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Measures for Assessing Subjective Effects of Potential Reduced Exposure Products

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Abstract

Potential reduced exposure products (PREPs) may reduce toxicant exposure and thereby may possibly reduce health risks associated with conventional tobacco use. However, lessened health risk to the individual or harm to the population through use of PREPs is unknown. Research is being conducted to evaluate the possible health effects associated with PREP use. As part of this evaluation, it is critical to provide sound measures of subjective responses to PREPs to determine the use and the abuse potential of a product, that is the likelihood that this product will lead to addiction. The goal of this paper is to conduct a systematic review of scales that have been used to measure the subjective responses to PREPs and examine their characteristics. In this paper, scales are identified and the items on the scales are described. Scales are also examined to determine whether they are sensitive in testing PREPs. Furthermore, scales to assess PREPs are recommended to investigators. Where no scales exist, items that may be critical for the development and validation of new scales are identified.

Keywords

Subjective effects; PREPs; tobacco product evaluation; scales; measures

INTRODUCTION

Potential reduced exposure products (PREPs) developed by the tobacco industry may reduce toxicant exposure and it is hypothesized that this can reduce health risks. Types of PREPs include oral noncombustible products such as snuff or snus (e.g., Marlboro and Camel Snus) that have varying levels of toxicant content, compressed tobacco lozenges (e.g., Stonewall, Ariva or Camel Orbs) and other products such as tobacco strips or sticks. Other kinds of PREPs are modified cigarettes or novel cigarette delivery devices. Modified cigarettes may have reduced toxins including lower amounts of nitrosamines, polyaromatic hydrocarbons and catechols or special filters that reduce volatile toxicants (e.g., Advance, Omni, Marlboro UltraSmooth). Novel cigarette delivery devices include devices that heat rather than burn tobacco so reduced amounts of combustion products and their associated toxins are emitted (e.g., Accord, Eclipse), or electronic 'cigarettes' that deliver nicotine in a vapor (1). These types of products are marketed to be used in lieu of or in addition to smoking cigarettes.

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However, whether these products lead to reduced health risk to the individual or reduced harm to the population compared to the use of conventional tobacco products is uncertain. Moreover, if people believe that PREPs are a safer alternative to conventional tobacco products, PREPs could cause harm by discouraging smokers from quitting or persuading nonsmokers to use PREPs (2).

Scientists both inside and outside of the tobacco industry are evaluating PREPs to determine the potential health effects associated with their use, using laboratory and clinical designs (3, 4). The goal of laboratory studies is to examine the acute effects such as short-term physiological responses, blood nicotine and carbon monoxide levels and subjective responses. Some laboratory studies are also conducted to determine the abuse liability or abuse potential of the product; that is the likelihood of uptake and persistent use of the product (5). In these trials, both subjective and behavioral responses to a product are assessed. Subjective responses such as product liking and good or bad effects of the product are often used in abuse liability studies because of their high reliability and face validity. These measures can be used during the laboratory administration of the product or used retrospectively to understand the complete experience of using the product and to determine the likelihood of using the product after being abstinent from the product for a period of time. Sensory stimuli associated with positive or negative responses to smoking that may also contribute to the abuse liability of a product can be observed by use of product effect scales with items such as “stimulated”, “dizzy”, or “heart pounding” (5). Behavioral responses can include whether the individual chooses one product or another and/or the extent the individual self-administers a product. Typically, in laboratory studies, products are compared against other PREPs, placebo, and/or usual brand products. Clinical trials, on the other hand, are conducted in the natural environment or in a residential facility and similarly compare the effects of a PREP against other PREPs, placebos or usual brands over a longer term or with a greater extent of use. In these clinical trials, the outcome measures include the same types of measures used in laboratory studies, but may also focus on the pattern of product use, the extent of toxicant exposure and biomarkers that measure toxicity or biological effects. Critical review and understanding of the strengths and limitations of measures used to assess product effects is important given the newly-granted Food and Drug Administration (FDA) authority to regulate tobacco products, including modified risk products.

An important and common assessment measure that is employed across different types of studies examining PREPs is the participant’s subjective responses to the PREP. These measures broadly encompass self-reported expressions of the participant’s experience using the product. The types of measures used to assess PREPs include product evaluation scales, sensory evaluation scales, drug-liking and drug effect ratings, and withdrawal scales described in Table 1. Investigators have developed their own scales or have used well-known measures such as the Minnesota Nicotine Withdrawal Scale (MNWS), the Cigarette Evaluation Questionnaire or the Direct Effects Scale. However, no consensus measure for subjective effects of PREPs has been developed, complicating cross-study comparisons.

Further, no systematic review of the various scales used by research groups has been conducted. This type of review is critical in providing sound measures to help to determine the abuse liability of a product, a major area of PREP evaluation. Evaluation of both positive (e.g., liking the product, satisfaction from the product) and negative reinforcing effects (e.g., reducing negative affect, withdrawal symptoms and craving) that may sustain the product’s use is an important part of assessing potential harm of a product. Products that are high in toxicant exposure and in abuse potential are likely to produce significant individual and population harm. On the other hand, products with low toxicant exposure and low abuse potential are likely to lead to less harm. Measuring the subject’s response to the effects of the product is just one area of assessment and compliments assessment of the consumer’s perception of the

product as a result of marketing, labeling and patterns of use in social networks. Reviews of methods and measures for evaluating tobacco consumer response and their application to assessing PREPs (4), and reviews of existing surveillance systems that enable the identifying and tracking of tobacco products including PREPs (6) have recently been conducted.

The purpose of the present paper is to: 1) identify scales that are used to evaluate PREPs and describe the items on the scales; 2) evaluate whether the scales and items are sensitive in testing PREPs (that is, can detect differences across products including placebo); and 3) recommend scales to investigators to assess PREPs or identify items that may be critical for the development and validation of new scales.

The criteria for evaluating the sensitivity of these subjective effects measures and items in detecting differences across products include: 1) whether the scale distinguishes placebo or no tobacco conditions from the PREP; 2) whether the scale or item demonstrates that PREPs are rated as good or less good than the usual brand of cigarettes; and 3) whether the scale or item distinguishes between PREP products. Where PREP studies and results exist, the relationship between the scales or items with behavioral measures will be described. This review is not intended to comprehensively examine the validity and reliability of the scales.

METHODS

PubMed was searched on April 14, 2008 and on June 1, 2009, limited to human studies published in English. The following search terms were used: reduced exposure products and tobacco; specific PREP product names (e.g., Eclipse, Accord, Advance cigarettes, Ariva, Snus, Stonewall, Quest, Next cigarettes, Omni); denicotinized cigarettes and tobacco; light cigarettes and tobacco; ultralight cigarettes and tobacco; low tar and tobacco; low yield and tobacco, electrically heated cigarettes; and smokeless and tobacco. Studies were included in the review if they assessed a PREP and used at least one subjective measure. The data was compiled to examine: a) the extent the scale was sensitive in measuring subjective responses to the PREP, and b) whether the scale was directly associated with other outcome measures or behavior. Three major categories of subjective effects measures were identified: craving, withdrawal symptoms and product responses.

RESULTS

Withdrawal Symptom and Craving Scales

Several different scales were used to measure withdrawal symptoms and craving. Many studies used the Minnesota Nicotine Withdrawal Scale (MNWS; (7) or a modified version of this scale (8–26)). Items were rated as 0=not present, 1=slight, 2=mild, 3=moderate, or 4=severe or as visual analogue scales (VAS) where items were presented above a horizontal line with anchors on the left “not at all” or “none” and right “extremely” or “severe”.

Many other studies used the Questionnaire of Smoking Urges (QSU) (27) or a short version of this scale (28) as a measure of urges to smoke (11–16,18–20,²²,23,26,29,30). The QSU includes 32 items (or 10 items on the short version) that are rated on a 7-point scale ranging from 0 (strongly disagree) to 6 (strongly agree). The scale yields 2 factors: Factor 1 (intention to smoke) and Factor 2 (anticipation of relief from withdrawal).

The Shiffman-Jarvik Withdrawal Scale (31) or an abbreviated version was used in 4 studies (19,29,32,33). This scale has 25-items presented as 7-point scales, 1 indicates “very definitely” and 7 indicates “very definitely not”. The items are divided into the five following subscales based on factor analysis: craving, psychological discomfort, physical symptoms, stimulation/sedation and appetite.

A Desire to Smoke VAS that was derived from Schuh and Stitzer (34) included 4 or 5 items and was used in 4 studies (19,21,29,30). Visual analog scales were presented as a 100-point horizontal line, anchored on the left side with “not at all” and on the right side with “very much”. Fagerström, Hughes, Rasmussen & Callas (35) measured withdrawal symptoms on a 5-point scale derived from the American Psychiatric Association and 2 studies used a nonreferenced scale (21,36).

Aims—There were 2 aims for using withdrawal symptom scales in PREP studies: 1) to measure the extent the product reduces withdrawal symptoms from cigarettes; and 2) to determine withdrawal symptoms from the product. To date, no studies have examined withdrawal symptoms from a PREP.

Aim 1: Extent product reduces withdrawal symptoms from cigarettes

Aim 1: Extent product reduces withdrawal symptoms from cigarettes: PREP compared to placebo or no tobacco: A few laboratory studies reported the effect of withdrawal symptoms and craving using a modified cigarette such as Advance (14), smokeless tobacco (ST) PREPs and a modified cigarette such as Ariva, Marlboro Snus, Camel Snus and Quest cigarettes (18), or ST PREPs such as Stonewall and General Snus (20) compared to a placebo condition. Two out of three of these studies found that compared to PREPs, the placebo condition showed fewer decreases in withdrawal symptoms or craving ratings (14,18). The laboratory component of another study, however, (20) reported decreased withdrawal symptoms for a non-tobacco placebo smokeless product, usual brand and loose moist snuff (General snus), but not in a ST PREP condition (Stonewall) for the item “craving a dip.” Additionally, the QSU Factor 1 score decreased significantly after the first use of the non-tobacco placebo smokeless product and a loose moist snuff and after the fourth use in all conditions.

A few clinic studies compared PREPs to no smoking or no ST and found ratings of withdrawal and craving in no tobacco conditions were at times higher than those in the PREP conditions including 2 studies that used modified cigarettes such as Advance (12) or denicotinized cigarettes (29), 1 study that used modified and heated cigarettes such as Advance and Eclipse (11) and 1 study that used ST PREPs such as Stonewall and General Snus (20).

PREP compared to usual brand: Several laboratory studies that compared PREPs to the subjects’ usual brand reported that there were fewer decreases in ratings of withdrawal symptoms and craving in the PREP conditions compared to usual brand including 1 study that used heated cigarettes such as Accord (15), and 2 studies that used modified and heated cigarettes such as denicotinized cigarettes, Accord and Eclipse (13) or denicotinized cigarettes and Accord (16). Alternatively, a different laboratory study that used denicotinized cigarettes compared to the subjects’ usual brand or a Light brand cigarette found that there were no significant brand effects or brand by time interactions for withdrawal symptoms (21).

A clinic study that used reduced nicotine cigarettes (9) reported some significant differences in ratings of withdrawal (e.g., irritability and increased eating) between reduced nicotine cigarettes and usual brand, whereas three other clinic studies that used modified cigarettes such as Omni (22) or Advance (12) or heated and modified cigarettes such as Advance and Eclipse (11) reported that in general, there were no differences between PREPs and usual brand.

Sensitivity of differences between PREPs: Several laboratory studies indicated that withdrawal symptoms and craving ratings decreased and there were no significant differences in the extent of reduction between denicotinized and nicotine cigarettes (17,19,23,26,30).

A few clinic studies also indicated no significant differences in ratings of withdrawal symptoms or craving between PREPs or as the dose of the PREP changed including the following studies:

1 study that used increasing amounts of heated cigarettes (Accord) with the option of using usual brand cigarettes (37), 1 study that used heated cigarettes (Eclipse) compared to a nicotine inhaler (36), and 1 study that used ST PREPs (Exalt and Ariva) compared to medicinal nicotine lozenge (MNL) (25).

However, some laboratory studies reported greater decreases in withdrawal symptoms as the dose of the PREP increased or among products that had higher doses of nicotine levels including 2 studies that used ST PREPs (10,24). For example, in a laboratory study, reduction in withdrawal symptoms was observed in a ST PREP study, in which smokers were administered Ariva tablets (1, 2 and 3 tablets in ascending order), at 90 minute intervals (10). Mean withdrawal scores decreased significantly following 3 Ariva tablets. In another laboratory study among ST users, single doses of ST PREPs (Ariva, Stonewall, Revel) medicinal nicotine (Commit lozenge) and moist snuff (Copenhagen) were administered (24). Withdrawal symptoms were lower during Copenhagen (high nicotine product) use than with Revel (lower nicotine product) use. Craving was lower in Copenhagen compared to the other 4 products and was lower in Stonewall, Ariva and Commit compared to Revel. There were no other significant differences between products for withdrawal symptoms or craving. Additionally, a clinic study using Eclipse compared to a nicotine inhaler also found some differences between products with regard to withdrawal symptoms, but there were no differences in craving between products (35).

Concordance of scales: Generally, laboratory studies that used more than one withdrawal symptom and craving scale showed similar overall results across scales (13–16,18,19,26,30). Likewise, for most clinic studies that used more than one withdrawal symptom and craving scale, the measures showed comparable results (11,12,20,22).

Withdrawal symptom scales' relationship to behavior or other outcome measures: Some studies related the results of the withdrawal symptom scales to other outcomes. For example, in a laboratory trial of ST PREPs, medicinal nicotine and Copenhagen among ST users, Kotlyar and colleagues (24) found a significant negative correlation between nicotine area under the concentration time curve (AUC) and craving score, but not between nicotine AUC and withdrawal symptoms. In another laboratory study, Dallery and colleagues (19) used a within-subject design in which subjects participated in one session each of rapid smoking (up to nine cigarettes with puffs every 6 seconds) and normal paced smoking with nicotine and denicotinized cigarettes and then were given a choice to smoke. They reported that craving ratings were significantly higher when subjects chose to smoke versus when they declined a chance to smoke.

Summary: There are many studies that measure withdrawal symptoms and craving, with the MNWS or an adapted version of the scale used most frequently in PREP studies. Most laboratory and clinic studies that compared PREPs to a placebo or no tobacco condition showed differences between PREPs and a placebo or no tobacco condition. Withdrawal symptoms and craving ratings showed fewer decreases in the placebo or no tobacco condition. On the other hand, in one of the laboratory studies comparing ST PREPs to a placebo, scores lessened for the item "craving a dip" in the placebo condition, but not for a ST PREP condition and showed decreases in QSU Factor 1 scores in the placebo and General snus conditions after the first use compared to decreases in a ST PREP and usual brand condition after the fourth use (20). Moreover, when PREPs were compared to subjects' usual brand, studies reported that withdrawal symptoms and craving ratings were generally lower for the subjects' usual brand or that there was no difference in ratings. Whether scales distinguish between PREPs depended on the product used or how much product was used. For example, there were no significant differences between denicotinized and nicotine cigarettes regarding the extent of withdrawal symptoms and craving reduction in several laboratory studies or between PREPs

in a few clinic studies. The lack of differences in withdrawal and craving suppression between denicotinized and nicotinized cigarettes points to the important role of sensory factors associated with these abstinence effects (38). Some studies, however, reported differences in withdrawal symptom and craving relief across different PREPs and across different doses of nicotine. For example, 2 ST PREP studies demonstrated greater withdrawal symptom or craving relief as the dose of Ariva increased (10) or for the product containing the most nicotine (24). For most laboratory and clinic studies that used more than one scale, there were no meaningful differences in ratings of withdrawal symptoms or craving between scales.

Few studies have examined the relationship between ratings on withdrawal and craving to other measures. Of the two existing studies, a relationship was observed between withdrawal symptoms or craving ratings and nicotine AUC levels (24) or smoking behavior (19).

In summary, withdrawal symptoms and craving assessments, with studies predominantly using the MNWS, have been found to be in the expected direction in some cases and not others. Withdrawal and craving symptoms are more severe in placebo or no smoking condition than with PREPs. On the other hand usual cigarettes do not always tend to reduce symptoms more than PREPs and PREPs with higher nicotine doses do not always reduce symptoms to a greater extent than PREPs with lower nicotine doses. These equivocal results may reflect the lack of sensitivity of the scales, no detectable differences between PREPs and usual brand cigarettes and among PREPs, or the fact that withdrawal is strongly associated with the sensory and behavioral aspects of smoking. Few studies have been conducted on the relationship between self-reported withdrawal and craving and behavioral or physiological response.

Product effects scales

Subjective responses to the product—In contrast to the measures of withdrawal and craving, no single scale has been used predominately in studies examining the use of modified cigarettes, heated cigarettes or ST PREPs. Many studies used scales that asked a combination of questions regarding the liking of the product including items such as “desire for the product” or “satisfaction”; sensory and physical effects of the product such as “nausea”, “heart race”, or “dizziness”; and product evaluation such as “tobacco strength” or “smoothness” (9,11,18, 19) (20,29,39). Other studies used scales that examined only the liking of the product and the product evaluation (17,21,26,32,40–42) or the liking of the product and the sensory and physical effects of the product (8,33,43). A few studies used scales that only examined the sensory and physical effects of the product (10,18,19), 1 study used a scale that examined the liking of the product (25) and 3 studies used a scale that evaluated the product and sensory and physical effects of the product (33,40,44).

Aims—There were 3 aims for using scales to measure the effects of the product in PREP studies: 1) to determine the extent to which the product is rewarding; 2) to determine the sensory and physical effects of the product; and 3) to assess characteristics of the product. Items that showed a positive finding are listed by study and product type for each category in Table 2. Items with nonsignificant results are not presented because the items that showed a positive finding may be ones that should be included in future scales and validated in future studies. However, a lack of significant findings may not necessarily indicate that the item should not be included in the future studies.

Aim 1: Extent product is rewarding

Aim 1: Extent product is rewarding: PREP compared to a placebo or no tobacco: In both a laboratory study that used modified (denicotinized) cigarettes (17) and a laboratory study that used ST PREPs (Ariva, Camel Snus, Marlboro Snus) and a modified (Quest) cigarette

(18), the PREP was rated higher than the placebo or no tobacco condition on measures of product liking.

PREP compared to usual brand: In several laboratory studies subjects preferred their usual brand compared to one or more PREPs on measures of product liking including studies that used modified cigarettes such as reduced nicotine content cigarettes (40) or Marlboro UltraSmooth cigarettes (with carbon filter) (43), and a study using ST PREPs such as Stonewall and General Snus (20).

Also, in the clinical component of this study using ST PREPs (Stonewall, General snus), subjects preferred their usual brand for the item “do you like the way this tastes?” more than General snus, but not Stonewall (20). Similarly, subjects rated usual brand higher on measures of product liking than PREPS in a clinic study that used modified reduced nicotine content cigarettes (9) and in a clinic study that used heated (Eclipse) and modified cigarettes (Advance) (11).

Sensitivity to differences between products: In 4 laboratory studies, subjects rated nicotine versus denicotinized cigarettes higher in satisfaction, pleasantness, drug effect or taste (17,19, 32,41). In other laboratory studies, differences were also observed on measures of liking, satisfaction and psychological reward. For example, highly ventilated cigarettes were rated higher than low nicotine content (0.02 mg nicotine) cigarettes on these items (33). In another laboratory study that examined the effects of two non-nicotine cigarettes with differing amounts of tar in which half of the subjects received the low-tar cigarette and half received the high-tar cigarette, the low-tar cigarette was rated higher on a measure of good drug effect compared to the high-tar cigarette (39). Another study observed that the direction of these ratings may depend on the amount of nicotine in the product (26). Higher ratings of “bad effects” and “taste” were observed with full-tar conventional cigarettes compared to full-tar denicotinized cigarettes, but higher “satisfaction” with full-tar denicotinized products. On the other hand, higher ratings of “bad effects” and lower ratings of “taste” were observed with reduced-tar denicotinized cigarettes compared to reduced-tar conventional cigarettes.

In a study that used 3 Quest cigarettes with different nicotine levels, the 0.6 mg nicotine cigarette was rated as more satisfying than the 0.3 and 0.05 mg nicotine cigarettes (42). Similarly, in a laboratory study among ST users comparing ST PREPs (Ariva, Stonewall, Revel), Copenhagen and Commit lozenge (all products with different nicotine yields), a significant difference between products was seen during use of Copenhagen (the highest nicotine containing product) on measures of feeling good effects from the product, satisfaction, liking and desirability, but not between the other products (24).

Two clinic studies were conducted among smokers that examined Exalt ST or Ariva versus MNL on measures of liking, desirability, and effectiveness, and as having more good effects, subjects rated MNL higher than Exalt (25). Ariva was rated as more desirable than MNL, but there was no significant difference found for liking and effectiveness.

Aim 2: Determining the sensory and physical effects of the product

Aim 2: Determining the sensory and physical effects of the product: PREP compared to placebo or no tobacco: In a ST PREP laboratory study (44) there were differences in ratings between PREPs and a non tobacco condition on measures of sensory and physical effects. This study conducted among ST users was designed to assess nicotine levels and physiological and subjective effects of ST products including Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits or non-tobacco mint snuff. Subjects rated Copenhagen highest in increased salivation, nausea, heart racing, head rush, anxious, and feeling alert (44). Scores on these items were lower for Skoal Long Cut Cherry and Skoal

Original Wintergreen, and lowest for mint snuff and Skoal Bandits, with no significant differences between Skoal Bandits, which achieved the lowest nicotine level across the tobacco products, and mint snuff.

PREP compared to usual brand: In a laboratory study that used research cigarettes with varying levels of nicotine (1 mg, 2 mg, 4 mg, 8 mg and 12 mg) compared to the subjects' usual brand, subjects gave similar ratings for cigarettes with 8 and 12 mg nicotine and the usual brand of cigarettes for feeling stimulated and feeling heart beating fast, but gave lower ratings for these items when smoking 1 mg cigarettes (40). In another laboratory study among smokers with 7 conditions (Ariva, Marlboro Snus, Camel Snus, Commit nicotine lozenge, usual brand, Quest and a sham cigarette), subjects reported significant increases compared to baseline for the following items: "calm you down", "help you concentrate", "reduce hunger", "dizzy" and "more awake" for usual brand with little or no higher ratings in the other noncombustible products. The item "salivation" increased significantly compared to baseline in the noncombustible products only and not in the usual brand condition (18). In a different laboratory study, subjects rated Marlboro UltraSmooth as having a lesser effect compared to their usual brand, but the same effect as Marlboro Ultra Lights (43).

A laboratory component of this ST PREP study among ST users comparing Stonewall and General snus to subjects' usual brand or placebo found higher ratings for subjects' usual brand compared to other conditions for the following items: heart race, head rush, relaxed and alert (20). In the clinical component of this ST PREP study in which subjects used smokeless tobacco products ad libitum (usual brand, Stonewall, General snus) or used no ST, General snus was scored highest for nausea, next was Stonewall, and then usual brand. For the item "salivation" Stonewall was rated highest, then usual brand, and General snus was lowest. (20). Another clinic study with 4 conditions (Advance, Eclipse, usual brand, or no smoking) determined that for the item "do the cigarettes make you sick?" usual brand received the lowest score, followed by Advance, with Eclipse scoring significantly higher than Advance. There was also a significant condition effect for items that measured calming down, concentration, awake and reduce hunger. Scores were typically highest for the subjects' usual brand and lowest for Eclipse (11).

Sensitivity to differences between products or dose: A few laboratory studies that used modified cigarettes (19,33,39,40) and 2 ST PREP studies (10,24) determined that there were differences between products on measures of sensory and physical effects. In one laboratory study, highly ventilated filter cigarettes were compared to low nicotine content cigarettes and were found to be rated higher in enjoyment of respiratory tract sensations whereas the low nicotine content cigarettes were rated as having greater intensity of respiratory tract sensations depending on the area of the respiratory tract affected (33). In a laboratory study of two non-nicotine cigarettes with differing amounts of tar, a low-tar cigarette was rated higher than a high-tar cigarette on the item "stimulated" (39). In another laboratory study that used nicotine and denicotinized cigarettes, rapid smoking of nicotine cigarettes significantly increased all ratings of nicotine effect items. Rapid smoking of denicotinized cigarettes significantly increased ratings of nausea, dizziness, light-headed, burning throat, heart racing, and headache (19). For the items nausea and dizziness, the smoking pace with either cigarette influenced the rating, with the nicotine cigarettes scoring highest. A different laboratory study used research cigarettes with varying levels of nicotine (1 mg, 2 mg, 4 mg, 8 mg and 12 mg) compared to the subjects' usual brand, and subjects reported significantly higher ratings of feeling high and light-headed or dizzy after smoking high-nicotine cigarettes (40).

In a ST PREP laboratory study that used Ariva, Stonewall, Revel, Commit and Copenhagen among ST users, there were no significant differences on some items (alert, relaxed, head rush, tremor in hands, arms or face; light-headed/dizzy; drowsy, energetic or jittery) (24). On other

items, however, Copenhagen was rated significantly higher than Commit or Revel for fast/pounding heart and significantly higher than Commit for felt high. In another ST PREP laboratory study designed to determine the effects of Ariva in cigarette smokers, subjects reported feeling more nauseous as the dose of Ariva increased (10). Other items such as dizzy, confused, lightheaded, and nervous were scored higher (although less consistently) after taking Ariva compared to baseline.

Aim 3: Determining product characteristics

Aim 3: Determining product characteristics: PREP compared to placebo or no tobacco:

A laboratory study reported differences between ST PREPs and a no tobacco condition with regard to product characteristics. Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits or non-tobacco mint snuff were compared among ST users. Copenhagen scored highest for the item “product strength” and lowest for “how well packed” (44).

PREP compared to usual brand: In several laboratory studies that used modified cigarettes (21,40), heated cigarettes (45), ST PREPs (20) or ST PREPs and a modified cigarette (18) compared to the subjects’ usual brand, subjects generally rated their usual brand most positively in terms of product characteristics. For example, one laboratory study examined denicotinized cigarettes, Light brand cigarettes and usual brand and found that subjects rated their usual brand as higher on items that measured “cigarette strength” and “more smoke than air” compared to the other conditions (21). The subjects’ usual brand was also rated more favorably compared to 2 heated cigarettes that were considered weaker, more difficult to draw from and less smooth (45). In a different laboratory study, subjects rated low-nicotine content cigarettes milder, smoother, less flavorful, of poorer quality, and having less nicotine than their usual brand (40). In another laboratory study among smokers with 7 conditions (Ariva, Marlboro Snus, Camel Snus, Commit nicotine lozenge, usual brand, Quest and a sham cigarette), subjects reported significant increases in the usual brand condition compared to baseline for the item “does the product taste like your own brand?” (18).

In the laboratory component of this ST PREP study using usual brand, Stonewall, General snus or placebo among ST users, subjects rated their usual brand higher than the other conditions on the items “tobacco pack” and “tobacco strength”. The item assessing the amount swallowed was rated significantly higher for Stonewall than the usual brand (20). In the clinical component of this ST PREP study during 5-day conditions (usual brand, Stonewall, General snus, and no ST) significant condition by day interactions were observed for items measuring tobacco strength and tobacco pack (20). Subjects rated these items similarly each day for usual brand, and lower most days for Stonewall and General snus. For the item “amount swallowed” Stonewall was rated highest, then usual brand, and next was General snus.

Another clinic study using 4 conditions (Advance, Eclipse, usual brand or no smoking), reported significant condition effects for the following items: “Do the cigarettes taste like your usual brand of cigarette?”, “Do the cigarettes feel like your usual brand of cigarette?” and “Do the cigarettes feel as mild as your usual brand of cigarette?” (11). Scores were typically highest for the subjects’ usual brand and lowest for Eclipse. Similarly, in a different clinic study, subjects rated reduced nicotine cigarettes as less strong, less flavorful, and of generally lower quality than their usual brand (9).

Sensitivity to differences between products: A laboratory study that measured ST PREPs (Kotlyar et al., 2007) and 3 laboratory studies that used modified cigarettes (39,41,42) found differences in subject ratings of PREPs with regard to product characteristics. For example, compared to ST PREPs, Copenhagen was rated as strongest among ST users (24). In a

laboratory study of two non-nicotine cigarettes with differing amounts of tar, subjects gave higher ratings for harshness, heaviness and intensity of flavor in the high-tar versus low-tar cigarette (39). In another laboratory study, subjects rated nicotine cigarettes higher in smoothness compared to denicotinized cigarettes (41). Alternatively, in different laboratory studies, there was no significant difference on measures of product characteristics in 3 studies that used denicotinized versus nicotine cigarettes (19,26,32).

Summary: Many different scales were used in PREP studies to evaluate the effects of the product although there was no scale that was used predominately. The Direct Effect Scale was used in 3 studies (11,18,20), but each used some items that were different. A couple of studies also used the Cigarette Evaluation Questionnaire (8,33) or the Direct Effects of Nicotine scale (10,18). Scales used in studies that asked questions about product liking, sensory and physical effects and product evaluation might provide the most information (see 9,11,18–20,29,39). The scales or items measuring the effects of PREPs seem to be sensitive in showing differences between the placebo or no tobacco conditions and a PREP, the usual brand typically performs the same or better than PREPs (greater liking, stimulatory or central nervous effects, and greater strength or quality), and scales or items distinguish between PREP products with products with greater nicotine content performing better than products with lower nicotine content with the exception of product evaluations where the results are equivocal.

Items that demonstrated a significant difference between PREPs compared to a placebo, usual brand or other PREPs were examined in terms of the 3 aims for using the scales in PREP studies. These items may be worthwhile to include in future scale development to determine their validity and reliability. For the aim of determining the extent to which the product is rewarding, the items that were most often rated significantly different with regard to PREPs, usual brand or placebo conditions were as follows: satisfying, less satisfying, taste good/like taste, liking, like/good drug effect, dislike/bad drug effect, desirability, and pleasant. Other items that were rated significantly different at least once were dislike taste, like cigarette, dislike cigarette, not as good, unpleasant, psychological reward, and effectiveness.

For the aim of determining the sensory and physical effects of the product the following items were most often significantly different between PREPs, usual brand or placebo conditions: nausea, dizziness, heart racing, head rush, calm you down, alert, help you concentrate, more awake, reduce hunger, salivation and feel high. Other items that were significantly different at least once were heart pounding/fast, anxious, relax, stimulated, make you sick, enjoyment of respiratory tract sensations, intensity of respiratory tract sensations, less intensity of drug effect, and light-headed.

The last aim of PREP effect scales is to assess characteristics of the product. The following items were most often significantly different between PREPs, usual brand or placebo conditions: strength, less flavorful, smoother, poorer/lower quality, and cigarettes taste like your usual brand of cigarette. Other items that were rated as significantly different at least once are as follows: intensity of flavor, tobacco pack, how well packed, less strong, weaker, milder, more smoke than air, more difficult to draw from, less smooth, harshness, less nicotine, amount swallowed, cigarettes feel like your usual brand, cigarettes feel as mild as your usual brand and heaviness. The items selected in a study will also vary according to the products that are being tested.

Scales to evaluate responses to tobacco products are still in the early stages of development and no concerted attempt has been made to validate the existing scales or to develop scales that may be better predictors of product use behavior. A couple of studies related the results of product effect scales to other outcomes. For example, in a laboratory study with smokers of Marlboro Lights that compared a carbon filter PREP (Marlboro UltraSmooth) to Marlboro

Ultra Lights in 48 hour conditions, low subjective ratings for MUS seemed to be associated with low levels of exposure (43). In another laboratory study conducted among ST users designed to assess nicotine levels and physiological and subjective effects of ST products including Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits or non-tobacco mint snuff, increases in the rating of product strength showed an association with plasma concentration during the first 10–15 minutes after product administration (44).

In summary, several items measuring rewarding effects, sensory and physical effects and product characteristics are able to distinguish the effects from different products and also produce results in the expected direction—that is, PREPs are rated more highly than placebos, usual brands are typically rated more highly than PREPs and high nicotine content products produce more central nervous system effects than low nicotine content products.

CONCLUSIONS

There are many scales used to test PREPs that focus on withdrawal symptoms and craving and the effects of the PREP. Scales used in PREP studies appear to measure withdrawal symptoms and craving effectively. The scales are able to detect decreases in withdrawal symptoms and craving and differences between PREP products and a placebo or no tobacco condition and sometimes although not consistently between PREP products or based on nicotine content of the product. For example, denicotinized and nicotinized cigarettes where no significant differences were observed between these types of cigarettes, which may indicate that withdrawal symptoms and craving are associated with factors beyond nicotine itself (e.g., the sensory aspects of smoking, the act of smoking). This review also showed that when studies used more than one scale, the results showed a concordance among the scales with a similar pattern of results. Therefore, each of the scales used in PREP studies may be an effective measure of withdrawal symptoms and craving. In the future, PREP studies should consider using standardized measures to allow comparisons across studies and products. To date, the most widely used scale has been the MNWS or its modified version. Additionally, individual items on the MNWS were examined more often in terms of time effects, smoking-bout by time interactions, product type by bout interactions, or no interactions compared to other scales. The second most used scale, the QSU, yields 2 factors: Factor 1 (intention to smoke) and Factor 2 (anticipation of relief from withdrawal) which provides a more thorough examination of urges to smoke. Therefore, at a minimum, these 2 scales may be the ones that should be included in a battery of assessments for PREPs. Future studies should be directed towards examining if the extent of withdrawal relief from a product is associated with how much the product will be used.

To date, no studies have examined the effects of abstaining from PREPs after long-term use. This area of research is important to provide further validation of scales. For example, it would be hypothesized that withdrawal from oral, low nicotine products would produce less withdrawal than a modified cigarette product with high levels of nicotine.

Another key area of evaluating PREPs is the subjective response to a product, which also plays a key role in the evaluation of abuse liability of a tobacco product (5). As described in the article on the assessment of abuse liability of tobacco products, subjective responses to tobacco products are measured across various research paradigms including acute dose-effects comparisons, drug-discrimination, self-administration, forced-drug choice and clinical trials, and serve as core tools to determine whether the product is likely to be used, the extent the use of the product is likely to be maintained and lead to addiction and the difficulty that consumers may experience when trying to stop using the product.

When considering the 3 primary areas of tobacco product evaluation, most laboratory and clinic studies reported that comparing PREPs to a placebo or no tobacco condition or to the subjects' usual brand, the subjects' usual brand was generally rated most positively. However, in several studies that used a placebo or no tobacco condition, no comparisons were made with this condition. Studies also found that for some items there were differences detected between PREPs, but for other items there were no differences between PREPs. Discrepancies in ratings were observed depending on smoking pace (19) or product dose (10).

Unlike the withdrawal symptoms and craving scales, no particular scale was used predominately to measure the effects of PREPs. However, it appears that assessing the 3 primary areas of tobacco product evaluation is critical. Development and validation of a product scale that measures these 3 areas should be a high priority research area. The scales should have core elements that are comparable across products as well as assessments of unique product-specific attributes that would not necessarily generalize across products, but is important information to ascertain, particularly for novel designs. Validation of these scales can include examining how effective the scales are in predicting amount of product self-administered, product choice, and discrimination across products with different nicotine yields or sensory properties, sustained use of the product and potentially dependence and abstinence effects from the product. Future research can also examine the relationship of these scales to product marketing, messaging and labeling with associated consumer perception of the product, price, social norms and attitudes toward the product and even tobacco control policies.

The determination of validity of these scales, that is relationship between subjective responses to actual use, is a critical area of research. In addition, assessment of subjective responses to products in nonsmokers is also important. How we can introduce cigarette PREPs to nonsmokers is a quandary. Another critical area of research is determining how a population of non-tobacco users may respond to PREP tobacco products, which would provide information on the potential uptake of these products among this population. This type of research can be conducted with occasional tobacco users or with products that are not highly likely to produce addiction such as nicotinized modified risk cigarettes. For example, studies have been conducted with medicinal nicotine products with nonsmokers (46) or nicotine nasal spray (47,48) in subjects naïve to tobacco use.

With the passing of the Family Smoking Prevention and Tobacco Control Act that gives the FDA jurisdiction over evaluation of products, it becomes vitally important that tools are available to effectively evaluate PREPs as well as other tobacco products. Assessing the abuse potential of a product involves determining the subjective responses to these products that are related to behavioral responses. Through these tools we will be able to assure protection of public health.

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Table 1

Scales and items used to measure subjective responses to PREPs

Scale	Studies That Used The Scale	Items
<i>Withdrawal Symptoms and Craving Scales</i>		
The Minnesota Nicotine Withdrawal Scale (7)	X (8) X (9) X (17) X (22) X (23) X (24) X (25) X (26)	Items were rated as 0=not present, 1=slight, 2=mild, 3=moderate, or 4=severe or as visual analogue scales (VAS) where items were presented above a horizontal line with anchors on the left "not at all" or "none" and right "extremely" or "severe". Items: cigarette craving; irritability/anger; anxiety/tension; difficulty concentrating; restlessness; impatience; problems with sleep; increased appetite; drowsiness; depressed mood.
13 item VAS Tobacco/nicotine Withdrawal Scale (adapted from Hughes & Hatsukami 1986)(7)	X (11) X (12) X (15)	Scale was anchored by "not at all" and "extremely". Items: urges to smoke; irritability/frustration/anger; anxious; difficulty concentrating; restlessness; hunger; impatient; craving a cigarette/nicotine; insomnia/disturbed sleep; increased eating; drowsiness; depression/feeling blue; desire for sweets.
11 item VAS Tobacco/nicotine Withdrawal Scale (adapted from Hughes & Hatsukami, 1986)(7)	X (10) X (13) X (14) X (16) X (18) X (20) X (21)	Scale was anchored by "not at all" and "extremely" or anchor points were "none" and "severe". Items: urges to smoke/dip; irritability/frustration/anger; anxious; difficulty concentrating; restlessness; hunger; impatient; craving a cigarette or dip/nicotine; drowsiness; depression/feeling blue; desire for sweets.
The Withdrawal Symptoms Questionnaire (adapted from Hughes and Hatsukami 1986)(7)	X (19)	Did not report how scale was anchored. Items: urges to smoke; irritable; anxious; difficulty concentrating; restless; impatient; excessive hunger; tremor; heart racing; sweating; dizziness; craving cigarettes; insomnia/disturbed sleep; increased eating; drowsiness; headache; bowel or stomach

Scale	Studies That Used The Scale	Items
		problems; depressed.
Questionnaire of Smoking Urges (QSU)(27)	X (11) X (12) X (13) X (14) X (15) X (16) X (19) X (20) X (22) (substituting the phrase "dip/tobacco" for "cigarette" or "dipping/using tobacco" for "smoking") X (23) X (29)	32 smoking-related items that are rated on a 7-point scale ranging from 0 (Strongly disagree) to 6 (Strongly agree). The QSU yields 2 factors: Factor 1 (intention to smoke) and Factor 2 (anticipation of relief from withdrawal). Items: Desire to smoke: I am not missing smoking right now; I don't want to smoke now; All I want right now is a cigarette; I have no desire for a cigarette right now; My desire to smoke seems overpowering; I crave a cigarette right now; I have an urge for a cigarette; I need to smoke now; Anticipation of positive outcome: Smoking would make me feel very good right now; Nothing would be better than smoking a cigarette right now; Smoking a cigarette would not be pleasant; Smoking would make me happier now; Smoking now would make things seem just perfect; I would not enjoy a cigarette right now; A cigarette would not taste good right now; A cigarette would not be very satisfying now; Relief of withdrawal or negative affect: I would be less irritable now if I could smoke; Smoking would make me less depressed; Smoking would not help me calm down now; If I were smoking this minute, I would feel less bored; Smoking right now would make me feel less tired; I could control things better right now if I could smoke; I would not feel better physically if I were smoking; If I were smoking now I could think more clearly; Intention to smoke: I will smoke as soon as I get the chance; If I were offered a cigarette, I would smoke it immediately; Starting now, I could go without smoking for a long time; Even if it were possible, I probably wouldn't smoke now; I am going to smoke as soon as possible; If I had a lit cigarette in my hand I probably wouldn't smoke it; I would do almost anything for a cigarette

Scale	Studies That Used The Scale	Items
		now; Right now, I am not making plans to smoke.
The short form (10 items) of the Questionnaire on Smoking Urges (QSU)(28)	X (18) X (26) X (30)	Items were rated on a 7-point scale ranging from 0 (Strongly disagree) to 6 (Strongly agree). Items: I have a desire for a cigarette right now; Nothing would be better than smoking a cigarette right now; If it were possible, I probably would smoke now; I could control things better right now if I could smoke; All I want right now is a cigarette; I have an urge for a cigarette; A cigarette would taste good now; I would do almost anything for a cigarette now; Smoking would make me less depressed; I am going to smoke as soon as possible.
4- or 5-item Measure to Rate Craving or Urge for a Cigarette/Desire to Smoke VAS (adapted from Schuh and Stitzer 1995)(34)	X (19) X (21) X (30) X (29)	Items were rated from “not at all” to “very much”. 4-items: How pleasant would a puff be right now?; How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking?; How much do you need to smoke right now, for relief?; How much do you want to smoke right now? Item 5 not reported (Donny et al., 2006).
3-item Craving/Satisfaction Scale	X (21)	Scale was anchored by “not at all” and “very much”. Items: How much did you like or enjoy the puff you just took?; How much do you want to smoke right now?; How satisfying was your last puff?
The Shiffman- Jarvik Smoking Withdrawal Questionnaire (31)	X (19) X (29) X (32) (abbreviated version) X (33) (abbreviated version)	Items were rated on 7-point scales, with 1=very definitely and 7=very definitely not; the items were divided into five subscales based on factor analysis: craving; psychological discomfort; physical symptoms; stimulation/sedation; appetite; abbreviated version: craving; negative affect; arousal (Rose & Behm, 2004); craving (Kassel et al., 2007)
Product Effects Scales		
The Drug Effects and Liking Visual Analog Scale (49–52)	X (25)	Scale was anchored by “not at all” and “extremely”. Items: liking

Scale	Studies That Used The Scale	Items
		and desire of the study product; any, good or bad effects from the study product; effectiveness of the product.
13 item VAS Direct Effects Scale	X (20)	Scale was anchored by “not at all” and “extremely”. Items: Overall, how strong is the tobacco?; What amount of the tobacco have you swallowed?; How well does the tobacco pack?; Has your salivation (spit) increased?; Does the tobacco produce any burning sensations?; Do you feel any tingling in your mouth when using the tobacco?; Do you feel any nausea when using the tobacco?; Does your heart race when using the tobacco?; Do you feel a head rush when using the tobacco?; Does the tobacco help you relax?; Do you like the way the tobacco makes you feel?; Do you like the way the tobacco tastes?; How alert does the tobacco make you feel?
14 item VAS Direct Effects of Tobacco Scale substituting “cigarette” for “product” (11,53,54)	X (18)	Scale was anchored by “not at all” and “extremely”. Items: Was the product satisfying?; Was the product pleasant?; Did the product taste good?; Did the product make you dizzy?; Did the product calm you down?; Did the product help you concentrate?; Did the product make you feel more awake?; Did the product reduce your hunger for food?; Did the product make you sick?; Did the product taste like your own brand of cigarette?; Did the product feel like your own brand of cigarette?; Did the product feel as harsh as your own brand of cigarette?; Did the product feel as mild as your own brand of cigarette?; Would you like more of the product right now?
15 item VAS Direct Effects of Smoking Questionnaire (53–55)	X (11)	Did not report how items were scored. Items: Are the cigarettes satisfying?; Are the cigarettes pleasant?; Do the cigarettes taste good?; Do the cigarettes make you dizzy?; Do the cigarettes calm you down?; Do the cigarettes help you

Scale	Studies That Used The Scale	Items
		concentrate?; Do the cigarettes make you feel more awake?; Do the cigarettes reduce your hunger for food?; Do the cigarettes make you sick?; Do you like the cigarettes?; Do you dislike the cigarettes?; Do the cigarettes taste like your own brand of cigarette?; Do the cigarettes feel like your own brand of cigarette?; Do the cigarettes feel as harsh as your own brand of cigarette?; Do the cigarettes feel as mild as your own brand of cigarette?
Nicotine Effects VAS (56)	X (19)	Scale was anchored by “none” and “severe”. Items: nausea; clammy skin; dizziness; lightheaded; burning throat; tingling sensations; heart racing.
Direct Effects of Nicotine (57,58)	X (10) X (18)	Scale was anchored by “not at all” and “extremely”. Items: nauseous; dizzy; lightheaded; nervous; sweaty; headache; excessive salivation; heart pounding; confused; weak.
VAS Questionnaire Asking about Nicotine Effects	X (40)	Items were rated as 0=not at all to 10=extremely. Items: I feel lightheaded or dizzy; I feel high; I feel nauseated; I feel anxious or tense; I feel stimulated; My heart is beating fast; I feel content; I feel alert and awake; I feel calm and relaxed; I am able to concentrate; strength of the dose.
Cigarette Evaluation Questionnaire (59)	X (8) X (33)	Items were rated as 0=not at all to 7=extremely. Items: satisfaction; psychological reward; nausea or dizziness; craving relief; enjoyment of airway sensations.
Cigarette Acceptability Questionnaire adapted from the Duke Cigarette Evaluation Scale and the Duke Sensory Questionnaire (59,60)	X (40)	Items were rated as 1 to 5 or 1 to 7, depending on the question: strength or mildness; smoothness or harshness; hotness; amount of flavor; flavor; overall quality; satisfaction; how the cigarette compared with their usual cigarette; how high in nicotine they thought the puffs were.

Scale	Studies That Used The Scale	Items
Cigarette Acceptance Questionnaire	X (9)	Items were rated on a 7-point scale. Items: that cluster into seven scales: satisfaction, similarity to usual brand, psychological reward, aversion, respiratory sensations, craving, perceived strength.
VAS Drug Effects and Taste Qualities of the Cigarettes Scale (49–52)	X (39)	Scale was anchored by “not at all” and “extremely”. Items: drug effect, bad drug effect, drug liking, drug strength, tobacco taste, similar to regular cigarette, desire to smoke your regular cigarette, desire to smoke cigarette you just smoked, quality of flavor, intensity of flavor, coolness of cigarette, freshness of cigarette, harshness of cigarette, dryness of cigarette, heaviness of cigarette, relaxed, dizziness, enjoyment, stimulated, taste of cigarette.
Subjective Rating of Products	X (44)	Scale was anchored by “not at all” and “extremely”. Items: overall product strength; amount swallowed; how well the product packed; increased salivation; burning sensations in the mouth; mouth tingling; nausea.
Cigarettes Effects Questionnaire (61)	X (29)	Scale was anchored by “not at all” and “extremely”. Items: satisfying; pleasant; unpleasant; like taste; dislike taste; smoke versus air (anchored with ‘mostly smoke’ to ‘mostly air’); harsh; strength; high in nicotine; like drug effect; dislike drug effect; like cigarette; dislike cigarette; calming; relaxing; comforting; less irritable; sense of wellbeing; more awake; easier to concentrate; exhilarating; pleasurable; excitement; dizziness; lightheaded; nauseating; nervous.
VAS Cigarette Effect (21)	X (19)	Scale was anchored by “not at all” and “extremely”; Items: pleasant, unpleasant, like taste, dislike taste, smoke versus air (anchored with “mostly smoke” to “mostly air”), harsh, strength, high in nicotine, like drug effect, dislike drug effect,

Scale	Studies That Used The Scale	Items
		satisfying, more awake, more calm, easier to concentrate, less irritable.
VAS Cigarette Ratings	X (17)	Scale anchors were specific to the item. Items: drug strength; good effects of drug; bad effects of drug; like effects of drug; cigarette strength; hotness of cigarette; harshness of cigarette; draw level of cigarette; taste of cigarette; overall satisfaction; good effects of cigarette; bad effects of cigarette.
VAS Rating Scale of Cigarette Features	X (42)	Scales contained “descriptive anchors”. Items: strength; harshness; heat; draw; taste (bad/good); satisfaction; burn rate; taste (mildness); too mild; harshness of smoke; after taste; staleness; strength of smoke; smoke smell (pleasantness).
Self-report Questionnaire	X (41)	Items were rated on a 10-point scale. Items: taste; enjoyment; drug effect; smoothness.
VAS Cigarette Characteristics Scale	X (26)	Scale anchors were specific to the item. Items: strength; taste; satisfaction; harshness; ease of draw; good effects; bad effects.
Cigarette Ratings (62)	X (32)	Items were rated as 0=not at all to 4=very much so. Items: harshness; strength; pleasantness of the cigarette.
An 8-item Cigarette Characteristics Measure	X (21)	Scale anchors were specific to the item. Items: How strong was the cigarette?; How hot was the cigarette?; How hard was it to draw smoke from the cigarette?; How harsh was the cigarette?; How much taste did you get from the cigarette?; How satisfying was the cigarette?; How much tobacco vs. ‘just air’ did you get from the cigarette?; What is the likelihood that you would buy cigarettes like these?
A Sensory Questionnaire	X (33)	Items were rated as 0=not at all to 7=extremely. Items: estimated nicotine delivery; similarity to usual brand; perceived strength on the tongue, nose, back of mouth and throat, windpipe, and chest.

Scale	Studies That Used The Scale	Items
"Feel drug effect" question and "Like drug effect" question (derived from Zacny, Conley & Galinkin, 1997)(63)	X (43)	Item was rated as 1=I feel no effect from it at all to 5=I feel a very strong effect. Item: rate the intensity of the drug effect as they currently experience it. Item was rated as 0=dislike a lot to 50=neutral to 100=like a lot. Item: how much they like the drug effect.

Table 2

Items that showed a positive finding in PREP evaluation studies by product used

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
Aim 1: Liking Product			
Scale Item			
Taste good/like taste	X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (11) (Advance, Eclipse) X (20) (Lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus)	X (26) (Reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes) X (41) (Denicotinized and nicotinized cigarettes)
Dislike taste			X (19) (Denicotinized and nicotinized cigarettes)
Like cigarette		X (11) (Advance, Eclipse)	
Dislike cigarette		X (11) (Advance, Eclipse)	
Like/good drug effect	X (17) (Denicotinized cigarettes, regular cigarettes vs. lettuce cigarettes)	X (43) (Marlboro UltraSmooth, Marlboro Ultra Lights vs. usual brand Marlboro Lights)	X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (25) (Exalt, Ariva, nicotine lozenge) X (41) (Denicotinized and nicotinized cigarettes) X (39) (2 non-nicotine cigarettes with different levels of tar)
Dislike/bad drug effect	X (29) (Denicotinized cigarettes, nicotinized cigarettes vs. no smoking)		X (19) (Denicotinized and nicotinized cigarettes) X (26) (Reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes)
Pleasant	X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (11) (Advance, Eclipse)	X (32) (Denicotinized cigarettes, high-yield nicotine cigarettes)

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
Unpleasant			X (19) (Denicotinized and nicotinized cigarettes)
Satisfying	X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (11) (Advance, Eclipse)	X (17) (Denicotinized cigarettes, regular cigarettes, lettuce cigarettes) X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (26) (Reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes) X (42) (Quest cigarettes)
Less satisfying		X (40) (5 cigarettes with different levels of nicotine) X (9) (5 cigarettes with progressively lower nicotine levels)	
Not as good		X (40) (5 cigarettes with different levels of nicotine)	
Liking			X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (25) (Exalt, Ariva, nicotine lozenge) X (26) (Reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes)
Psychological reward			X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes)
Desirability			X (24) (Ariva, Stonewall, Revel,

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
			nicotine lozenge, Copenhagen) X (25) (Exalt, Ariva, nicotine lozenge)
Effectiveness			X (25) (Exalt, Ariva, nicotine lozenge)
Aim 2: Sensory & Physical Effects			
Scale Item			
Nausea	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (20) (Clinic component of study: Stonewall, General Snus)	X (10) (Ariva) X (19) (Denicotinized and nicotinized cigarettes)
Heart racing	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (20) (Lab component of study: Stonewall, General Snus)	
Heart pounding/fast			X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen)
Head rush	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (20) (Lab component of study: Stonewall, General Snus)	
Anxious	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)		
Relax		X (20) (Lab component of study: Stonewall, General Snus)	
Calm you down		X (11) (Advance, Eclipse) X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Alert	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (20) (Lab component of study: Stonewall, General Snus)	
Help you concentrate		X (11) (Advance, Eclipse) X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
More awake		X (11) (Advance, Eclipse) X (18) (Ariva, Marlboro Snus,	

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
		Camel Snus, nicotine lozenge, Quest cigarettes)	
Stimulated			X (39) (2 non-nicotine cigarettes with different levels of tar)
Reduce hunger		X (11) (Advance, Eclipse) X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Make you sick		X (11) (Advance, Eclipse)	
Enjoyment of respiratory tract sensations			X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes)
Intensity of respiratory tract sensations			X (33) (Low nicotine content cigarettes and conventional highly ventilated filter cigarettes)
Dizziness		X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	X (40) (5 cigarettes with different levels of nicotine) X (19) (Denicotinized and nicotinized cigarettes)
Light-headed			X (40) (5 cigarettes with different levels of nicotine)
Felt high			X (40) (5 cigarettes with different levels of nicotine) X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen)
Less intensity of drug effect		X (43) (Marlboro UltraSmooth, Marlboro Ultra Lights)	
Salivation	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes) X (20) (Clinic component of study: Stonewall, General Snus)	

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
Aim 3: Product Evaluation			
<i>Scale Item</i>			
Less flavorful		X (40) (5 cigarettes with different levels of nicotine) X (9) (5 cigarettes with progressively lower nicotine levels)	
Intensity of flavor			X (39) (2 non-nicotine cigarettes with different levels of tar)
Tobacco pack		X (20) (Lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus)	
How well packed	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)		
Strength	X (44) (4 brands of moist snuff vs. a non-tobacco mint snuff)	X (20) (Lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus) X (21) (Next denicotinized cigarettes, Winston Lights)	X (24) (Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (42) (Quest cigarettes)
Less strong		X (9) (5 cigarettes with progressively lower nicotine levels)	
Weaker		X (45) (Accord, Oasis, Marlboro Ultra)	
Milder		X (40) (5 cigarettes with different levels of nicotine)	
More smoke than air		X (21) (Next denicotinized cigarettes, Winston Lights)	
More difficult to draw from		X (45) (Accord, Oasis, Marlboro Ultra)	
Smoother		X (40) (5 cigarettes with different levels of nicotine)	X (41) (Denicotinized and nicotinized cigarettes)

	Placebo vs. PREP	Usual Brand vs. PREP	Differences Across PREPs
Less smooth		X (45) (Accord, Oasis, Marlboro Ultra)	
Harshness			X (39) (2 non-nicotine cigarettes with different levels of tar)
Poorer/lower quality		X (40) (5 cigarettes with different levels of nicotine) X (9) (5 cigarettes with progressively lower nicotine levels)	
Less nicotine		X (40) (5 cigarettes with different levels of nicotine)	
Amount swallowed		X (20) (Lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus)	
Do the cigarettes taste like your usual brand of cigarette?		X (11) (Advance, Eclipse) X (18) (Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Do the cigarettes feel like your usual brand of cigarette?		X (11) (Advance, Eclipse)	
Do the cigarettes feel as mild as your usual brand of cigarette?		X (11) (Advance, Eclipse)	
Heaviness			X (39) (2 non-nicotine cigarettes with different levels of tar)