3, p < .05$, as well as significant main effects of condition, $F(3, 60) = 4.6, p < .05$, and time, $F(4, 80) = 43.7, p < .05$. The means ($\pm SEM$) for all conditions across time are depicted in Figure 2. As the figure shows, prior to the first use period, HR means did not differ significantly by condition. Mean HR increased significantly over time for the 4 mg, 8 mg, and OB conditions during and after the first use period ($ps < .05$, Tukey's HSD). For example, for the 4 mg condition, baseline mean HR was 64.6 ($SD = 10.9$) beats per minute (bpm) and increased to 72.5 ($SD = 10.8, p < .05$) bpm following the first use period; for the 8 mg condition, baseline mean HR was 65.1 ($SD = 10.8$) bpm and increased to 76.5 ($SD = 8.7, p < .05$) bpm following the first use period; for the OB condition, baseline mean HR was 66.5 ($SD = 8.2$) bpm and increased to 76.3 ($SD = 7.9, p < .05$) bpm following the first use period (see Figure 2).

During the first use period (at 15 minutes), mean HR was significantly lower in the 2 mg condition ($M = 69.5$ bpm, $SD = 10.5$) when compared to 8 mg ($M = 74.9$ bpm, $SD = 11.8$) and OB ($M = 75.9$ bpm, $SD = 9.7; ps < .05$). Following the first use period (at 30 minutes), mean HR was significantly lower in the 2 mg condition ($M = 70.1$ bpm, $SD = 9.8$) when compared to 8 mg ($M = 76.5$ bpm, $SD = 8.7$) and OB ($M = 76.3$ bpm, $SD = 7.9; ps < .05$).

For the second use period, mean HR increased significantly following product use for the 2 mg, 4 mg, and OB conditions ($ps < .05$). For example, for the 2 mg condition, pre-use mean HR was 65.2 ($SD = 11.0$) bpm and increased to 70.3 ($SD = 9.2, p < .05$) bpm following the second use period; for the 4 mg condition, pre-use mean HR was 67.0 ($SD = 11.3$) bpm and increased to 73.1 ($SD = 10.9, p < .05$) bpm; for the OB condition, pre-use mean HR was 70.0 ($SD = 10.0$) bpm and increased to 75.4 ($SD = 7.3, p < .05$) bpm.

For the second use period, pre-use mean HR differed significantly by condition, with mean HR significantly lower in the 2 mg condition ($M = 65.2$ bpm, $SD = 11.0$) when compared to the 8 mg condition ($M = 70.2$ bpm, $SD = 10.2$) and OB ($M = 70.0$ bpm, $SD = 10.0$; $ps < .05$). Following the second use period, mean HR was significantly lower in the 2 mg condition ($M = 70.3$ bpm, $SD = 9.2$) when compared to OB ($M = 75.4$ bpm, $SD = 7.3$, $p < .05$).

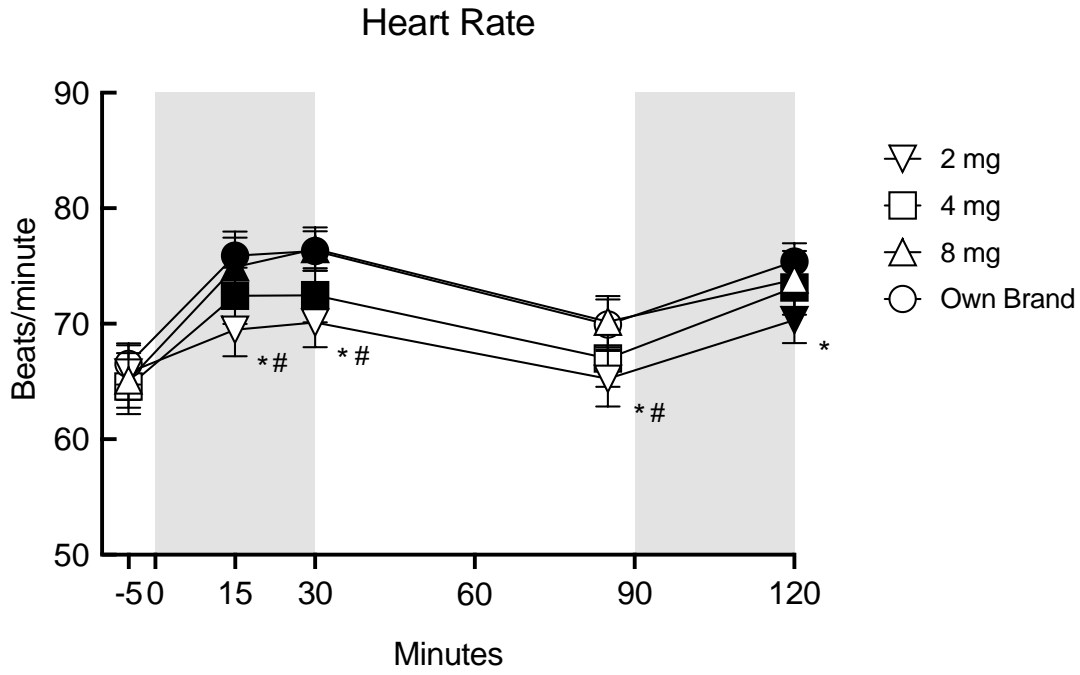


Figure 2. Mean data (\pm SEM) for heart rate (HR) across conditions ($N = 21$). In all other respects, the figure is identical to Figure 1.

Subjective Effects

Hughes-Hatsukami

As Table 2 shows, statistically significant Condition x Time interactions were observed for the following items: Craving, Hunger, and Urge. Significant main effects of condition and/or time were observed for the following items: Difficulty Concentrating, Drowsiness, Irritable, Anxious, Depression, Impatient, Restless, and Desire for Sweets (see Table 2). These items are detailed below, beginning with those items for which a significant Condition x Time interaction was observed followed by those for which a significant main effect of time and/or condition was observed.

Items with a Significant Condition x Time Interaction.

Craving. For “Craving a dip/nicotine”, the means (\pm SEM) for all conditions across time are depicted in Figure 3. As the figure shows, prior to the first use period, mean ratings of craving did not differ significantly by condition. However, mean ratings of craving decreased significantly over time for all conditions following the first use period ($ps < .05$, Tukey’s HSD). For example, for the 2 mg condition, pre-use mean craving was 65.0 ($SD = 29.7$) and decreased to 45.7 ($SD = 32.1$, $p < .05$) following the first use period; for the 4 mg condition, pre-use mean craving was 62.5 ($SD = 30.2$) and decreased to 32.5 ($SD = 27.4$, $p < .05$) following the first use period; for the 8 mg condition, pre-use mean craving was 68.1 ($SD = 19.7$) and decreased to 28.7 ($SD = 24.9$, $p < .05$) following the first use period; for the OB condition, pre-use mean craving was 63.3 ($SD = 31.6$) and decreased to 21.0 ($SD = 23.7$, $p < .05$) following the first use period (see Figure 3).

Mean ratings of craving were significantly greater during the first use period (at 15 minutes) in the 2 mg condition ($M = 48.7$, $SD = 31.6$) when compared to 4 mg ($M = 26.2$, $SD =$

26.5), 8 mg ($M = 29.4$, $SD = 22.1$), and OB ($M = 16.9$, $SD = 18.1$; $ps < .05$). Following the first use period, mean ratings of craving were significantly greater in the 2 mg condition ($M = 45.7$, $SD = 32.1$) when compared to OB ($M = 21.0$, $SD = 23.7$, $p < .05$).

For the second use period, mean ratings of craving decreased significantly following product use for the OB condition only; immediately before the second use period, mean craving was 40.7 ($SD = 28.6$) and decreased to 13.9 ($SD = 17.1$, $p < .05$) following product use.

Following the second use period, mean ratings of craving were significantly greater in the 2 mg condition ($M = 44.1$, $SD = 35.9$) when compared to 8 mg ($M = 22.7$, $SD = 22.5$) and OB ($M = 13.9$, $SD = 17.1$; $ps < .05$).

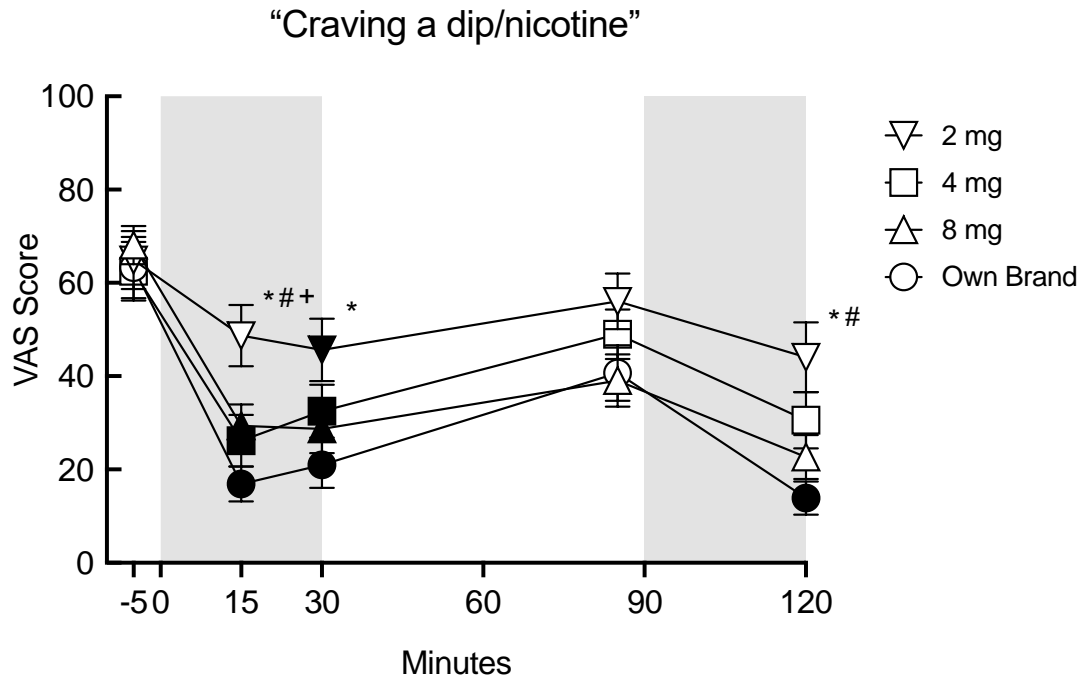


Figure 3. Mean data (\pm SEM) for the Hughes-Hatsukami “Craving a dip/nicotine” item, ($N = 23$). In all other respects, the figure is identical to Figure 1.

Hunger. For “Hunger”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 4. As the figure shows, prior to the first use period, mean ratings of hunger did not differ significantly by condition. However, mean ratings of hunger decreased significantly over time for the OB condition during the first use period (at 15 minutes) and for the 8 mg condition following the first use period ($ps < .05$, Tukey’s HSD). For example, for the OB condition, mean ratings of hunger were 47.0 ($SD = 26.0$) and decreased to 27.0 ($SD = 19.9$, $p < .05$) during the first use period; for the 8 mg condition, pre-use mean ratings of hunger were 48.2 ($SD = 27.3$) and decreased to 29.5 ($SD = 25.9$, $p < .05$; see Figure 4).

No significant differences were observed across condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

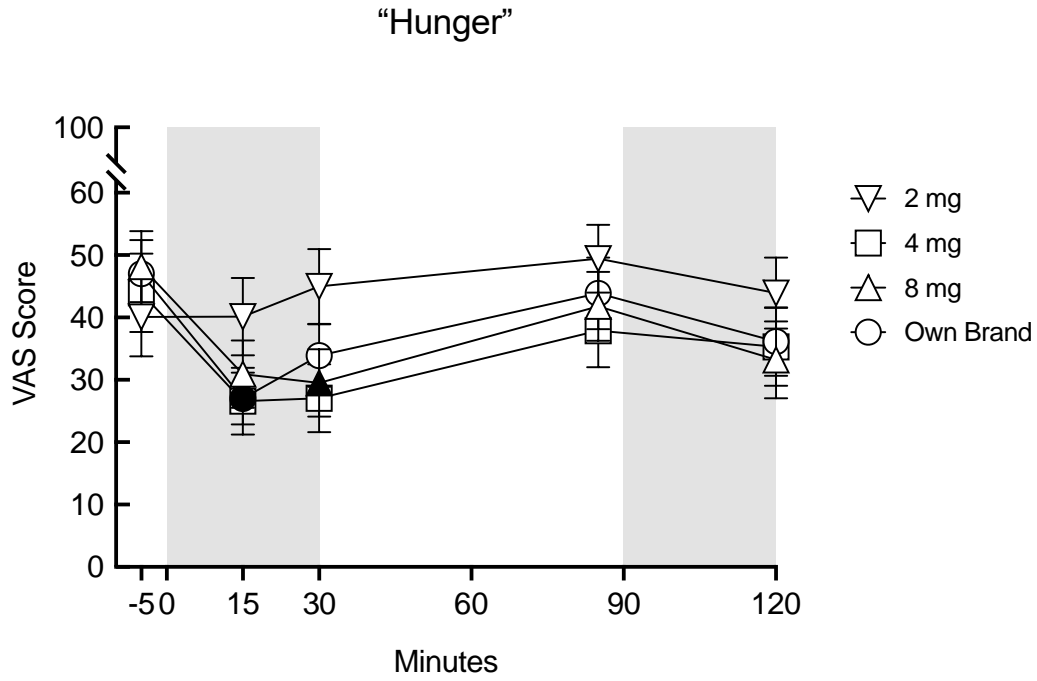


Figure 4. Mean data (\pm SEM) for the Hughes-Hatsukami “Hunger” item, ($N = 23$). In all other respects, the figure is identical to Figure 1.

Urge. For “Urges to dip”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 5. As the figure shows, prior to the first use period, mean urge ratings did not differ significantly by condition. However, mean urge ratings decreased significantly over time for the 4 mg, 8 mg, and OB conditions during and after the first use period ($ps < .05$, Tukey’s HSD). For example, for the 4 mg condition, pre-use mean urge was 64.5 ($SD = 29.0$) and decreased to 36.0 ($SD = 23.6$, $p < .05$) following the first use period; for the 8 mg condition, pre-use mean urge was 70.0 ($SD = 18.3$) and decreased to 31.3 ($SD = 25.7$, $p < .05$) following the first use period; for the OB condition, pre-use mean urge was 67.9 ($SD = 23.8$) and decreased to 28.1 ($SD = 29.1$, $p < .05$) following the first use period (see Figure 5).

Mean ratings of urge were significantly greater during the first use period (at 15 minutes) in the 2 mg condition ($M = 48.4$, $SD = 29.9$) when compared to OB ($M = 24.3$, $SD = 26.9$, $p < .05$). Following the first use period (at 30 minutes), mean ratings of urge were significantly greater in the 2 mg condition ($M = 47.2$, $SD = 29.5$) when compared to OB ($M = 28.1$, $SD = 29.1$, $p < .05$). No significant differences were observed across pouch conditions during or following the first use period.

For the second use period, mean ratings of urge decreased significantly following product use for the 4 mg and OB conditions ($ps < .05$, Tukey’s HSD). For example, for the 4 mg condition, immediately before the second use period, mean urge was 46.0 ($SD = 31.3$) and decreased to 28.9 ($SD = 27.3$, $p < .05$) following product use; for the OB condition, immediately before the second use period, mean urge was 43.6 ($SD = 30.8$) and decreased to 16.5 ($SD = 19.4$, $p < .05$) following product use (see Figure 5).

Following the second use period, mean ratings of urge were significantly greater in the 2 mg condition ($M = 42.9$, $SD = 33.8$) when compared to OB ($M = 16.5$, $SD = 19.4$, $p < .05$) after

the second use period. No significant differences were observed across pouch conditions following the second use period.

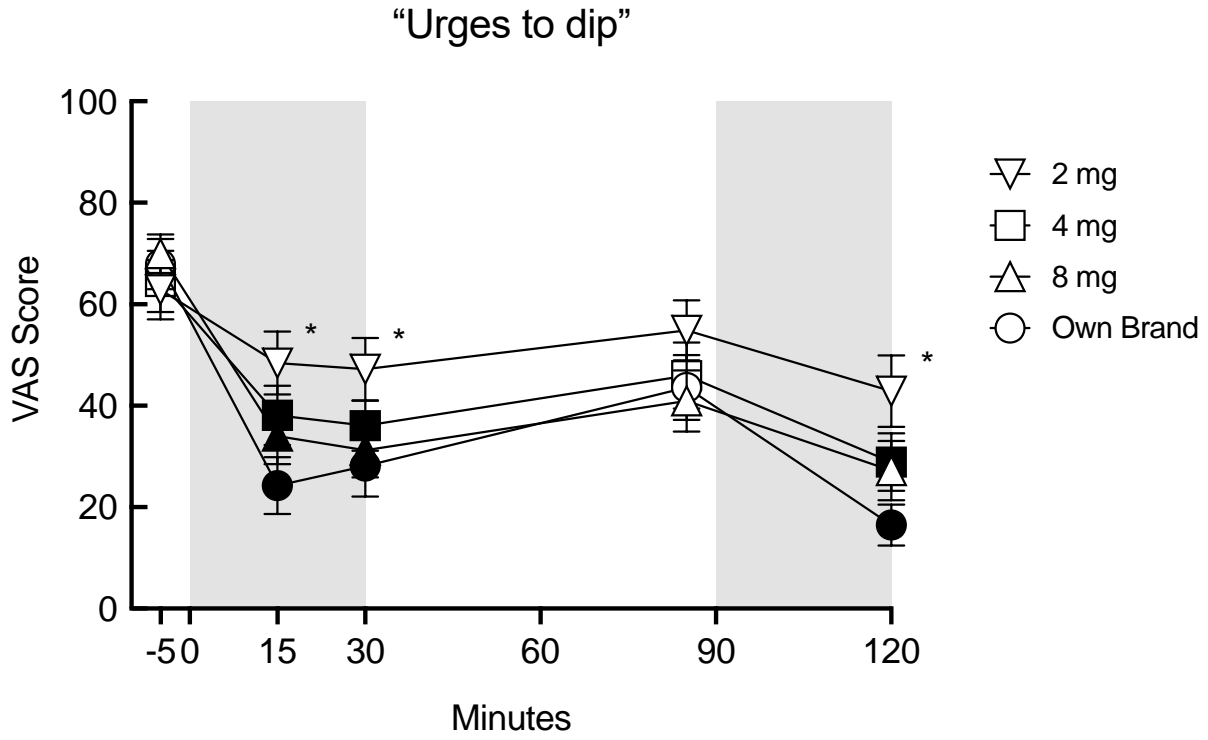


Figure 5. Mean data (\pm SEM) for the Hughes-Hatsukami “Urges to dip” item, ($N = 23$). In all other respects, the figure is identical to Figure 1.

Items with a Significant Main Effect of Condition and/or Time.

Anxious. For “Anxious”, the means (\pm SEM) for all conditions across time are depicted in Figure 6, Panel A. As the figure shows, prior to the first use period, mean anxious ratings did not differ significantly by condition. However, mean anxious ratings decreased significantly over time for the 4 mg, 8 mg, and OB conditions during the first use period, and for the 8 mg and OB conditions following the first use period ($ps < .05$, Tukey’s HSD). For example, for the 4 mg condition, pre-use mean anxious ratings were 27.1 ($SD = 31.9$) and decreased to 15.0 ($SD = 20.4$, $p < .05$) following the first use period; for the 8 mg condition, pre-use mean anxious ratings were 29.5 ($SD = 27.8$) and decreased to 13.0 ($SD = 20.3$, $p < .05$) following the first use period; for the OB condition, pre-use mean anxious ratings were 26.7 ($SD = 28.6$) and decreased to 12.4 ($SD = 15.2$, $p < .05$) following the first use period (see Figure 6, Panel A).

No significant differences were observed across condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

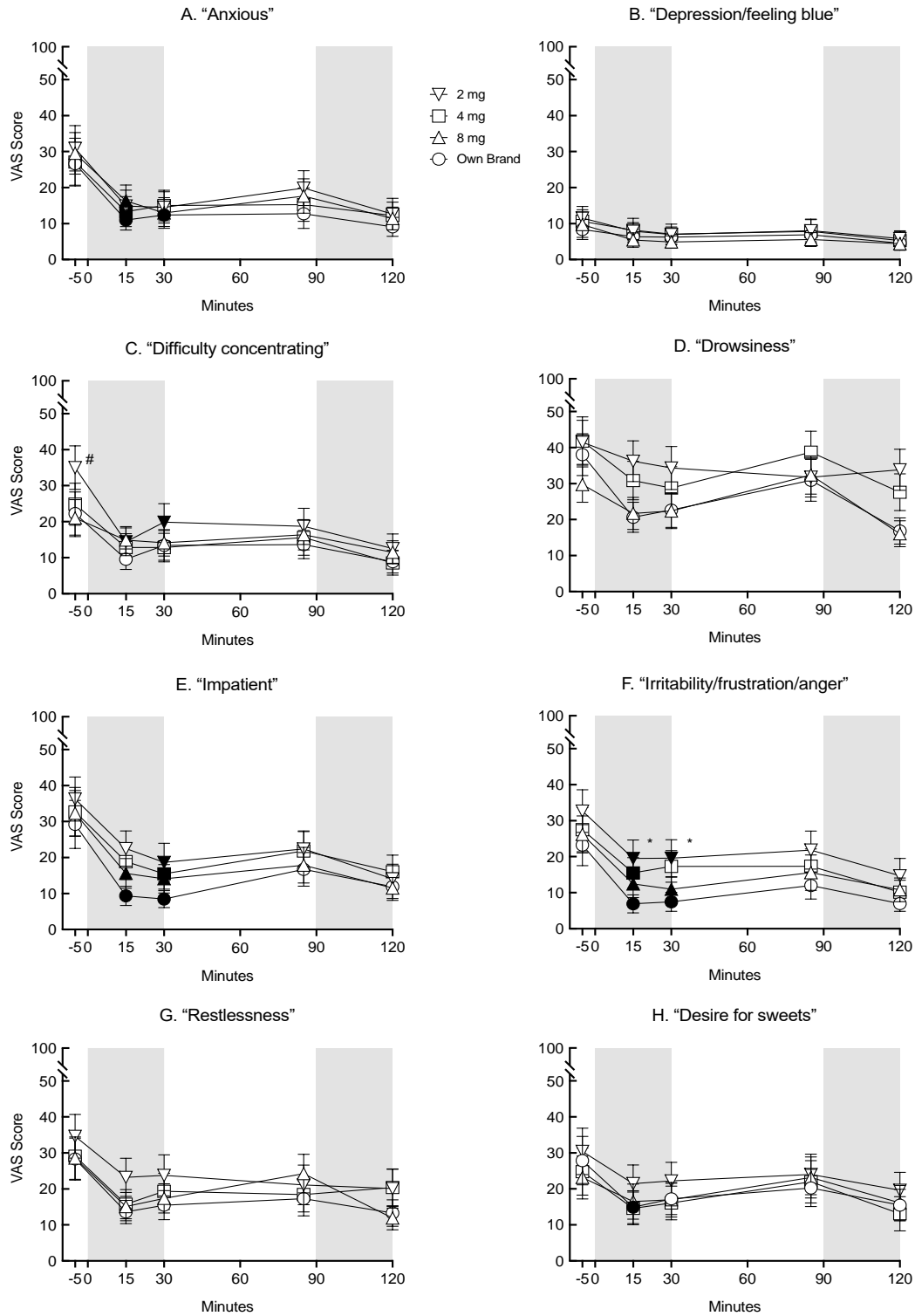


Figure 6. Mean data (\pm SEM) for all Hughes-Hatsukami items with a main effect of condition and/or time, ($N = 23$). In all other respects, each panel of the figure is identical to Figure 1.

Depression. For “Depression/feeling blue”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel B. No significant differences were observed across time or condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Difficulty Concentrating. For “Difficulty concentrating”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel C. As the figure shows, prior to the first use period, mean difficulty concentrating ratings differed significantly by condition ($ps < .05$, Tukey’s HSD). Specifically, mean difficulty concentrating ratings for the 2 mg condition ($M = 35.0$, $SD = 29.1$) were significantly greater at baseline when compared to the 8 mg condition ($M = 21.0$, $SD = 24.6$, $p < .05$). Also, mean difficulty concentrating ratings changed significantly over time for the 2 mg condition during and following the first use period; pre-use mean difficulty concentrating ratings were 35.0 ($SD = 29.1$) and decreased to 14.4 ($SD = 18.4$) during use (at 15 minutes) and increased to 19.9 ($SD = 25.0$; $ps < .05$) following the first use period.

No significant differences were observed across condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Drowsiness. For “Drowsiness”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel D. No significant differences were observed across time or condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Impatient. For “Impatient”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel E. As the figure shows, prior to the first use period, mean impatient ratings did not differ significantly by condition. However, mean impatient ratings decreased

significantly over time for all conditions following the first use period ($ps < .05$, Tukey's HSD). For example, for the 2 mg condition, pre-use mean impatient ratings were 36.3 ($SD = 29.5$) and decreased to 18.7 ($SD = 25.5$, $p < .05$) following the first use period; for the 4 mg condition, pre-use mean impatient ratings were 32.7 ($SD = 32.7$) and decreased to 15.5 ($SD = 20.5$, $p < .05$) following the first use period; for the 8 mg condition, pre-use mean impatient ratings were 32.3 ($SD = 30.2$) and decreased to 14.1 ($SD = 19.1$, $p < .05$) following the first use period; for the OB condition, pre-use mean impatient ratings were 29.2 ($SD = 32.1$) and decreased to 8.5 ($SD = 11.3$, $p < .05$; See Figure 6, Panel E) following the use period.

No significant differences were observed across condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Irritability. For "Irritability/frustration/anger", the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel F. As the figure shows, prior to the first use period, mean irritability ratings did not differ significantly by condition. However, mean irritability ratings decreased significantly over time for all conditions during the first use period and for the 2 mg, 8 mg, and OB conditions following the first use period ($ps < .05$, Tukey's HSD). For example, for the 2 mg condition, pre-use mean irritability ratings were 32.7 ($SD = 28.5$) and decreased to 19.5 ($SD = 24.6$) during use (at 15 minutes) and to 19.6 ($SD = 24.7$; $ps < .05$) following the first use period; for the 4 mg condition, pre-use mean irritability ratings were 27.5 ($SD = 29.4$) and decreased to 15.5 ($SD = 20.4$, $p < .05$) during use (at 15 minutes); for the 8 mg condition, pre-use mean irritability ratings were 26.2 ($SD = 24.7$) and decreased to 12.4 ($SD = 18.2$) during use (at 15 minutes) and to 11.0 ($SD = 16.0$; $ps < .05$) following the first use period; for the OB condition, pre-use mean irritability ratings were 23.2 ($SD = 27.4$) and decreased to 6.9

($SD = 12.0$) during use (at 15 minutes) and to 7.5 ($SD = 12.7$; $ps < .05$) following the first use period (See Figure 6, Panel F).

Mean irritability ratings were significantly greater during the first use period (at 15 minutes) in the 2 mg condition ($M = 19.5$, $SD = 24.6$) when compared to OB ($M = 6.9$, $SD = 12.0$, $p < .05$). Following the first use period, mean irritability ratings were significantly greater in the 2 mg condition ($M = 19.6$, $SD = 24.7$) when compared to OB ($M = 7.5$, $SD = 12.7$, $p < .05$).

No significant differences were observed across time or condition following the second use period.

Restless. For “Restless”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel G. No significant differences were observed across time or condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Desire for Sweets. For “Desire for sweets”, the means ($\pm SEM$) for all conditions across time are depicted in Figure 6, Panel H. As the figure shows, prior to the first use period, mean ratings of desire for sweets did not differ significantly by condition. However, mean ratings of desire for sweets decreased significantly over time for the OB condition during the first use period ($p < .05$, Tukey’s HSD). Specifically, for the OB condition, pre-use mean ratings of desire for sweets were 27.9 ($SD = 32.4$) and decreased to 14.9 ($SD = 22.0$, $p < .05$) during the first use period (at 15 minutes).

No significant differences were observed across condition during and following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

Direct Effects of Nicotine

All items were analyzed using a two factor within-subjects ANOVA. A statistically significant Condition x Time interaction was observed in the Lightheaded item only, and a statistically significant main effect of time was observed in the Salivation item only. These items are detailed below.

Items with a Significant Condition x Time Interaction.

Lightheaded. For “Lightheaded”, the means (\pm SEM) for all conditions across time are depicted in Figure 7. As the figure shows, prior to the first use period, mean lightheaded ratings did not differ significantly by condition. However, mean lightheaded ratings increased significantly over time for the 8 mg condition only ($ps < .05$, Tukey’s HSD). For the 8 mg condition, pre-use mean lightheaded ratings were 4.4 ($SD = 9.7$) and increased to 18.5 ($SD = 27.3$, $p < .05$) following the first use period.

No significant differences were observed across condition following the first use period. Additionally, no significant differences were observed across time or condition following the second use period.

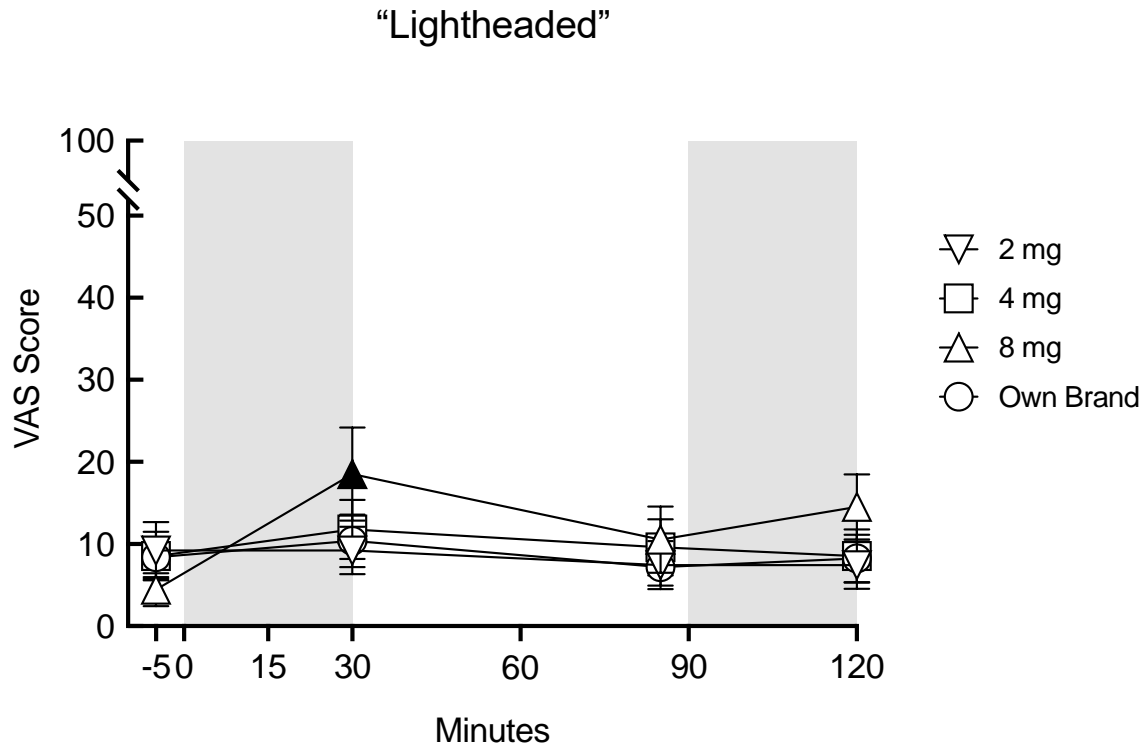


Figure 7. Mean data (\pm SEM) for the Direct Effects of Nicotine “Lightheaded” item, ($N = 23$). In all other respects, the figure is identical to Figure 1.

Items with a Significant Main Effect of Condition and/or Time.

Salivation. For “Excessive salivation”, the means (\pm SEM) for all conditions across time are depicted in Figure 8. As the figure shows, prior to the first use period, mean salivation ratings did not differ significantly by condition. No significant differences were observed across time or condition following the first use period.

Following the second use period, salivation ratings increased significantly for the OB condition only ($ps < .05$, Tukey’s HSD). Pre-use mean salivation ratings were 13.8 ($SD = 16.4$) and increased to 30.3 ($SD = 26.1$, $p < .05$) following the second use period (see Figure 8). No significant differences were observed across conditions following the second use period.

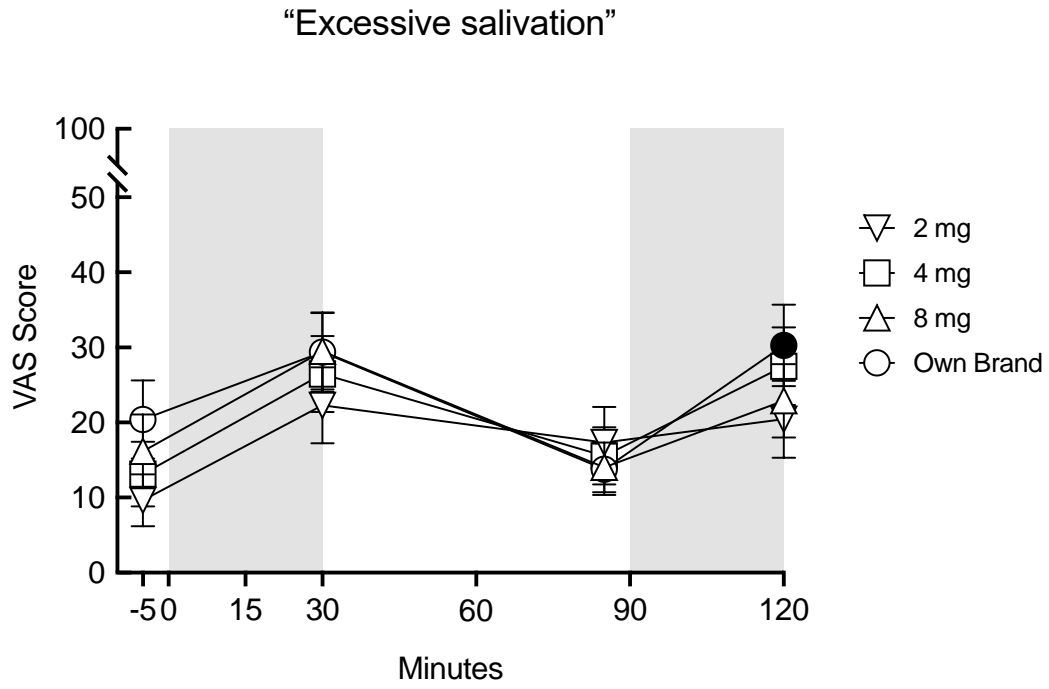


Figure 8. Mean data (\pm SEM) for the Direct Effects of Nicotine “Excessive salivation” item, ($N = 23$). In all other respects, the figure is identical to Figure 1.

Direct Effects of Smokeless Tobacco

The direct effects of SLT was administered during and after the first administration period, and after the second administration period. Therefore, the first and second use periods were analyzed separately, and the factor of time was included in analysis for the first use period only. Statistically significant main effects of condition and time were observed in items “Head Rush”, “Like Feeling”, and “Tingling”. A statistically significant main effect of condition was observed in items “Alert”, “Amount Swallowed”, “Heart Racing”, “Like Taste”, “Nausea”, and “Strong”. A statistically significant main effect of time was observed for the item “Relaxed”, with ratings of “relaxed” greater during the first use period (at 15 min) when compared to following the first use period (at 30 min). However, there were no significant Condition x Time interactions observed for any items; therefore, all items in the first use period were re-analyzed and time was not included as a factor (analyses were restricted to data collected immediately following administration). As displayed in Table 3, a statistically significant effect of condition was observed in items: Alert, Amount Swallowed, Head Rush, Like Feeling, Like Taste, Strong, (both use periods) as well as Nausea and Tingling (first use period only). Means for each item with a statistically significant main effect of condition are displayed in Table 4, and selected items with the largest effect size (“Like Feeling”, “Like Taste”, and “Strong”) are detailed below.

Table 3. Statistical Analysis Results for One-Factor Analysis of Variance, DESLT.

Direct Effects of Smokeless Tobacco	First Use Period			Second Use Period		
	F	<i>p</i>	η_p^2	F	<i>p</i>	η_p^2
Alert ^a	3.675	.020	.143	5.888	.001	.219
Amount Swallowed ^a	11.703	<.001	.347	8.672	<.001	.292
Headrush ^a	7.756	.002	.261	7.427	.002	.261
Heart Racing ^a	3.163	.059	.126	1.258	.297	.057
Like Feeling ^a	12.996	<.001	.371	10.443	<.001	.332
Like Taste ^a	27.114	<.001	.552	23.198	<.001	.525
Nausea ^a	4.577	.025	.172	1.249	.296	.056
Relaxed ^b	1.691	.178	.071	.140	.878	.007
Strong ^c	17.184	<.001	.450	18.585	<.001	.470
Tingling ^a	5.745	.003	.207	1.889	.147	.083

^a *df* First Use Period = (3, 66), Second Use Period = (3, 63)

^b *df* First Use Period = (3, 66), Second Use Period = (3, 60)

^c *df* First Use Period = (3, 63), Second Use Period = (3, 63)

Table 4. Means (*SDs*) of DESLT Items with a Significant Main Effect of Condition.

	2 mg	4 mg	8 mg	Own Brand (OB)
Alert				
<i>First Use Period</i>	38.0 (19.8) *	39.3 (23.3)	43.0 (20.1)	53.7 (25.1)
<i>Second Use Period</i>	38.2 (21.9) *	36.3 (24.3) *	40.4 (20.2) *	54.7 (22.6)
Amount Swallowed				
<i>First Use Period</i>	50.3 (40.5) *	52.2 (41.0) *	55.0 (39.8) *	17.2 (25.5)
<i>Second Use Period</i>	50.9 (38.1) *	52.1 (39.8) *	53.6 (40.6) *	20.5 (25.3)
Headrush				
<i>First Use Period</i>	10.6 (14.4) #	17.1 (22.5)	29.3 (30.0) *	14.9 (20.1)
<i>Second Use Period</i>	7.0 (10.0) #	10.9 (16.6) #	24.7 (25.2)	15.2 (23.6)
Like Feeling				
<i>First Use Period</i>	46.1 (23.6) *	45.7 (28.4) *	47.3 (24.3) *	77.2 (17.8)
<i>Second Use Period</i>	47.2 (23.2) *	44.9 (23.9) *	45.6 (21.0) *	71.6 (17.5)
Like Taste				
<i>First Use Period</i>	38.4 (23.1) *	37.4 (26.8) *	39.7 (23.3) *	79.7 (17.0)
<i>Second Use Period</i>	40.1 (25.7) *	33.5 (25.6) *	37.7 (23.5) *	76.4 (16.8)
Nausea				
<i>First Use Period</i>	5.0 (7.5)	8.3 (16.0)	19.0 (28.4)	5.7 (8.0)
<i>Second Use Period</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Strong				
<i>First Use Period</i>	18.5 (21.4) *#+	36.0 (24.0) *#	54.6 (26.8)	56.9 (25.8)
<i>Second Use Period</i>	23.0 (22.4) *#	30.6 (19.4) *#	45.9 (27.0) *	61.2 (17.7)
Tingling				
<i>First Use Period</i>	13.0 (17.7) #	16.5 (20.5) #	28.0 (27.7)	17.4 (21.4)
<i>Second Use Period</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>

Asterisk (*) indicates significant difference from OB in same use period. Pound sign (#) indicates significant difference from 8 mg in same use period. Plus sign (+) indicates significant difference from 4 mg in same use period. *ns* indicates item/use period results were not significant (i.e., a statistically significant effect of condition was not observed).

Like Feeling. A significant effect of condition was observed for the item “Do you like the way the product makes you feel?” following the first use period, $F(3, 66) = 13.0, p < .05$, and the second use period, $F(3, 63) = 10.4, p < .05$. The means (*SDs*) for all conditions are reported in Table 4. Following both use periods, mean like feeling ratings were significantly lower in all ONP conditions when compared to OB ($ps < .05$, Tukey’s HSD). For the first use period, mean like feeling ratings were significantly lower in the 2 mg condition ($M = 46.1, SD = 23.6$), the 4 mg condition ($M = 45.7, SD = 28.4$), and the 8 mg condition ($M = 47.3, SD = 24.3$) when compared to OB ($M = 77.2, SD = 17.8; ps < .05$). For the second use period, mean like feeling ratings were significantly lower in the 2 mg ($M = 47.2, SD = 23.2$), 4 mg ($M = 44.9, SD = 23.9$), and 8 mg conditions ($M = 45.6, SD = 21.0$) when compared to OB ($M = 71.6, SD = 17.5; ps < .05$).

Like Taste. A significant effect of condition was observed for the item “Do you like the way the product tastes?” following the first use period, $F(3, 66) = 27.1, p < .05$, and the second use period, $F(3, 63) = 23.2, p < .05$. The means (*SDs*) for all conditions are reported in Table 4. Following both use periods, mean like taste ratings were significantly lower in all ONP conditions when compared to OB ($ps < .05$, Tukey’s HSD). For the first use period, mean like taste ratings were significantly lower in the 2 mg condition ($M = 38.4, SD = 23.1$), the 4 mg condition ($M = 37.4, SD = 26.8$), and the 8 mg condition ($M = 39.7, SD = 23.3$) when compared to OB ($M = 79.7, SD = 17.0; ps < .05$). For the second use period, mean like taste ratings were significantly lower in the 2 mg ($M = 40.1, SD = 25.7$), 4 mg ($M = 33.5, SD = 25.6$), and 8 mg conditions ($M = 37.7, SD = 23.5$) when compared to OB ($M = 76.4, SD = 16.8; ps < .05$).

Strong. A significant effect of condition was observed for the item “Overall, how strong is the product?” following the first use period, $F(3, 63) = 17.2, p < .05$ and the second use period,

$F(3, 63) = 18.9, p < .05$. Following the first product use period, mean strong ratings were significantly lower in the 2 mg ($M = 18.5, SD = 21.4$) and 4 mg ($M = 36.0, SD = 24.0$) conditions when compared to OB ($M = 56.9, SD = 25.8; ps < .05$, Tukey's HSD).

Following the second use period, mean strong ratings were significantly lower in the 2 mg ($M = 23.0, SD = 22.4$), 4 mg ($M = 30.6, SD = 19.4$), and 8 mg conditions ($M = 45.9, SD = 27.0$) when compared to OB ($M = 61.2, SD = 17.7; ps < .05$).

General Labeled Magnitude Scale

The gLMS was administered once per session, following the second administration period. Data were analyzed using a one factor (condition; 4 levels) repeated measures ANOVA; results revealed a statistically significant effect of condition in both gLMS items, Harshness and Flavor.

Harshness. A significant effect of condition was observed, $F(3, 66) = 9.9, p < .05$. The means (+ *SEM*) for all conditions are depicted in Figure 9. As the figure shows, mean flavor ratings were significantly lower in the 2 mg condition ($M = 5.1, SD = 5.0$) and the 4 mg condition ($M = 11.7, SD = 10.2$) when compared to OB ($M = 25.3, SD = 21.3; ps < .05$, Tukey's HSD).

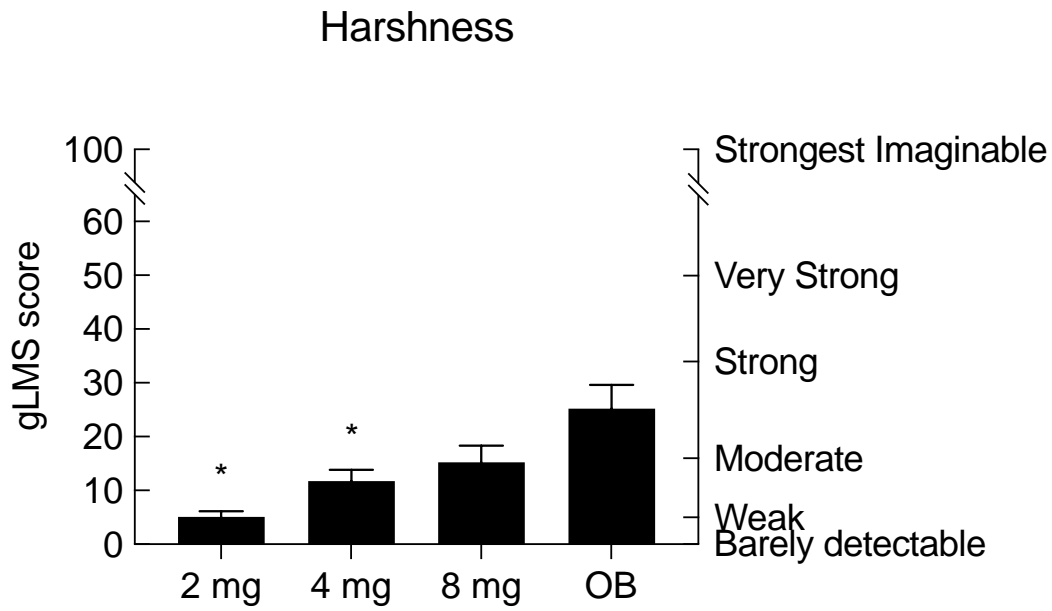


Figure 9. Mean Data (+ *SEM*) for the gLMS “Harshness” Item, ($N = 23$). Asterisks (*) indicate a significant difference from OB.

Flavor. A significant effect of condition was observed, $F(3, 66) = 51.7, p < .05$. The means (+ *SEM*) for all conditions are depicted in Figure 10. As the figure shows, mean flavor ratings were significantly lower in all ONP conditions when compared to OB ($ps < .05$, Tukey's HSD). Specifically, mean flavor ratings were significantly lower in the 2 mg condition ($M = 12.3, SD = 11.3$), the 4 mg condition ($M = 15.7, SD = 17.4$) and the 8 mg condition ($M = 16.0, SD = 14.3$) when compared to OB ($M = 59.2, SD = 21.9; ps < .05$).

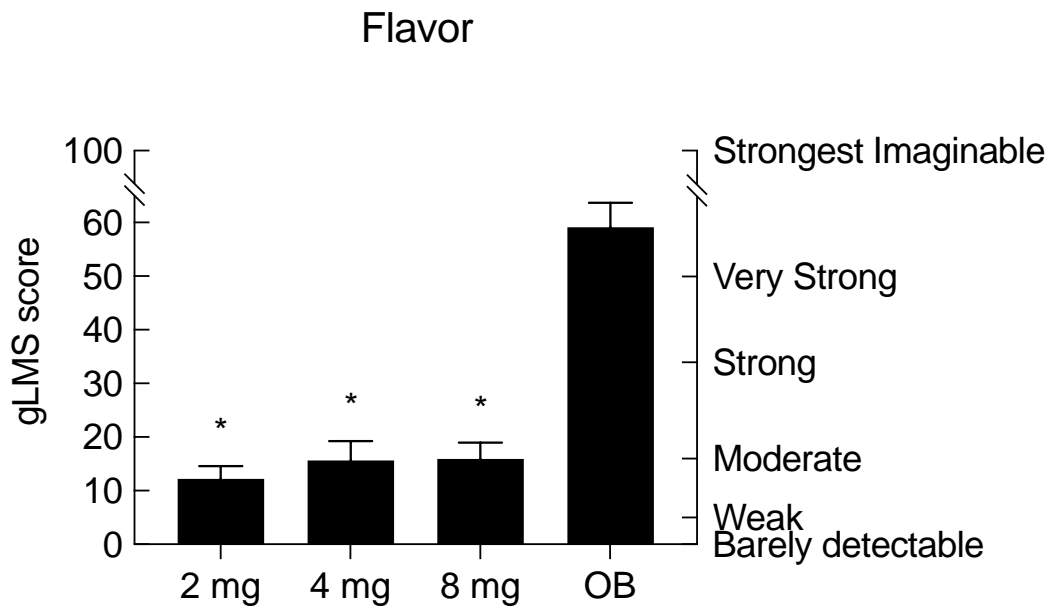


Figure 10. Mean Data (+ *SEM*) for the gLMS “Flavor” Item, ($N = 23$). Asterisks (*) indicate a significant difference from OB.

Own Brand (OB) Weight

Participants' OB product containers were weighed before and after each use period on OB session days, and these values were used to determine OB Weight for each use period. Each participants' brand, flavor, and OB weight for each use period is depicted in Table 5.

Table 5. Participants' Own Brand, Flavor, and Weight (g).

PARTICIPANT	BRAND	FLAVOR	OB Weight (g) FIRST USE PERIOD	OB Weight (g) SECOND USE PERIOD
1	Camel Snus	Mellow	0.55	0.53
2	General	Mint	1.08	0.99
3	Skoal Snus	Mint	1.13	2.24
4	Grizzly	Wintergreen	1.13	1.01
5	Grizzly	Wintergreen	1.25	1.29
6	Copenhagen	Mint	1.58	1.54
7	Copenhagen	Mint ^a	2.96	2.73
8	Grizzly	Wintergreen	3.25	3.09
9	Grizzly	Wintergreen	3.32	4.44
10	Grizzly	Original	3.5	2.99
11	Copenhagen	Wintergreen	3.51	3.52
12	Grizzly	Wintergreen ^a	3.72	3.91
13	Grizzly	Dark Wintergreen	3.76	4.32
14	Copenhagen	Straight	3.88	4.75
15	Grizzly	Wintergreen	4.01	3.93
16	Copenhagen	Straight	4.21	5.02
17	Skoal	Mint	4.82	3.08
18	Copenhagen	Wintergreen	5.97	3.75
19	Grizzly	Wintergreen	5.99	3.98
20	Copenhagen	Mint	6.32	4.74
21	Copenhagen	Wintergreen	6.4	7.62
22	Big Duke	Original	8.2	7.25
23	Copenhagen	Mint	9.02	9.22
Mean (SD)			3.9 (2.3)	3.7 (2.2)

^a = Pouches

Purchase Tasks

The single product purchase task and cross product purchase task were administered once per session, following the second administration period. Outcomes for these tasks include: elasticity, intensity, and cross-price elasticity. For all single product purchase task outcomes, 2 participants were removed due to missing data. Additionally, for intensity analyses, 3 participants were removed because they did not report a value at the lowest price (\$0). Finally, for elasticity analyses only, 7 participants were removed because they reported no demand across all prices (4 in the 2 mg condition, 3 in the 8 mg condition). Thus, a total of 5 participants were removed from intensity analyses (final $N = 18$) and a total of 9 participants were removed from elasticity analyses (final $N = 14$). For the cross product purchase task, 1 participant was removed due to missing data (final $N = 22$).

Single Product Purchase Task. Data for the single product purchase task were analyzed using a one factor (condition; 4 levels) repeated measures ANOVA. The intensity and elasticity for all conditions are depicted in Table 6, and the demand curves for all conditions (in the sample used for intensity analysis, $N = 18$) are depicted in Figure 11. Intensity of demand (i.e., purchase behavior at \$0) did not differ significantly across conditions. Also, among those participants who reported some demand for all conditions ($N = 14$), elasticity did not differ significantly across conditions.

Table 6. Results for ONPs and OB SLT in the Single Product Purchase Task.

Session	Product	Intensity ^{a, b}	95% confidence interval	Elasticity ^c	95% confidence interval
	2 mg	10.22	[9.23, 11.24]	0.028	[0.019, 0.042]
	4 mg	9.11	[8.48, 9.75]	0.027	[0.018, 0.040]
	8 mg	8.34	[7.65, 9.03]	0.010	[0.007, 0.013]
	OB	8.59	[8.04, 9.15]	0.019	[0.013, 0.027]

^a Intensity = the number of pouches/dips at \$0

^b $N = 18$

^c $N = 14$

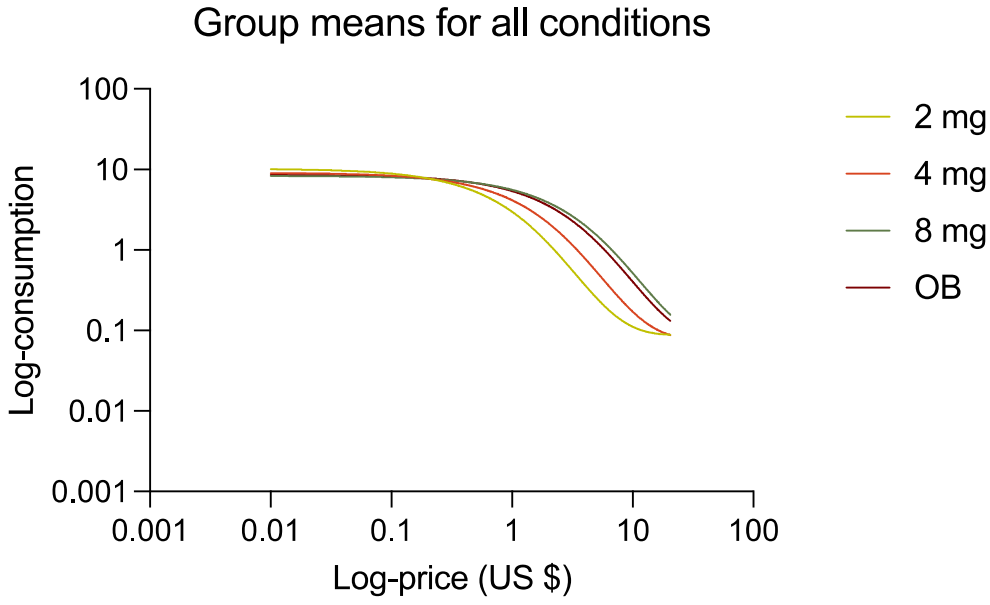


Figure 11. Demand Curves for the Single Product Purchase Task ($N = 18$).

Cross Product Purchase Task. Data for the cross product purchase task were analyzed using a linear regression, with log-price of OB SLT regressed on to log-consumption of ONP condition. The regression coefficient (i.e., slope) indicated the cross-price elasticity of each ONP condition. A positive, significant slope would indicate that the ONP condition functioned as a substitute for OB SLT, such that demand for the ONP increased as OB SLT prices increased. The regression coefficients for all conditions are depicted in Table 7. Results revealed positive and significant regression coefficients for all ONP conditions ($ps < .01$, see Table 7), indicating all ONP conditions functioned as OB SLT substitutes ($N = 22$). Results from the 95% confidence intervals revealed a considerable overlap across conditions (see Figure 12), indicating a non-significant difference based on ONP nicotine content.

Table 7. Changes in log-ONP Consumption with Changes in log-Price of OB SLT from the Cross Product Purchase Task ($N = 22$).

Pouch Condition	Coefficient	p	95% confidence interval
2 mg	0.335	<.001	[0.30, 0.49]
4 mg	0.255	<.001	[0.19, 0.37]
8 mg	0.273	<.001	[0.23, 0.42]

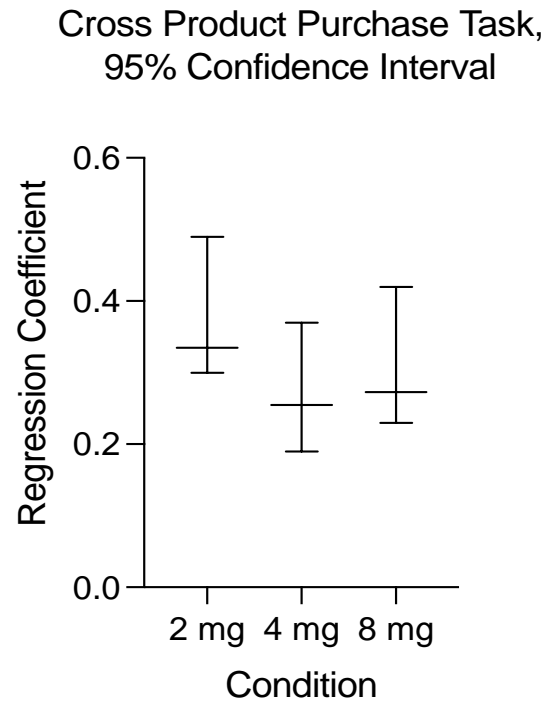


Figure 12. Regression Coefficients and 95% Confidence Intervals for the Cross Product Purchase Task, ($N = 22$).

Discussion

Overview

ONPs were introduced to the US market in 2016 (Robichaud et al., 2019) and consist of a pouch filled with nicotine, flavorants, sweeteners, and pH buffers. ONPs are marketed in the US as “tobacco free” and use prevalence is increasing, especially for the two brands that make up the majority of the market share, Zyn and ON! (Majmundar et al., 2022; Schneller et al., 2023). Indeed, these two ONP brands are among the ONPs with the highest pH and the highest percentage of freebase nicotine (Stanfill et al., 2021). Freebase nicotine crosses the mucosal membranes more readily than protonated nicotine, and traditional SLT products with higher pH (and thus, a greater proportion of freebase nicotine) deliver significantly more nicotine when compared to SLT products with lower pH (Pickworth, 2014; Tomar & Henningfield, 1997; Wilhelm et al., 2021). Accordingly, ONPs with a pH > 8 would be expected to have the most efficient nicotine delivery profile and the greatest subjective effects (e.g., the greatest suppression of abstinence symptoms), relative to ONPs with lower pH and thus a lower percentage of freebase nicotine (Benowitz, 2022). However, data concerning ONP nicotine delivery and other effects have been produced, almost without exception, by tobacco industry-funded/-affiliated authors. This dissertation offers the first comprehensive report of the results of an industry-independent study using clinical laboratory methods to examine the physiological and subjective effects of ON! brand ONPs in people who use SLT regularly. Study hypotheses were that plasma nicotine and abstinence symptom suppression will be influenced directly by pouch nicotine content, such that the 2 mg and 4 mg conditions would deliver significantly less nicotine and suppress abstinence symptoms significantly less effectively than the 8 mg and OB conditions. In general, results in this study provide partial support for these hypotheses (i.e., 2

and 8 mg differed significantly on several outcomes; 2 and 4 mg differed significantly on plasma nicotine) and indicate that labeled pouch nicotine content (i.e., 2, 4, or 8 mg) influences nicotine delivery, heart rate, and subjective effects (see following paragraphs for details). As discussed below, these results are consistent with previous independent research examining the effects of ONPs in people who smoke cigarettes (Keller-Hamilton et al., 2024a), with a preliminary report of the effects of Zyn brand ONPs in people who use SLT (Keller-Hamilton, et al., 2024b), as well as with industry-sponsored research (Liu et al., 2022; Lunell et al., 2020; Rensch et al., 2021). Taken in combination with real-world purchase data, study results offer preliminary support for the notion that some ONPs may substitute for SLT in the population from which this sample was drawn (i.e., people who use SLT regularly in the US). Moreover, results also are consistent with the idea that lower nicotine content ONPs may serve as a “starter” product for more nicotine naïve individuals due to their nicotine delivery profile and associated subjective effects. These types of products are purported to lead to “graduation” to higher nicotine content ONPs or other products that deliver nicotine more effectively. Finally, one policy-related implication of these results is that regulating ONP pH (and SLT pH) such that there is an upper limit on the pH of these products may help reduce the likelihood that nicotine-naïve individuals who begin using these products will continue that use over the long-term. Each of these topics are addressed below, along with some study limitations.

Physiological Effects

In this study, physiological effects involved measurement of participant plasma nicotine concentration and HR. Overall, plasma nicotine concentration and HR significantly increased in the 4 mg and 8 mg ONP conditions following product use, indicating that these ONPs reliably delivered nicotine to participants in amounts that were physiologically active.

With respect to how ON! ONP nicotine content influenced plasma nicotine concentration, following the first use period, mean plasma nicotine concentration increased in an ONP nicotine content-dependent manner (i.e., as nicotine content increased, plasma nicotine concentration also increased), with significant increases from baseline in the 4 mg and 8 mg ON! ONP conditions (and also in the OB condition). Following both use periods, mean plasma nicotine concentration was more pronounced (but not significantly so) in the 8 mg condition relative to the 4 mg ON! ONP condition (see Figure 1). Notably, the observed mean increase in plasma nicotine concentration of the 2 mg ON! ONP did not differ significantly from baseline and was significantly lower when compared to the 4 mg and 8 mg conditions (see Figure 1). Results were similar following the second use period. Thus, in this study, ON! ONPs with 4 or 8 mg total nicotine content delivered nicotine reliably, while the 2 mg ON! ONP did not.

These results are consistent with recent industry-funded/affiliated work examining the effects of ON! (Liu et al., 2022, Rensch et al., 2021) and other ONP brands (Lunell et al., 2020), as well as independent work examining the effects of ONPs in people who smoke cigarettes (Keller-Hamilton et al., 2024a) and people who use SLT (Keller-Hamilton et al., 2024b). Specifically, in two industry-funded studies, an increase in labeled nicotine content of ON! ONPs was associated with greater nicotine plasma concentration (Liu et al., 2022), and results regarding the nicotine delivery of the 4 mg ON! ONP in “Original” flavor ($C_{max} = 9.6$ ng/ml, $SD = 2.6$; Suppl. Table 2, Rensch et al., 2021) appear to not differ markedly from the mean plasma nicotine concentration observed in the present study following use of the 4 mg ONP (e.g., first use period: $M = 8.4$ ng/ml, $SD = 4.6$). Additionally, the results observed in this study were consistent with two studies examining the effects of Zyn brand ONPs. Specifically, increases in ONP nicotine content were associated with greater mean plasma nicotine concentration in an

independent study (Keller-Hamilton et al., 2024a) and an industry-funded study (Lunell et al., 2020) examining the effects of 3mg and 6 mg Zyn ONPs. Importantly, mean plasma nicotine concentration appeared somewhat higher after 30 minutes in the independent study (3 mg, $M = 9.5$ ng/ml, $SD = 5.6$; 6 mg, $M = 17.5$ ng/ml, $SD = 9.8$; Keller-Hamilton et al., 2024a) when compared to the C_{max} results after 60 minutes in the industry study (3 mg, $C_{max} = 7.7$ ng/ml, CI: 6.3, 9.0; 6 mg, $C_{max} = 14.7$, CI: 12.3, 17.1; Lunell et al., 2020). In fact, among the industry-funded/affiliated studies, results regarding the nicotine delivery of ONPs have been inconsistent across brands (see above). This inconsistency may be influenced by differences in product characteristics (e.g., pH) and/or aspects of study design (e.g., length of product use). Regarding the influence of pH, the high pH of ON! brand ONPs (9.4 – 9.6) may result in greater nicotine delivery relative to other brands with lower pH (e.g., Zyn, 8.4 – 8.6; Stanfill et al., 2021), though the results observed in this study and other independent work suggest that may not be the case. Importantly, in Stanfill et al., the pH measurement was conducted in a solution of water, and using a saliva solution may deliver a more accurate measurement of the pH of ONPs when they are being used. Additionally, results indicate that ONPs with low nicotine content (e.g., 2 mg) may deliver significantly less nicotine when compared to other SLT products (and ONPs with greater total nicotine content). In sum, these observations that plasma nicotine concentration increased significantly following use of the 4 mg and 8 mg but not the 2 mg ON! ONPs demonstrate that nicotine content influences the nicotine delivery of ON! ONPs, and this demonstration is consistent with previous research.

Interestingly, for some participants, the 8 mg ONP delivered substantially more nicotine than their OB SLT, though this effect was not reliable across the entire sample. For example, when nicotine boost values were compared, the 8 mg ONP delivered more nicotine than OB for

10 participants; among those 10, 7 had a difference ≥ 10.0 ng/ml. Thus, for at least some people who use SLT, switching to a high nicotine content ONP may increase their nicotine exposure considerably, potentially increasing their nicotine dependence and making quitting nicotine even more difficult, should they seek treatment for nicotine dependence. While industry-sponsored work regarding the nicotine delivery of ONPs is inconsistent, results from some studies are consistent with the notion that ONPs may not deliver as much nicotine as OB SLT/cigarettes (Liu et al., 2022; Rensch et al., 2021; Lunell et al., 2020). However, results from the present study as well as recent independent work (Keller-Hamilton et al., 2024a, 2024b) suggest that ONPs with high nicotine content may be capable of delivering as much or more nicotine than OB SLT/cigarettes.

Regarding HR, significant increases in HR were observed in the 4 mg and 8 mg ONP conditions (and also in the OB condition) following both product use periods, confirming the physiological effects of the nicotine delivered by these ONPs (see Figure 2). However, for the ONP with the lowest nicotine content (2 mg), the observed mean increase did not differ significantly from baseline and was significantly lower when compared to the 8 mg ONP condition (and also the OB condition). This observation that higher ONP nicotine content is associated with increased HR is consistent with a recent industry study of ONPs (Lunell et al., 2020). Specifically, increased ONP nicotine content was associated with significantly greater increases in HR following ONP use. The observation from this study that HR increased following use of the 4 mg and 8 mg ONP demonstrate that ONP nicotine content influences the nicotine delivery and, correspondingly, the cardiovascular response to ONPs.

Subjective Effects

In this study, subjective effects involved measurement of tobacco/nicotine abstinence symptom severity, the direct effects of nicotine, and the direct effects of SLT. Additional subjective measures addressed the specific sensations associated with ONP use (via the gLMS). Overall, significant differences were observed on measures of abstinence symptom severity and the direct effects of nicotine (see Table 2), as well as the DESLT (see Tables 3 and 4) and both gLMS items (see Table 5). These differences indicate that ONP nicotine content influenced the subjective profile of ONPs in a nicotine content-dependent manner for some subjective effects measures (i.e., the Hughes-Hatsukami measure of abstinence symptoms), while other subjective effects (i.e., those that measure preference and sensation; the direct effects of SLT and gLMS) were not sensitive to ONP nicotine content.

Abstinence symptoms (i.e., Hughes-Hatsukami items) were reduced following both use periods for some ONP conditions, with significant reductions observed on some VAS items (“Craving a dip/nicotine”, “Urges to dip”). Significant reductions in abstinence symptom ratings were observed in all conditions for the items assessing “Craving a dip/nicotine” and “Urges to dip.” With respect to how ONP nicotine content influenced craving ratings, following the first use period, the mean reduction in craving ratings was less pronounced (though not significantly so) in the 2 mg ONP condition when compared to the 4 mg and 8 mg conditions (see Figure 3). Following the second use period, mean reduction in craving ratings was significantly lower in the 2 mg ONP condition when compared to the 8 mg condition (and also the OB condition) (see Figure 3). Similar effects were observed after the first use period for the item “Urges to dip” (see Figure 5). This observation that higher ONP nicotine content is associated with more pronounced reduction in craving ratings is consistent with industry-funded studies (Rensch et al., 2021; Liu et

al., 2021). Specifically, higher nicotine content was associated with significantly more pronounced reduction in craving ratings, and ONPs with lower nicotine content do not reduce abstinence symptoms significantly. In sum, these observations that ratings of abstinence symptoms were reduced following use of the 4 mg and 8 mg ONPs, but not the 2 mg ONP, demonstrate that ONP nicotine content influences the tobacco/nicotine abstinence symptom suppression of ONPs. However, in other studies, ONPs at higher concentrations were less effective at reducing abstinence symptoms when compared to participants' OB across brands (ON!, Liu et al., 2022; Zyn, Keller-Hamilton et al., 2024a), populations (people who smoke cigarettes, Rensch et al., 2021; people who use SLT, Keller-Hamilton et al., 2024b), and funding sources (industry-funded/affiliated, Liu et al., 2022; independent, Keller-Hamilton et al., 2024a).

Significant differences were observed between conditions for items that measured the direct effects of nicotine and the direct effects of SLT. Significant increases in ratings of the direct effects of nicotine were observed for the item "Lightheaded" for the 8 mg condition only. Examining the effect of ONP nicotine content, significant increases in mean lightheaded ratings following the first use period were observed within the 8 mg condition only (see Figure 7). These observations that higher ONP nicotine content is associated with increased ratings of the direct effects of nicotine are consistent with previous industry studies of ONPs. Specifically, increases in nicotine content were associated with significant increases in ratings of the direct effects of nicotine (Lunell et al., 2020; Liu et al., 2022).

Significant effects were observed for the DESLT, including the items "Like Feeling", "Like Taste", and "Strong" following both use periods. In general, ratings of "Like Feeling" and "Like Taste" were significantly greater in the OB condition when compared to all ONP conditions and did not differ across ONP conditions. Ratings of "Strong" differed significantly

across condition, with the 2 mg and 4 mg conditions rated as significantly less strong than the 8 mg and OB conditions. Additionally, significant differences in specific sensations (i.e., flavor and harshness) based on condition were observed. Specifically, participants rated all ONP conditions as significantly less harsh and with less flavor sensation when compared to OB, and ratings of both items did not differ significantly across ONP conditions. This pattern of responding might be explained, at least as regards ratings of flavor sensation, by the fact that, in this study, participants used the unflavored “original” ON! ONP. In sum, results indicate that ratings of the direct effects of nicotine increased as ONP nicotine content increased and ratings of the DESLT did not differ based on ONP nicotine content, suggesting that nicotine content may influence some of the effects of ONPs (e.g., the drug effects of nicotine), while other effects may be less sensitive to differences in ONP nicotine content (e.g., those that measure preference and/or sensation).

Considered together, these observations of changes in abstinence symptom severity, the direct effects of nicotine, the direct effects of SLT, and sensation demonstrate nicotine content influences the subjective profile of ONPs. Specifically, increases in ONP nicotine content were associated with greater reduction of abstinence symptoms and higher ratings of the direct effects of nicotine. Results in this study are consistent with the idea that ONPs, especially those with greater nicotine content, may have utility as an alternative to other, more traditional SLT products that contain tobacco leaf (and thus contain tobacco specific nitrosamines/carcinogens). Specifically, measures of abstinence suppression support the notion that ONPs with high nicotine content may have potential as reduced harm alternative products. However, results regarding the 2 mg pouch indicate some lower nicotine content ONPs may not be capable of relieving abstinence symptoms. All ONP conditions were rated as significantly less strong, less harsh, and

with less flavor sensation when compared to OB SLT, establishing some subjective effects as insensitive to changes in ONP nicotine content.

Purchase Tasks

In this study, a single product and cross product purchase task were administered to examine the demand of ON! ONPs and the feasibility of these products as SLT substitutes. Overall, purchase task results did not differ significantly across conditions, including across ONPs and OB. The outcomes of interest (i.e., intensity and elasticity) did not differ significantly based on ONP nicotine content, and there were no significant differences observed when comparing ONPs to OB SLT. Additionally, positive and significant regression coefficients on the cross-product purchase task indicate all ONP conditions functioned as substitutes for OB SLT. From a behavioral economic standpoint, these results indicate the demand for and substitution feasibility of ONPs is not sensitive to nicotine content. However, the analyses conducted in this study did not include all of the typical estimates derived from these tasks (i.e., breakpoint, O_{max} , P_{max}), and thus there could have been differences based on nicotine content that were not observed. The observation that ONPs may serve as a substitute for OB SLT regardless of nicotine content should be regarded as preliminary due to the use of novel adapted purchase task measures and small sample size. Further exploration of the feasibility of ONPs as SLT substitutes would benefit from “real-choice” (as opposed to hypothetical) measures. Previous work has established the concurrent and predictive validity of hypothetical purchase tasks in the measure of alcohol demand (Martínez-Loredo et al., 2021; Motschman et al., 2022; Murphy et al., 2015; Strickland et al., 2019), yet there is conflicting evidence regarding the validity of these tasks when used to measure cigarette demand. In summary, this conflicting evidence includes findings from a meta-analysis examining the concurrent validity of hypothetical cigarette

purchasing tasks found that greater cigarette demand is associated with greater cigarette consumption and nicotine dependence (González-Roz et al., 2019), yet evidence for predictive validity is mixed (Koffarnus et al., 2015; Mackillop et al., 2016; Wilson et al., 2016), suggesting these tasks may be an accurate measure of current, but perhaps not future, tobacco use behavior. For these reasons, the hypothetical purchasing tasks used in this study should be regarded as preliminary evidence justifying further investigation via real-choice purchase tasks and/or hypothetical purchase tasks that include a larger sample size and/or a negative control condition (e.g., nicotine gum, as in Johnson et al., 2017). In sum, these observations indicate ONPs may function as substitutes for SLT, yet further research is needed.

Implications

The present study is the first independent, comprehensive examination of the physiological and subjective effects of ON! brand ONPs in people who use SLT. Independent data, including the results from this study, are integral to understand the effects of these products and their impact on individual and public health. For decades, oral tobacco products have been characterized as reduced harm alternatives for people who smoke cigarettes as well as “starter products” intended to initiate nicotine use and facilitate graduation to dependence (Beaglehole & Bonita, 2024; Benowitz, 2011; Elias et al., 2018; Hatsukami et al., 2004; Henningfield & Fagerstrom, 2001; Kozlowski, 2002; Rodu, 1994), and these characterizations now include ONPs (Grandolfo et al., 2024; Patwardhan & Fagerström, 2022). Results from the present study suggest that nicotine content influences the potential for ON! brand ONPs as a substitute for SLT and/or other tobacco products, as well as the potential for lower nicotine content ON! ONPs to serve as a “starter product” that may include graduation to other nicotine/tobacco products that contain more nicotine and/or toxicants. In order to protect public health, regulation of these

products must take into account abuse liability and palatability to people who use tobacco products and those who do not (i.e., nicotine naïve people). One way in which this accounting for both populations might be accomplished is regulations targeted at limiting the pH of oral nicotine products.

ONPs do not contain tobacco leaf, and therefore contain fewer tobacco-specific toxicants compared to other SLT products, presumably making them a less harmful product. For this reason, the substitution capability of ONPs is one important factor when considering their public health impact. Results from the present study demonstrate that ONPs with higher nicotine content can deliver nicotine and suppress abstinence symptoms in people who use SLT, and thus some ONPs may be capable of substituting for SLT. Specifically, the 4 mg and 8 mg ONP conditions did not differ significantly from OB SLT on measures of nicotine delivery and abstinence suppression. Additionally, this is the first study known to the author to examine the behavioral economic demand of an ONP, and significant regression coefficient results on the cross product purchase task indicate ONPs functioned as substitutes for OB SLT regardless of nicotine content (though these results should be considered preliminary due to the small sample size, as detailed above). Overall, the results of this study provide preliminary support for the notion that ONPs can substitute for SLTs. If ONPs are shown to have lower health risk than SLT, that may suggest a potential harm reduction strategy and/or a role for ONP in SLT treatment aimed at first transitioning from SLT to ONP, and then transitioning to NRT or potentially a nicotine free life.

The tobacco industry has a history of deceptive practices in pursuit of profits to the detriment of human life, including the design and marketing of “starter products” intended to facilitate tobacco use in people who are nicotine naïve (Connolly, 1995; Hendlin et al., 2017).

Starter products were flavored SLT products manipulated to be more palatable to nicotine naïve people via lower pH and/or nicotine content (Hendlin et al., 2017; Kostygina & Ling, 2016). These products were often marketed to young “potential” or “new” customers via advertising as well as peer influence campaigns (Ernster, 1989; Qian et al., 2021). Importantly, internal industry documents establish that one tobacco corporation specified new SLT customers as “age group 15-35” (Connolly, 1995) and another asserted “since all are pre-disposed to tobacco use, all are potential [SLT] consumers” (US Tobacco, 1983). Recently, concerns have been raised by parents and lawmakers regarding increased youth and young adult exposure to ONPs via TikTok/social media influencers (Dreyfuss, 2024; Gabbatt, 2024; Perrone, 2024). There are potential parallels between the peer-based marketing campaigns for starter products of the past and the recent reports of widespread promotion of ONPs on TikTok, an app on which the majority of users are under the age of 25 (Curry, 2024). Additionally, results from the present study confirm parallels in the acute effects of starter products and low nicotine content ONPs. Specifically, the nicotine delivery results observed in the 2 mg ONP condition mirror those observed previously in low nicotine content/low pH SLT “starter products” (Fant et al., 1999). Also, subjective effects results indicate the 2 mg ONP is not effective at reducing abstinence symptoms (e.g., craving). Tobacco corporations have often characterized SLT, and now ONPs, as an alternative product intended to be used by individuals who already use tobacco/nicotine (Carpenter et al., 2009; Rhee et al., 2021; Timberlake et al., 2011). If ONPs are designed to be a reduced harm alternative used by nicotine dependent individuals, the ineffective nicotine delivery and abstinence suppression observed in the 2 mg condition would suggest low nicotine content ONPs are inadequately designed, defective products. However, the tobacco industry has a history of meticulous product design (Bates et al., 1999; Center for Tobacco Products, 2016;

Kessler, 1994; Wayne & Carpenter, 2009; Wayne & Connolly, 2002), and the similarities between SLT starter products and low nicotine content ONPs engender a healthy dose of skepticism with regard to the promise of these products as reduced harm alternatives intended to promote public health. Perhaps more plausibly, these present results from the 2 mg ONP condition might be interpreted, along with recent ONP promotional tactics, as intentional, profit-motivated action intended to target and hook nicotine naïve individuals, maintaining the tobacco industry's perspective that "all are potential consumers" (US Tobacco, 1983).

Alternatively, ONPs with low nicotine content may be intended to be used as a final step in a graduated process leading to complete nicotine cessation, similar to the way some NRT products are intended to be used (see: [Fiore et al., 2008](#)). However, a graduation down to nicotine cessation using ONPs with higher nicotine content as the initial step could result in the development of lower nicotine content ONPs as conditioned reinforcers (Siegel, 1988, 2005). Accordingly, the step(s) down to low nicotine content ONPs would then risk eliciting a drug onset cue response, leading to increased abstinence symptoms and an increased likelihood of nicotine self-administration (Caggiula et al., 2001; Ferguson & Shiffman, 2009; Siegel & Ramos, 2002), making cessation more difficult. Further research is needed to explore the potential utility and risk(s) involved in a graduated cessation process using ONPs.

Regulation of ONPs must take into account the motives and practices of the tobacco industry. Specifically, the tobacco industry has continued to make low nicotine content products available for purchase, presumably in service to a profit motive. There is an ever-present need to remain aware of the utility of low nicotine products as "starter" products that are intended to initiate a graduation to products with higher nicotine content and increase the likelihood of sustained nicotine dependence. While products with fewer toxicants certainly have the potential

to impact public health positively as reduced harm alternatives, these products must be carefully regulated so as to ensure that the likelihood of initiation to tobacco use is minimized. Reducing the abuse liability of tobacco products is a prime target for regulation, yet this target may lack broad and/or sustained efficacy if considered via nicotine content alone. In order to reduce the abuse liability of ONPs (and other tobacco products) without subsequently increasing the palatability of these products for nicotine naïve individuals, class-specific regulations to product pH may be a practical and effective regulatory target. Limits to pH designed to reduce the abuse liability of inhaled tobacco/nicotine products (e.g., cigarettes, ENDS) may designate a lower limit (e.g., products with a pH under 7.5 would not be FDA-authorized) to increase the proportion of freebase nicotine, ensuring that inhaled tobacco products are sufficiently harsh as to be intolerable to people using them for the first-time. Additionally, limits to pH designed to limit the abuse liability of oral tobacco products (e.g., SLT/ONPs) may designate an upper limit (e.g., products with a pH over 6.5 would not be FDA-authorized) to limit the proportion of freebase nicotine, ensuring that the reinforcing effects remain minimal to all users. Limiting tobacco product pH in a class-specific manner (and, further, hindering the ability of the tobacco industry to manipulate nicotine delivery via pH) brings the regulatory goal of reducing the harms caused by current tobacco use as well as limiting tobacco use initiation within reach.

Limitations

There are several limitations in the present study. First, this study was not designed to detect differences based on participant demographics (e.g., minoritization, gender identity). Additionally, the participants in this study were almost entirely white men; while this sample is reflective of the population of SLT users in the US, it does not reflect the global demographic of SLT users. Future studies would benefit from larger sample sizes in order to detect potential

differences based on participant characteristics, as well as a more diverse sample that may reflect more accurately the demographic of SLT users globally. Also, future studies may benefit from examinations of OB and ONP flavor preferences as participant characteristics that may influence study results/subjective outcomes.

Second, the “ON!” brand ONPs in “original” flavor used in this study may not be indicative of the typical brand and/or flavor used by consumers. In fact, the most popular ONP brand used in the US is Zyn (Majmundar et al., 2022), and research suggests mint/menthol may be the most popular flavor among ONP users (Dowd et al., 2024; Kramer et al., 2023). However, in a recently published study examining the acute effects of the Zyn brand ONP in people who smoke cigarettes, similar results were observed, with higher nicotine content associated with greater nicotine delivery (Keller-Hamilton et al., 2024a). In this study, the “original” flavor ONP was chosen in an effort to minimize potential threats to internal validity, ensuring that product characteristics (besides those being examined, i.e., nicotine content) were unlikely to influence study results. Future studies would benefit from examining the influence of additional characteristics that vary within and between brands (e.g., flavor, pH; see Keller-Hamilton et al., 2024b; Stanfill et al., 2021) on the nicotine delivery and subjective profile of ONPs.

Third, the absence of a controlled amount/weight of OB SLT does not allow a systematic comparison to traditional SLT products. This limitation is important considering the subjective outcomes (e.g., harshness, strength), as participants were able to adjust the amount of OB used to minimize known aversive effects in the OB condition only. However, this study aimed to compare ONPs to participants’ own brand of SLT as opposed to SLT as a product class, and thus allowing participants to use their typical amount of SLT maintained study validity. Future studies would benefit from including a controlled OB amount/weight condition as a direct comparison to

ONP nicotine content(s) to further characterize the manner in which ONP nicotine delivery may differ from other SLT products.

Finally, the laboratory setting may limit the generalizability of the present study. Future studies of ONPs would benefit from naturalistic observations and ambulatory data collection to improve external validity.

Conclusions

This clinical laboratory study assessed the acute effects of ONPs in people who use SLT. Specifically, this study examined the physiological and subjective effects of three ONPs that differed based on nicotine content (2 mg, 4 mg, and 8 mg; ON! brand) compared to participants' OB SLT. The results demonstrated that the nicotine delivery and subjective profile of ONPs is influenced by ONP nicotine content, such that higher nicotine content is associated with greater nicotine delivery and subjective effects. Importantly, the 2 mg ONP delivered significantly less nicotine and was significantly less effective at suppressing abstinence symptoms when compared to higher nicotine content ONPs and OB, suggesting these products may be designed and intended to be used as "starter products" by nicotine naïve individuals.

Results from this study establish the influence of nicotine content on the nicotine delivery and subjective profile of ONPs, and these products may have differential impacts on public health based on nicotine content. Particularly, some ONPs may have sufficient nicotine content to substitute for more traditional SLT, and the lack of tobacco leaf suggests they may be less harmful. However, some ONPs may deliver nicotine at such low levels as to be ineffective as alternative products for nicotine dependent individuals (e.g., 2 mg ONPs), and these ONPs may be more palatable to nicotine naïve people. For this reason, nicotine content is an important factor in determining the nicotine delivery and subjective profile of ONPs, and specific

considerations related to nicotine exposure and palatability are important when considering effective ONP regulations. Overall, the present study provides the first independent evidence of the acute effects of ONPs in people who use SLT, and may be used as a foundation onto which further study may elucidate the role of product characteristics in abuse liability and regulatory action.

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Appendix A

“ON!” Brand Nicotine Pouches



One of several ONPs marketed in the US, “ON!” brand nicotine pouches are available in 5 doses (1.5, 2, 3.5, 4, and 8 mg) and 7 flavors including unflavored “original.”

Appendix B

Hughes & Hatsukami, 1986
 (revised for smokeless tobacco users)

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel **RIGHT NOW** by drawing a vertical mark anywhere along the horizontal line.

	Not at all	Extremely
1. URGES to dip	_____	_____
2. Irritability/frustration/anger	_____	_____
3. Anxious	_____	_____
4. Difficulty concentrating	_____	_____
5. Restlessness	_____	_____
6. Hunger	_____	_____
7. Impatient	_____	_____
8. CRAVING a dip/nicotine	_____	_____
9. Drowsiness	_____	_____
10. Depression/feeling blue	_____	_____
11. Desire for sweets	_____	_____

Appendix C

Direct Effects of Nicotine Scale

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

Not at all

Extremely

1. Nauseous	-----
2. Dizzy	-----
3. Lightheaded	-----
4. Nervous	-----
5. Sweaty	-----
6. Headache	-----
7. Excessive salivation	-----
8. Heart pounding	-----
9. Confused	-----
10. Weak	-----

Appendix D

Direct Effects of Smokeless Tobacco Scale

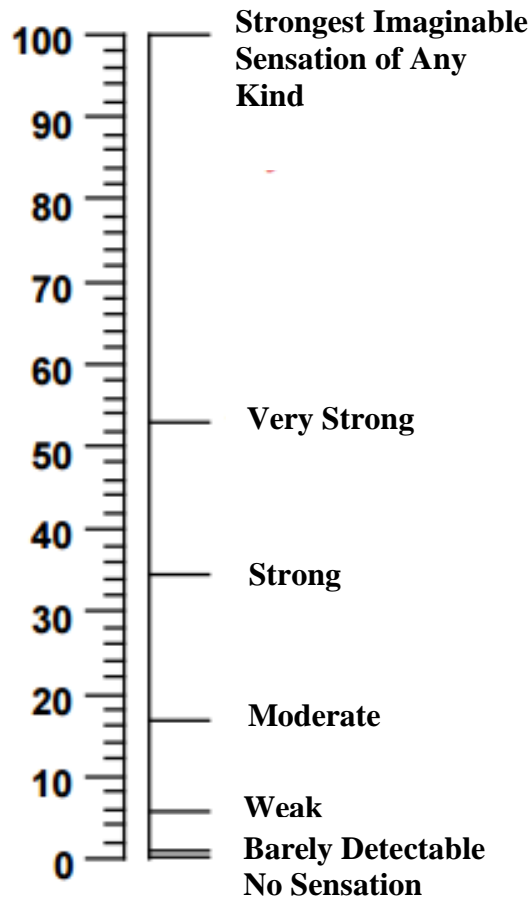
These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel **RIGHT NOW** by drawing a vertical mark anywhere along the horizontal line.

	Not at all	Extremely
1. Overall, how strong is the tobacco?		
2. What amount of tobacco have you swallowed?		
3. Has your salivation increased?		
4. Does the tobacco product produce any burning sensations?		
5. Do you feel any tingling in your mouth?		
6. Do you feel any nausea?		
7. Is your heart racing?		
8. Do you feel a head rush?		
9. Are you relaxed?		
10. Do you like the way the tobacco makes you feel?		
11. Do you like the way the tobacco tastes?		
12. How alert does the tobacco make you feel?		

Appendix E
General Labeled Magnitude Scale

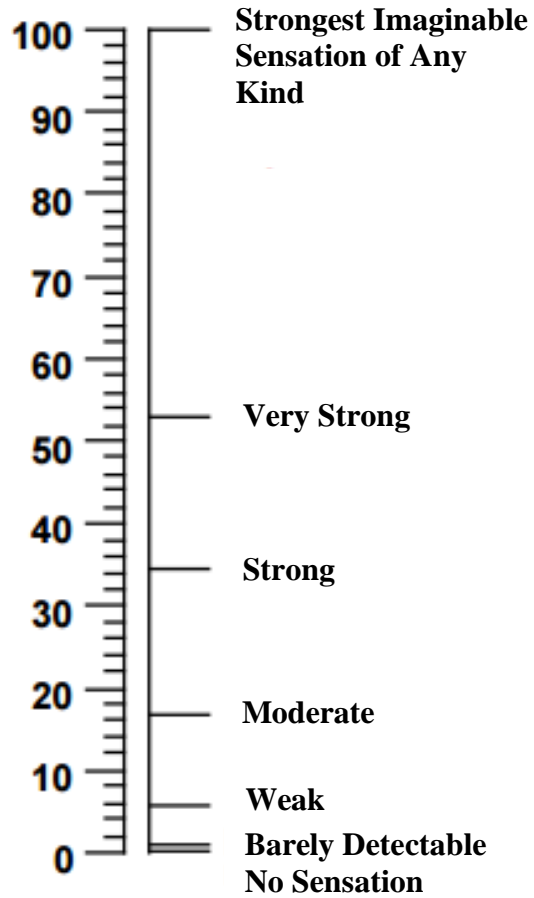
For each item, please indicate how you would describe the product you just used by placing a mark on the vertical numbered line.

How would you describe the overall flavor sensation of the product you just used?



Please specify the number you indicated with the horizontal line

How would you describe
the overall
harshness/irritancy of the
product you just used?



A square box intended for the user to write the numerical value corresponding to their sensation level on the scale.

Please specify the number
you indicated with the
horizontal line

Appendix F

Single Product & Cross Product Smokeless Tobacco Purchase Task

Own Brand Smokeless Tobacco Purchase Task

- Imagine a TYPICAL DAY during which you use smokeless tobacco/“dip”.
- The following questions ask how many dips of your own brand smokeless tobacco you would buy if they cost various amounts of money.
- The only available smokeless tobacco is your own brand.
- Assume that you have the same income/savings that you have now and NO ACCESS to any smokeless tobacco or nicotine products other than those offered at these prices.
- In addition, assume that you would consume the dips that you request on that day; that is, you cannot save dips for a later date.
- Please respond to these questions honestly.

-If 1 dip of your own brand smokeless tobacco cost **X**:

-How many **dips** of your own brand smokeless tobacco would you buy to consume in one day?

-Equation (hidden)

-You would buy **Y** dips of your own brand smokeless tobacco for **\$Z**.

<i>Y dips of your own brand smokeless tobacco you would buy (numeric response by participant)</i>	<i>X (price)</i>
	\$0 (free)
	\$0.01
	\$0.02
	\$0.04
	\$0.08
	\$0.16
	\$0.32
	\$0.64
	\$1.28
	\$2.56
	\$3.84
	\$5.12
	\$6.40
	\$7.68
	\$8.96
	\$10.24
	\$11.52

	\$12.80
	\$14.08
	\$15.36
	\$16.64
	\$17.92
	\$19.20
	\$20.48

Session Specific Oral Nicotine Pouch Purchase Task

- Imagine a TYPICAL DAY during which you use smokeless tobacco/“dip”.
- The following questions ask how many pouches of the session specific oral nicotine pouch product you would buy if they cost various amounts of money.
- The only available oral nicotine pouches are this session’s product.
- Assume that you have the same income/savings that you have now and NO ACCESS to any oral nicotine pouches, dip, or nicotine products other than those offered at these prices.
- In addition, assume that you would consume the pouches that you request on that day; that is, you cannot save or stockpile pouches for a later date.
- Please respond to these questions honestly.

- If 1 pouch of the session specific oral nicotine pouches cost **X**:

-How many **pouches** of the session specific oral nicotine pouch would you buy to consume in one day?

-Equation (hidden)

-You would buy **Y** pouches of the session specific oral nicotine pouch for **\$Z**.

<i>Y pouches of the session specific oral nicotine pouch you would buy (numeric response by participant)</i>	<i>X (price)</i>
	\$0 (free)
	\$0.01
	\$0.02
	\$0.04
	\$0.08
	\$0.16
	\$0.32
	\$0.64
	\$1.28
	\$2.56
	\$3.84
	\$5.12
	\$6.40
	\$7.68
	\$8.96
	\$10.24

	\$11.52
	\$12.80
	\$14.08
	\$15.36
	\$16.64
	\$17.92
	\$19.20
	\$20.48

Cross-product Own Brand Smokeless Tobacco Purchase / Session Specific Oral Nicotine Pouch Task

- Now imagine another TYPICAL DAY during which you use smokeless tobacco/“dip”.
- The following questions ask how many dips of your own brand smokeless tobacco and pouches of the session specific oral nicotine pouch you would buy if your own brand smokeless tobacco cost various amounts of money but the price of the session specific oral nicotine pouch stayed the same.
- The only available smokeless tobacco is your own brand and the only available oral nicotine pouches are this session’s product.
- Assume that you have the same income/savings that you have now and NO ACCESS to any smokeless tobacco, oral nicotine pouches, or nicotine products other than those offered at these prices.
- In addition, assume that you would consume the dips and/or pouches that you request on that day; that is, you cannot save or stockpile dips and/or for a later date.
- Please respond to these questions honestly.

-If 1 dip of your own brand smokeless tobacco/“dip” cost **X1** and 1 pouch of the session specific oral nicotine pouches cost **X2**:

- How many **dips** of your own brand smokeless tobacco/“dip” would you buy to consume in one day?

-How many **pouches** of the session specific oral nicotine pouches would you buy to consume in one day?

- You would buy **Y1** dips of your own brand smokeless tobacco for **\$Z1** and **Y2** pouches of the session specific oral nicotine pouches for **\$Z2** for a total of **\$Z3**.

<i>Y1 dips of your own brand smokeless tobacco you would buy (numeric response by participant)</i>	<i>X1 (smokeless tobacco price)</i>	<i>Y2 pouches of the session specific oral nicotine pouch you would buy (numeric response by participant)</i>	<i>X2 (oral nicotine pouch price)</i>
	\$0 (free)		\$0.10
	\$0.01		\$0.10
	\$0.02		\$0.10
	\$0.04		\$0.10
	\$0.08		\$0.10
	\$0.16		\$0.10
	\$0.32		\$0.10
	\$0.64		\$0.10
	\$1.28		\$0.10
	\$2.56		\$0.10

	\$3.84		\$0.10
	\$5.12		\$0.10
	\$6.40		\$0.10
	\$7.68		\$0.10
	\$8.96		\$0.10
	\$10.24		\$0.10
	\$11.52		\$0.10
	\$12.80		\$0.10
	\$14.08		\$0.10
	\$15.36		\$0.10
	\$16.64		\$0.10
	\$17.92		\$0.10
	\$19.20		\$0.10
	\$20.48		\$0.10

Vita

Alisha Nicole Eversole was born on September 9, 1986, in Ypsilanti, Michigan, and she is a graduate of Belleville High School in Belleville, Michigan. Alisha earned her B.A. in Psychology with a minor in Gender & Women's Studies from the University of Kentucky in Lexington, Kentucky in 2014. Alisha began the Health Psychology doctoral program at Virginia Commonwealth University in August 2019 and earned her M.S. in Psychology in December 2021.