Evaluation of a botanical extract that mimics the respiratory cues of cigarette smoke

ABSTRACT

Introduction: Cigarette addiction results from both pharmacological effects of nicotine and the rewarding effects of associated cues, including respiratory tract sensations.

Aims: This study sought to evaluate the initial acceptability of a non-nicotine botanical formulation that provided similar respiratory tract cues.

Methods: Two active test products and matching placebos were evaluated. One test product, an e-cigarette-like device, delivered a visible aerosol upon puffing; the other test product delivered an invisible vapor at ambient temperature. Test products delivered botanical extract with flavorings and vehicle; the placebos delivered flavorings and vehicle only. Sixteen participants had three-hour *ad libitum* access to each test product and associated placebos, and were deprived of combustible cigarettes for one hour before, and throughout the three-hour evaluation period. Subjects rated the satisfaction (primary outcome) and other sensory qualities of the products. Safety evaluations included pulmonary function testing and monitoring vital signs.

Results: Satisfaction ratings (7-point scale) were significantly greater for the active e-cigarette-like condition; M=3.18, SD=1.04 vs. M=2.69, SD=1.22. Safety evaluations showed no clinically significant changes.

Conclusions: The results support the potential acceptability of a non-nicotine cigarette substitute in providing satisfaction to smokers. This approach merits further evaluation for safety and acceptability in tobacco harm reduction and cessation.

Keywords:

e-Cigarette

Chemosensation

Airway Sensation

Harm Reduction

Tobacco

1.1 INTRODUCTION

Smoking remains one of the leading causes of preventable morbidity and mortality throughout the world (Jamal, 2016). The World Health Organization notes that tobacco use causes nearly 6 million deaths per year, with an estimated 8 million deaths a year by 2030, should current trends continue ("WHO | Noncommunicable diseases," n.d.). The Centers for Disease Control and Prevention has stated that smoking is the leading cause of preventable death in the U.S. (Carter, Freedman, & Jacobs, 2015), where there are an estimated 540,000 premature deaths a year due to cigarette smoking, and the economic cost of smoking is estimated to exceed $300 billion a year (Xu, Bishop, Kennedy, Simpson, & Pechacek, 2015). In addition to providing smokers with effective smoking cessation treatment options, new approaches are needed to substitute for the rewarding effects of smoking using less harmful alternatives.

Multiple studies have shown that habitual cigarette smoking is sustained via several factors, including the pharmacological effects of nicotine, as well as the behavioral and sensory cues associated with the act of smoking (Naqvi & Bechara, 2005; J. Rose & Behm, 2004). The limited success of current FDA-approved smoking cessation treatments, which yield long-term success rates generally under 30% (Panel, 2008a, 2008b), may be due to the failure to provide smokers with satisfaction dervied from smoking-related sensory cues. Among these cues are respiratory tract sensations, often referred to as "impact" or "throat hit" (Etter, 2016). The neurophysiological substrate mediating this chemosensory input from cigarette smoke is complex; major routes include sensory pathways involving the vagus nerve (cranial nerve X), the trigeminal nerve (cranial nerve V), and the glossopharyngeal nerve (cranial nerve IX) ("SENTIENS SCIENCE -

Chemosensation | Sentiens LLC," n.d.). Local blockade of smoking-related respiratory tract sensations, using the local anesthetic lidocaine, or the peripherally-acting nicotinic receptor antagonist trimethaphan, acted to reduce smoking satisfaction and attenuate the ability of cigarette smoking to alleviate craving (J. E. Rose, Westman, Behm, Johnson, & Goldberg, 1999; J. E. Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984).

Smoking-related respiratory tract sensations can be simulated without inhalation of nicotine or toxic products of burning tobacco. For example, in previous studies, inhalation of an aerosol containing citric acid or ascorbic acid reduced craving for cigarettes (Levin et al., 1993; F. M. Behm, Schur, Levin, Tashkin, & Rose, 1993); a clinical trial using a cigarette-sized dry powder citric acid delivery system subsequently showed efficacy in smoking cessation treatment relative to a lactose placebo, when combined with nicotine replacement therapy (NRT) (Westman, Behm, & Rose, 1995). In other studies, inhalation of minute quantities of capsaicin, or vapor from black pepper essential oil, replicated some of the respiratory tract sensations associated with cigarette smoking and provided partial satisfaction of the desire for a cigarette (Frederique M. Behm & Rose, 1994; J. E. Rose & Behm, 1994).

A botanical extract containing chemosensory stimulating constituents has been developed commercially ("BotanicBoost," Novus brand products, produced by Sentiens, LLC., Charlotte, NC), which, upon inhalation, mimics the respiratory tract chemosensory cues associated with inhalation of nicotine. The proprietary botanical extract includes (listed alphabetically) small amounts of *Aframomum Meleguate* extract, allspice extract, cedar absolute extract, diluent (glycerin and propylene glycol), ethanol, extract from *Eucalyptus*, eugenol oil, galangal, mustard seed extract, rosemary extract, Szechuan

pepper extract, and thyme leaves (US8646461 B2, 2014). The microgram-level quantities of these constituents, all of which have been classified as "generally regarded as safe" (GRAS), represent levels significantly lower than found in a typical meal made with the constituent spices. Also included in the extract was flavoring (without nicotine) derived from tobacco. Since this product has been marketed prior to August 8, 2016, pre-market review was not required according to the relevant FDA guidance for industry ("81 FR 28974," n.d.). Additional safety information is available from the manufacturer via White Papers ("SENTIENS SCIENCE - Guiding Principles and Safety | Sentiens LLC," n.d.; "SENTIENS SCIENCE - Novus for Healthcare Professionals | Sentiens LLC," n.d.).

The purpose of this study was to evaluate the ability of two products containing this botanical extract—one delivering an aerosol in an e-cigarette-like device, and one delivering an invisible vapor from a porous cigarette-sized rod—to provide satisfaction to smokers during a period of smoking abstinence. Secondary outcomes included strength and harshness ratings of each product. The main goal of the study was limited: to determine whether smoking-related sensations could be mimicked by the botanical extract evaluated, in order to produce an incremental change in subjective satisfaction. Nicotine was not the focus of this study and hence a direct comparison with combustible cigarettes was not included. This study did not assess efficacy or effectiveness for smoking cessation. Pending the successful development of an adequate sensory substitute for cigarette smoking, this formulation could ultimately be combined with methods for delivering nicotine, with the goal of sustaining a level of overall reward and satisfaction that might successfully compete with cigarette smoking.

1.2 METHODS

1.2.1 Design

A randomized, double-blind, placebo-controlled, counterbalanced 2x2 designed study, compared active versus placebo e-cigarette-like products, and active versus placebo invisible vapor products. The protocol was reviewed and approved by the Schulman Institutional Review Board (IRB) to ensure the study was conducted in accordance with Good Clinical Practice (GCP) based on guidelines from the current International Conference on Harmonisation (ICH), the Basic Principles of the Declaration of Helsinki, United States Code of Federal Regulations governing protection of human subjects (Title 21 CFR Part 50 and Title 21 CFR Part 56), and all applicable legal and regulatory requirements. External funding for this study was limited to supplying of study products by Sentiens, LLC, which has a sponsored research and commercialization agreement with the study center. The study recruited subjects from Raleigh and Charlotte, North Carolina, utilizing a private database of over 10,000 cigarette smokers who have expressed interest in participating in research studies. The database was generated using IRB approved generic advertisements. Current cigarette smokers (men and women) between the ages of 19 and 65 years of age, with no restriction on race or ethnicity, were recruited for this study. Criteria for participation included smoking on average at least 10 commercially available combustible cigarettes per day, having an exhaled carbon monoxide level of at least 10 parts per million at the first visit, and no indicated intention of quitting smoking within 60 days of study enrollment. Subjects were excluded if they had abnormal pulmonary function test (evidence of restrictive or obstructive lung disease), had difficulty providing blood or urine samples, had

uncontrolled psychiatric disease by self-report or as noted on the Patient Health Questionnaire (PHQ-9), were pregnant or breastfeeding, had elevated scores on the Alcohol Use Disorder Identification Test (AUDIT), or reported chronic use of opioids or daily use of sleep aids. Additionally, subjects were excluded if they used illicit drugs (by self-report or as noted on an unexplained positive urine drug screen for amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, opiates, buprenorphine, methadone, oxycodone, phencyclidine, propoxyphene, or tricyclic antidepressants), used nicotine replacement therapy, or used non-combustible tobacco products within 14 days of the initial screening visit. Each subject was evaluated by a physician and determined to be healthy and free of any significant medical issues. After obtaining informed consent, the study enrolled eligible adult male and female current cigarette smokers. Each subject could participate in evaluation of both the e-cigarette-like product and the invisible vapor delivery product, matched to the flavoring corresponding to their usual brand cigarette (tobacco flavor or menthol flavor). However, if a subject's participation ended before completing all four sessions, the data for active and placebo conditions for the product sessions they completed were used. As it happened, 15 of 16 subjects in the vapor product condition also participated in the e-cigarette-like product evaluation. One subject did not complete the e-cigarette-like product (menthol flavor) evaluation sessions, requiring enrollment of one additional subject. Research staff and subjects remained blinded to the specific product (active versus placebo) throughout the entire study.

Seventeen subjects were enrolled at sites in Raleigh and Charlotte, North Carolina in order to obtain 16 complete sets of data for each test product (and matching placebo).

For each test product, eight subjects were assigned to receive the "menthol" flavor and eight subjects were assigned to receive the "tobacco" flavor, corresponding to the flavor of their usual brand of cigarette. Subjects were asked to attend four laboratory sessions, each conducted after one hour of supervised abstinence from any tobacco/nicotine containing products. During each three-hour laboratory session, subjects were not allowed to smoke but could use the assigned product *ad libitum*. The order of product use for each laboratory session was randomly assigned at enrollment using one of eight sequences of product exposure, which counterbalanced the order of active versus placebo products and the order of e-cigarette-like versus invisible vapor products. Participants were administered sensory questionnaires every 30 minutes during the three-hour *ad libitum* period. The questionnaire assessed ratings of satisfaction, liking, harshness, similarity to the usual brand of cigarettes, and strength of sensations in different regions of the respiratory tract. The initial screening session lasted approximately three hours, and each laboratory session lasted approximately five hours (Figure 1). All five visits (screening and four laboratory sessions) were completed within an eight-week period, with a minimum of 24 hours between each session.

<Insert Figure 1 here>

Lung function was analyzed by obtaining pulmonary function testing, including Pulmonary Function Tests (PFTs, spirometry) at screening, and at the end of each three-hour *ad libitum* use period. Measurements taken, in accordinate with 2005 guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on Standardization of spirometry, were Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC), and Forced Expiratory Flow during the mid-portion

of forced expiration (FEF25-75). Peak Expiratory Flow Rate (PEFR) measurements were obtained as a measurement of acute responses, and were recorded at baseline and at 60-minute intervals during the three-hour *ad libitum* sessions. PEFR testing was performed in accordance with the National Institute of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) guidelines. Vital signs, including blood pressure, heart rate, and respiratory rate were measured at the beginning of each session, and at 60 minute intervals until the end of each session.

1.2.2 Test products

The active e-cigarette-like test product used a battery-operated coil to heat a vehicle containing chemostimulating botanical extract, propylene glycol, tobacco flavoring extracted from tobacco, and other flavorings. It was similar in shape and size to many e-cigarette products on the market, with the same length and circumference of a combustible cigarette, and an actuating button that is pressed to generate the vapor for inhalation. The placebo e-cigarette-like device was identical to the test product, and delivered all constituents except for the botanical extract.

The active invisible vapor delivery system consisted of a 100% paper rod, the same size and shape as a cigarette, with a porous plug infused with ethanol, flavoring and the botanical extract. It uses the same outer paper and tipping paper as cigarettes, with the inner paper infused with the botanical extract. Again, the placebo test product was identical except for the absence of the botanical extract. None of the test products contained nicotine. Both active test products were commercially available as of August 8, 2016 and hence were exempt from a pre-market authorization requirement by the Food and Drug Administration's Center for Tobacco Products (Products, n.d.).

1.2.3 Statistical analyses

As delineated a priori in the IRB-approved protocol, a single primary outcome was designated: the self-reported rating of satisfaction, using a scale ranging from 1 ("not at all") to 7 ("extremely"). Ratings were compared between each active product and its respective placebo using paired t-tests. Given the *a priori* designation of a single outcome measure, no correction for multiple statistical comparisons was made; secondary outcome comparisons were viewed as purely exploratory. Also, in view of the unambiguous directional nature of the hypothesis (i.e., that the active formulation would increase, rather than decrease satisfaction ratings, based on several previous studies in which stimulation of respiratory tract sensations elicited satisfaction), one-tailed statistical tests were employed. Additional subjective ratings (e.g., liking, harshness, similarity to usual brand of cigarette, strength of sensation in different regions of the respiratory tract) were collected and tabulated for descriptive purposes, without conducting statistical comparisons. Safety was evaluated by assessment of vital sign measurements and pulmonary function testing (using spirometry and measuring peak expiratory flow rates).

Based on a predicted large effect size for the difference between active and placebo conditions (Cohen's d=1.0), a sample size of 16 for each within-subject comparison would yield a power of greater than 80% to detect the expected differences.

1.3 RESULTS

Subjects in the e-cigarette-like device test product evaluation included seven males, nine females, (nine whites, one Asian, and six African Americans) had a mean age of 42.67 (SD=8.11) and smoked on average 16.06 cigarettes/day (SD=5.11) with an FTND

(Fagerstrom Test for Nicotine Dependence) score of 5.31 (SD=1.92). Subjects in the invisible vapor test product evaluation included six males, 10 females, (nine whites, one Asian, and six African Americans), had a mean age of 42.41 (SD=8.24) and smoked on average 15.56 cigarettes/day (SD=5.09) with an FTND score of 5.31 (SD=1.92). One additional subject was enrolled in order to obtain eight complete data sets for the menthol smoking group (one subject failed to attend both e-cigarette-like device test product sessions).

Mean satisfaction ratings were significantly greater for the active e-cigarette-like device condition (M=3.18, SD=1.04) than for the placebo e-cigarette-like device (M=2.69 SD=1.22); $t(15)=2.26$, P=0.02, 1-tailed. Although a 1-tailed test was specified a priori, and justified based on the previously mentioned statistical analyses, this test would have yielded a statistically significant P=0.04 had a 2-tailed test been conducted. There was also a trend for the vapor condition to be rated higher than the placebo (M=2.27, SD=1.45 vs. M=1.83, SD=1.22), with this comparison falling short of statistical significance; $t(15)=1.68$, P=0.06 (1-tailed). Other subjective ratings are depicted in Table 1.

<Insert Table 1 here>

No serious adverse events were observed, and there were no clinically significant changes in vital signs or pulmonary functions associated with product use. Sitting heart rates for all subjects remained within normal ranges with the use of the active e-cigarette-like product, the e-cigarette-like placebo, the invisible vapor product, and the invisible vapor placebo product (see Table 2). Mean Arterial Pressures also remained stable, with no significant changes associated with the use of any of the products or

placebos (Table 2).

<Insert Table 2 here>

Analysis of lung function showed no clinically significant effects on spirometry (FEV1/FVC or FEF25-75) for any subjects after using either of the products or their placebos (Table 2). Peak Expiratory Flow Rates also showed no significant effects associated with the use of either of the products evaluated, or their corresponding placebos (Table 2).

1.4 DISCUSSION

The active chemosensory formulation, delivered in an e-cigarette-like platform provided moderate levels of satisfaction to cigarette smokers, which were significantly higher than the placebo. Similarly, there was a trend for the active invisible vapor product to be rated higher in satisfaction than the corresponding placebo. To place the satisfaction ratings in perspective, in a study of 41 cigarette smokers using marketed nicotine-containing products for three days, Steinberg et al. reported mean satisfaction ratings of 5.0 for a popular brand of e-cigarette and 2.6 for the FDA-approved nicotine inhaler (Steinberg et al., 2014). Thus, the current active e-cigarette-like test product, despite the absence of nicotine, compared favorably with at least one marketed nicotine-containing product. Although not formally compared, the e-cigarette-like product tended to be rated more satisfying than the invisible vapor product, which is not surprising given that the former delivered an aerosol that elicited respiratory tract sensations more similar to those of cigarette smoke, which is itself an aerosol. Further studies will be needed in order to evaluate whether this is a reliable difference between the two types of products.

It should be noted that the placebo products were themselves "active" in the sense that they provided behavioral substitution components (handling, puffing) as well as flavor and (in the case of the e-cigarette-like test product) visual sensory cues that mimicked those of cigarette smoke. Thus, the overall impact of active product use compared to a no-device control condition would likely have been greater than the active-placebo difference noted here. Also, we are aware of no other published studies showing that a currently marketed product containing no nicotine elicits greater satisfaction than placebo. Given this dirth of acceptable non-nicotine alternatives for cigarettes, our findings, while preliminary, offer a novel and potentially important line of future investigation.

The safety evaluation showed no adverse effects of using the test products in an acute three-hour session. Lung function parameters, including FEV1/FVC, PEFR, and FEF25-75 showed no clinically significant changes from baseline. Further studies will be clearly needed to evaluate safety with longer-term use.

In conclusion, the study results suggest that a non-nicotine formulation that stimulates sensory nerve endings in the respiratory tract may be a fruitful approach to providing a degree of satisfaction to cigarette smokers. This approach merits further study as a practical approach to tobacco harm reduction by reducing consumption of combustible cigarettes. Depending on the context, the e-cigarette-like version or the invisible vapor version might provide more acceptability or conform to regulatory restrictions. In addition to evaluating the potential for smoking reduction, the technology merits further evaluation for acceptability and efficacy in smoking cessation treatment, alone or in combination with NRT.

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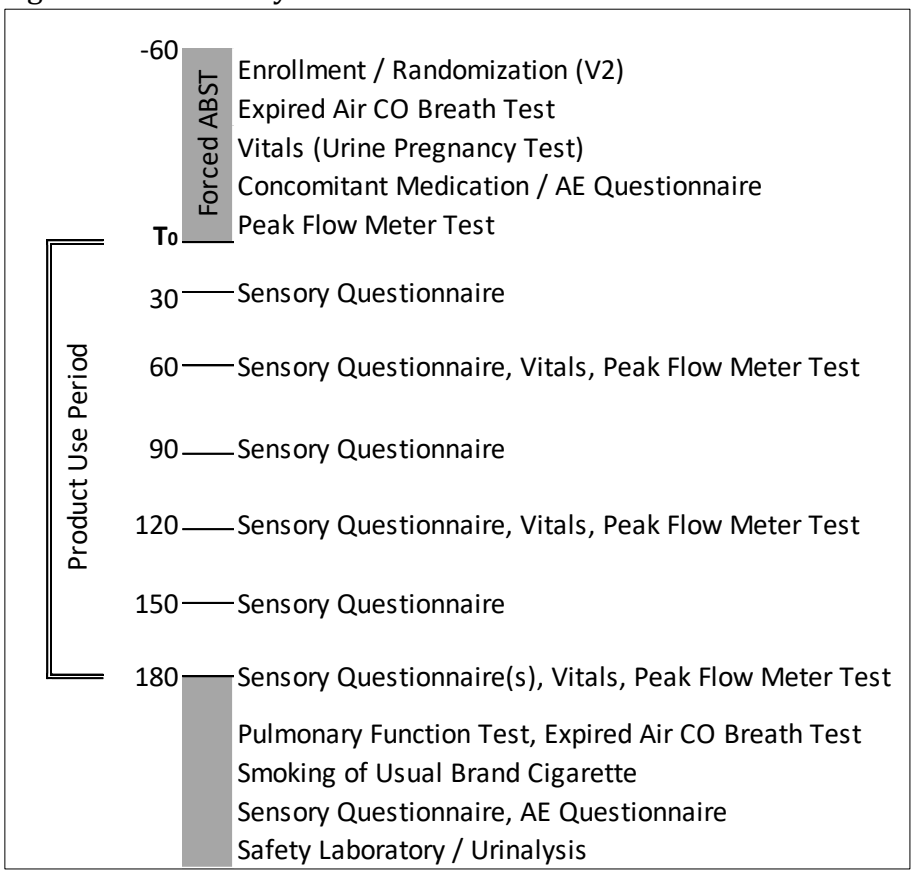
Figure 1: Laboratory Session Schedule of Events



ABST = Abstinence, V2 = Visit 2, CO = Carbon Monoxide, AE = Adverse Events

NOTE: This figure is also provided as a ".pdf" file.

Table 1: Results

Questions	e-Cigarette-Like Device	e-Cigarette-Like Placebo	Vapor	Vapor Placebo
How satisfying were the puffs you took?	3.18 (1.04)	2.69 (1.22)	2.27 (1.45)	1.83 (1.22)
How much did you like the puffs you took?	3.54 (0.89)	3.32 (1.24)	2.70 (1.50)	2.07 (1.15)
How harsh were the puffs you took?	2.41 (1.14)	1.88 (1.16)	1.93 (1.13)	1.73 (1.23)
How similar to your own brand were the puffs?	1.99 (1.11)	1.98 (1.23)	1.64 (1.22)	1.25 (0.49)
Strength of puffs on tongue?	2.38 (1.21)	2.10 (1.15)	2.24 (1.06)	1.91 (1.06)
Strength of puffs in nose?	1.79 (1.20)	1.68 (1.20)	1.73 (1.03)	1.51 (0.98)
Strength of puffs in the back of the mouth & throat?	2.47 (1.20)	1.95 (1.20)	2.39 (1.21)	1.80 (1.05)
Strength of puffs in windpipe?	2.42 (1.27)	1.93 (1.35)	1.96 (1.12)	1.63 (1.01)
Strength of the puffs in chest?	1.97 (1.33)	1.78 (1.36)	1.63 (1.10)	1.42 (0.81)

Values are reported as *Mean (Standard Deviation)*. Ratings are on a 7-point scale ranging from 1 ("not at all") to 7 ("extremely"). This questionnaire was administered every 30 minutes during the product use periods.

Table 2: Vital Signs and Pulmonary Functions

Safety Data	Screening/ Baseline	e-Cigarette-Like Device	e-Cigarette-Like Placebo	Vapor	Vapor Placebo
Heart Rate bpm (SD)	72.6 (12.2)	74.7 (10.8)	73.3 (13.3)	74.0 (10.8)	73.8 (12.5)
MAP mmHg (SD)	90.3 (9.2)	91.0 (10.8)	92.0 (9.8)	92.5 (10.6)	92.6 (8.5)
FEV1/FVC % (SD)	78.0 (4.5)	77.3 (5.8)	77.9 (6.9)	79.3 (5.9)	79.6 (6.0)
FEF 25-75 L/sec (SD)	2.86 (0.94)	2.84 (1.42)	2.71 (0.91)	3.01 (0.85)	2.90 (0.87)
PEFR L/sec (SD)	8.03 (1.98)	7.90 (1.94)	7.75 (1.83)	8.02 (1.85)	7.68 (1.90)

Values are reported as *Mean (Standard Deviation)*.
bpm: beats per minute. MAP: Mean Arterial Pressure. mmHg: millimeters of mercury. SD: Standard Deviation. L/sec: Liters per second.
FEV1/FVC: Forced Expiratory Volume in 1 Second/Forced Vital Capacity Ratio at screening and end of each three-hour *ad libitum* session.
FEF 25-75: Forced Expiratory Flow during the mid-portion of forced expiration at screening and end of each three-hour *ad libitum* session.
PEFR: Peak Expiratory Flow Rate at baseline, prior to any testing, and averaged over each three-hour *ad libitum* session.