

*Review***Measures for Assessing Subjective Effects of Potential Reduced-Exposure Products**Karen Hanson,¹ Richard O'Connor,² and Dorothy Hatsukami¹¹University of Minnesota Tobacco Use Research Center, Minneapolis, Minnesota; and ²Roswell Park Cancer Institute Department of Health Behavior, Buffalo, New York**Abstract**

Potential reduced-exposure products (PREP) 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 the 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 the 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 article, 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. (Cancer Epidemiol Biomarkers Prev 2009;18(12):3209–24)

Introduction

Potential reduced-exposure products (PREP) 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 toxicants in the tobacco product itself (e.g., tobacco specific nitrosamines) or a special filter that reduces volatile toxicants. Examples of these modified cigarettes are Advance, Omni, and Marlboro UltraSmooth which are no longer on the market. 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.

However, whether these products lead to reduced health risk to the individual or reduced harm to the pop-

ulation compared with 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 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 physiologic 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 the 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 they can be 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,

Received 9/17/09; revised 10/19/09; accepted 10/19/09; published online 12/3/09.

Grant support: National Cancer Institute contract N01-64402 - Laboratory Assessment of Tobacco Use Behavior and Exposure to Toxins Among Users of New Tobacco Products. This article is one in a series of articles on the methods and measures for the evaluation of potential reduced exposure products.

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doi:10.1158/1055-9965.EPI-09-0971

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. A 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 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 the 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 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 the potential harm of a product. Products that are high in toxicant exposure and in abuse potential are likely to produce significant harm to the individual and the population. 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 it complements 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 identification and tracking of tobacco products including PREPs (6) have recently been conducted.

The purpose of the present paper is to: (a) identify scales that are used to evaluate PREPs and describe the items on the scales; (b) evaluate whether the scales and items are sensitive in testing PREPs (that is, whether they can detect differences across products including placebo); and (c) 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: (a) whether the scale distinguishes placebo or no-tobacco conditions from the PREP; (b) whether the scale or item shows that PREPs are rated as good or less good than the usual brand of cigarettes; and (c) 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.

Materials and Methods

PubMed was searched on April 14, 2008 and on June 1, 2009, with the search 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 were 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 Symptoms and Craving Scales. Several different scales were used to measure withdrawal symptoms and craving. Many studies used the MNWS (7) or a modified version of this scale; refs. 8-26). Items were rated as follows: 0, not present; 1, slight; 2, mild; 3, moderate; or 4, severe, or as visual analogue scales where items were presented above a horizontal line with anchors on the left ("not at all" or "none") and the right ("extremely" or "severe").

Many other studies used the Questionnaire of Smoking Urges (QSU; ref. 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 two factors: intention to smoke (factor 1) and anticipation of relief from withdrawal (factor 2).

The Shiffman-Jarvik Withdrawal Scale (31) or an abbreviated version was used in four studies (19, 29, 32, 33). This scale has 25 items presented in a 7-point scale, with 1 indicating "very definitely" and 7 indicating "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 visual analogue scale that was derived from Schuh and Stitzer (34) included four or five items and was used in four studies (19, 21, 29, 30). Visual analogue 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, and Callas (35) measured withdrawal symptoms on a 5-point scale derived from the American Psychiatric Association, and two studies used a nonreferenced scale (21, 36).

Aims. There were two aims for using withdrawal symptom scales in PREP studies: (a) to measure the extent the product reduces withdrawal symptoms from cigarettes; and (b) 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

PREP compared with 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 (Ariva, Marlboro Snus, Camel Snus) and a modified cigarette (Quest) (18), or ST PREPs such as Stonewall and General Snus (20) compared with a placebo condition. Two of three of these studies found that compared with 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 nontobacco 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 nontobacco placebo smokeless product and a loose moist snuff and after the fourth use in all conditions.

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

PREP compared with usual brand. Several laboratory studies that compared PREPs with the subjects' usual brand reported that there were fewer decreases in ratings of withdrawal symptoms and craving in the PREP conditions compared with the usual brand, including one study that used heated cigarettes such as Accord (15) and two 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 with 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 clinical 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 clinical studies that used modified cigarettes such as Omni (22) or Advance (12) or heated and modified cigarettes such as Advance and Eclipse (11) re-

ported that, in general, there were no differences between PREPs and the usual brand.

Sensitivity of Differences between PREPs. Several laboratory studies indicated a decrease in withdrawal symptoms and craving ratings, and no significant differences in the extent of reduction between denicotinized and nicotized cigarettes (17, 19, 23, 26, 30).

A few clinical studies also indicated no significant differences in ratings of withdrawal symptoms or craving between PREPs or as the dose of the PREP changed, including one study that used increasing amounts of heated cigarettes (Accord) with the option of using usual brand cigarettes (37), one study that used heated cigarettes (Eclipse) as against a nicotine inhaler (36), and one study that used ST PREPs (Exalt and Ariva) compared with medicinal nicotine lozenges (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 two studies that used ST PREPs (10, 24). For example, in one laboratory study, reduction in withdrawal symptoms was observed in a ST PREP study, in which smokers were administered Ariva tablets (one, two, and three tablets in ascending order), at 90-minute intervals (10). Mean withdrawal scores decreased significantly following three 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 with the other four products and was lower in Stonewall, Ariva, and Commit compared with Revel. There were no other significant differences between products for withdrawal symptoms or craving.

Additionally, a clinical study using Eclipse compared with 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 clinical 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 9 cigarettes with puffs every 6 seconds) and normal-paced smoking with nicotized and denicotinized cigarettes and then were given a choice to smoke. They reported that craving ratings were significantly higher

Table 1. Scales and items used to measure subjective responses to PREPs

Scale	Studies that used the scale	Items
Withdrawal symptoms and craving scales		
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 on the 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 and Hatsukami, 1986; ref. 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 and Hatsukami, 1986; ref. 7)	X (10) X (13) X (14) X (16) X (18) X (20) X (21) X (19)	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; ref. 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 problems, depressed.
Questionnaire of Smoking Urges (QSU; ref. 27)	X (11) X (12) X (13) X (14) X (15) X (16) X (19) X (20) X (ref. 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 two factors: intention to smoke (factor 1) and anticipation of relief from withdrawal (factor 2). 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 now; Right now, I am not making plans to smoke.

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Table 1. Scales and items used to measure subjective responses to PREPs (Cont'd)

Scale	Studies that used the scale	Items
The short form (10 items) of the 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; ref. 34)	X (19) X (21) X (30) X (29)	Items were rated from "not at all" to "very much." Four 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 (29).
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 (ref. 32; abbreviated version) X (ref. 33; abbreviated version)	Items were rated on a 7-point scale, 1 being very definitely and 7 being very definitely not. The items were divided into five subscales based on factor analysis: craving, psychological discomfort, physical symptoms, stimulation/sedation, appetite; for the abbreviated version: craving, negative affect, arousal (33); craving (32)
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 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?

(Continued on the following page)

Table 1. Scales and items used to measure subjective responses to PREPs (Cont'd)

Scale	Studies that used the scale	Items
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 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.
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.

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Table 1. Scales and items used to measure subjective responses to PREPs (Cont'd)

Scale	Studies that used the scale	Items
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, 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.
"Feel drug effect" question and "Like drug effect" question (derived from Zacny, Conley and Galinkin, 1997; ref. 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.

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 clinical studies that compared PREPs with 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 with 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 with decreases in a ST PREP and usual brand condition after

the fourth use (20). Moreover, when PREPs were compared with the 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 nicotinized cigarettes regarding the extent of withdrawal symptoms and craving reduction in several laboratory studies or between PREPs in a few clinical 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 symptoms and craving relief across different PREPs and across different doses of nicotine. For example, two ST PREP studies showed

greater withdrawal symptoms or craving relief as the dose of Ariva increased (10) or for the product containing the most nicotine (24). For most laboratory and clinical 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 but not in others. Withdrawal and craving symptoms are more severe in placebo or no-smoking conditions 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 physiologic response.

Product Effects Scales

Subjective responses to the product. In contrast to the measures of withdrawal and craving, no single scale to measure product effects 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), one study used a scale that examined the liking of the product (25), and three studies used a scale that evaluated the product and the sensory and physical effects of the product (33, 40, 44).

Aims. There were three aims for using scales to measure the effects of the product in PREP studies: (a) to determine the extent to which the product is rewarding; (b) to determine the sensory and physical effects of the product; and (c) to assess the 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 future studies.

Aim 1: extent product is rewarding

PREP compared with 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 with usual brand. In several laboratory studies subjects preferred their usual brand compared with 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; ref. 43), and a study using ST PREPs such as Stonewall and General Snus (20). Moreover, in the clinical component of this study using ST PREPs (Stonewall, General snus), subjects preferred their usual brand over General snus, but not Stonewall, for the item "do you like the way this tastes?" (20). Similarly, subjects rated usual brand higher than PREPs on measures of product liking in a clinical study that used modified reduced-nicotine-content cigarettes (9) and in a clinical study that used heated (Eclipse) and modified cigarettes (Advance; ref. 11).

Sensitivity to differences between products. In four laboratory studies, subjects rated nicotized cigarettes higher than denicotinized cigarettes in terms of 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 cigarettes with low nicotine content (0.02 mg nicotine) on these items (33). In another laboratory study that examined the effects of two nonnicotine 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 with 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 with full-tar denicotinized cigarettes, and 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 with reduced-tar conventional cigarettes.

In a study that used three 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 product containing the highest nicotine) on measures of feeling good effects from the product, satisfaction, liking, and desirability, but not between the other products (24).

Two clinical studies were conducted among smokers to examine Exalt ST or Ariva versus medicinal nicotine lozenges on measures of liking, desirability, and effectiveness.

As to having more good effects, subjects rated medicinal nicotine lozenges higher than Exalt (25). Ariva was rated as more desirable than medicinal nicotine lozenges, but there was no significant difference found for liking and effectiveness.

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

PREP compared with placebo or no tobacco. In a ST PREP laboratory study (44) there were differences in ratings between PREPs and a nontobacco condition on measures of sensory and physical effects. This study conducted among ST users was designed to assess nicotine levels and physiologic and subjective effects of ST products, including Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits or nontobacco mint snuff. Subjects rated Copenhagen highest in increased salivation, nausea, heart racing, head rush, anxiety, 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 with 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 with 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 cigarettes with 1 mg nicotine (40). In another laboratory study among smokers involving seven conditions (Ariva, Marlboro Snus, Camel Snus, Commit nicotine lozenge, usual brand, Quest, and a sham cigarette), subjects reported significant increases compared with baseline for the items "calm you down," "help you concentrate," "reduce hunger," "dizzy," and "more awake" for the usual brand, with not many or no higher ratings in the other noncombustible products. The item "salivation" increased significantly compared with 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 with 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 the subjects' usual brand or placebo found higher ratings for the subjects' usual brand compared with 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, followed by Stonewall and then the usual brand. For salivation, Stonewall was rated highest, then the usual brand, with General snus the lowest (20). Another clinical study with four 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 two 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 with 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 nonnicotine 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-headedness, burning throat, racing heart, and headache (19). For 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 with 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; ref. 24). On other items, however, Copenhagen was rated significantly higher than Commit or Revel for fast/pounding heart and significantly higher than Commit for feeling high. In another ST PREP laboratory study designed to determine the effects of Ariva on cigarette smokers, subjects reported feeling more nauseous as the dose of Ariva increased (10). Other items such as feeling dizzy, confused, lightheaded, and nervous were scored higher (although less consistently) after taking Ariva compared with deprivation prior to taking Ariva.

Aim 3: determining product characteristics

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

PREP compared with usual brand. In several laboratory studies that compared modified cigarettes (21, 40), heated cigarettes (45), ST PREPs (20), or ST PREPs and a modified cigarette (18) with 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,

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 (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (ref. 11; Advance, Eclipse) X (ref. 20; lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus)	X (ref. 26; reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes) X (ref. 41; denicotinized and nicotine cigarettes)
Dislike taste		X (ref. 19; denicotinized and nicotine cigarettes)	
Like cigarette		X (ref. 11; Advance, Eclipse)	
Dislike cigarette		X (ref. 11; Advance, Eclipse)	
Like/good drug effect	X (ref. 17; denicotinized cigarettes, regular cigarettes vs. lettuce cigarettes)	X (ref. 43; Marlboro UltraSmooth, Marlboro Ultra Lights vs. usual brand Marlboro Lights)	X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (ref. 25; Exalt, Ariva, nicotine lozenge) X (ref. 41; denicotinized and nicotine cigarettes) X (ref. 39; 2 nonnicotine cigarettes with different levels of tar)
Dislike/bad drug effect	X (ref. 29; denicotinized cigarettes, nicotine cigarettes vs. no smoking)		X (ref. 19; denicotinized and nicotine cigarettes) X (ref. 26; reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes)
Pleasant	X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (ref. 11; Advance, Eclipse)	X (ref. 32; denicotinized cigarettes, high-yield nicotine cigarettes)
Unpleasant			X (ref. 19; denicotinized and nicotine cigarettes)
Satisfying	X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest Cigarettes vs. sham smoking)	X (ref. 11; Advance, Eclipse)	X (ref. 17; denicotinized cigarettes, regular cigarettes, lettuce cigarettes) X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (ref. 26; reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes) X (ref. 42; Quest cigarettes)
Less satisfying		X (ref. 40; 5 cigarettes with different levels of nicotine) X (ref. 9; 5 cigarettes with progressively lower nicotine levels)	
Not as good		X (ref. 40; 5 cigarettes with different levels of nicotine)	
Liking			X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (ref. 25; Exalt, Ariva, nicotine lozenge) X (ref. 26; reduced- and full-tar standard cigarettes and reduced- and full-tar denicotinized cigarettes) X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes)

(Continued on the following page)

Table 2. Items that showed a positive finding in PREP evaluation studies by product used (Cont'd)

	Placebo vs. PREP	Usual brand vs. PREP	Differences across PREPs
Psychological reward			X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes)
Desirability			X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (ref. 25; Exalt, Ariva, nicotine lozenge)
Effectiveness			X (ref. 25; Exalt, Ariva, nicotine lozenge)
Aim 2: sensory and physical effects			
Scale item			
Nausea	X (ref. 44; 4 brands of moist snuff vs. a nontobacco mint snuff)	X (ref. 20; clinic component of study: Stonewall, General Snus)	X (ref. 10; Ariva) X (ref. 19; denicotinized and nicotinized cigarettes)
Heart racing	X (ref. 44; 4 brands of moist snuff vs. a non-tobacco mint snuff)	X (ref. 20; lab component of study: Stonewall, General Snus)	
Heart pounding/fast			X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen)
Head rush	X (ref. 44; 4 brands of moist snuff vs. a non-tobacco mint snuff)	X (ref. 20; lab component of study: Stonewall, General Snus)	
Anxious	X (ref. 44; 4 brands of moist snuff vs. a nontobacco mint snuff)		
Relax		X (ref. 20; lab component of study: Stonewall, General Snus)	
Calm you down		X (ref. 11; Advance, Eclipse) X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Alert	X (ref. 44; 4 brands of moist snuff vs. a nontobacco mint snuff)	X (ref. 20; lab component of study: Stonewall, General Snus)	
Help you concentrate		X (ref. 11; Advance, Eclipse) X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
More awake		X (ref. 11; Advance, Eclipse) X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Stimulated		X (ref. 39; (2 nonnicotine cigarettes with different levels of tar)	
Reduce hunger		X (ref. 11; Advance, Eclipse) X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Make you sick		X (ref. 11; Advance, Eclipse)	
Enjoyment of respiratory tract sensations			X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes)
Intensity of respiratory tract sensations			X (ref. 33; low-nicotine-content cigarettes and conventional highly ventilated filter cigarettes)
Dizziness		X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	X (ref. 40; 5 cigarettes with different levels of nicotine) X (ref. 19; denicotinized and nicotinized cigarettes)
Light-headed			X (ref. 40; 5 cigarettes with different levels of nicotine)
Felt high			X (ref. 40; 5 cigarettes with different levels of nicotine) X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen)

(Continued on the following page)

Table 2. Items that showed a positive finding in PREP evaluation studies by product used (Cont'd)

	Placebo vs. PREP	Usual brand vs. PREP	Differences across PREPs
Less intensity of drug effect		X (ref. 43; Marlboro UltraSmooth, Marlboro Ultra Lights)	
Salivation	X (ref. 44; 4 brands of moist snuff vs. a non-tobacco mint snuff)	X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes) X (ref. 20; clinical component of study: Stonewall, General Snus)	
Aim 3: product evaluation Scale item			
Less flavorful		X (ref. 40; 5 cigarettes with different levels of nicotine) X (ref. 9; 5 cigarettes with progressively lower nicotine levels)	
Intensity of flavor			X (ref. 39; 2 nonnicotine-cigarettes with different levels of tar)
Tobacco pack		X (ref. 20; lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus)	
How well packed	X (ref. 44; 4 brands of moist snuff vs. a nontobacco mint snuff)		
Strength	X (ref. 44; 4 brands of moist snuff vs. a non-tobacco mint snuff)	X (ref. 20; lab component of study: Stonewall, General Snus; clinic component of study: Stonewall, General Snus) X (ref. 21; Next denicotinized cigarettes, Winston Lights) X (ref. 9; 5 cigarettes with progressively lower nicotine levels)	X (ref. 24; Ariva, Stonewall, Revel, nicotine lozenge, Copenhagen) X (ref. 42; Quest cigarettes)
Less strong		X (ref. 45; Accord, Oasis, Marlboro Ultra)	
Weaker		X (ref. 40; 5 cigarettes with different levels of nicotine)	
Milder		X (ref. 21; Next denicotinized cigarettes, Winston Lights)	
More smoke than air		X (ref. 45; Accord, Oasis, Marlboro Ultra)	
More difficult to draw from		X (ref. 40; 5 cigarettes with different levels of nicotine)	X (ref. 41; denicotinized and nicotinized cigarettes)
Smoother		X (ref. 45; Accord, Oasis, Marlboro Ultra)	
Less smooth			
Harshness			X (ref. 39; 2 nonnicotine cigarettes with different levels of tar)
Poorer/lower quality		X (ref. 40; 5 cigarettes with different levels of nicotine) X (ref. 9; 5 cigarettes with progressively lower nicotine levels)	
Less nicotine		X (ref. 40; 5 cigarettes with different levels of nicotine)	
Amount swallowed		X (ref. 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 (ref. 11; Advance, Eclipse)	

(Continued on the following page)

Table 2. Items that showed a positive finding in PREP evaluation studies by product used (Cont'd)

	Placebo vs. PREP	Usual brand vs. PREP	Differences across PREPs
Do the cigarettes feel like your usual brand?		X (ref. 18; Ariva, Marlboro Snus, Camel Snus, nicotine lozenge, Quest cigarettes)	
Do the cigarettes feel as mild as your usual brand of cigarette?		X (ref. 11; Advance, Eclipse)	
Heaviness			X (ref. 39; 2 nonnicotine cigarettes with different levels of tar)

and usual brand, and found that subjects rated their usual brand higher on items that measured "cigarette strength" and "more smoke than air" compared with the other conditions (21). The subjects' usual brand was also rated more favorably compared with two 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 involving seven 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 with 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 conditions 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, followed by usual brand, then General snus.

Another clinic study using four 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 clinical 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 (24) and three laboratory studies that used modified cigarettes (39, 41, 42) found differences in subject ratings of PREPs with regard to product characteristics. For example, compared with ST

PREPs, Copenhagen was rated as strongest among ST users (24). In a laboratory study of two nonnicotine cigarettes with differing amounts of tar, subjects gave higher ratings for harshness, heaviness, and intensity of flavor to the high-tar versus the low-tar cigarette (39). In another laboratory study, subjects rated nicotine cigarettes higher in smoothness compared with denicotinized cigarettes (41). Alternatively, in different laboratory studies, there was no significant difference on measures of product characteristics in three 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 three 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 refs. 9, 11, 18-20, 29, 39). In general, the scales or items measuring these effects seem to be sensitive in showing differences between the placebo or no-tobacco conditions and a PREP. Furthermore, the usual brand is more highly rated or rated similarly to PREPs (greater liking, stimulatory or central nervous effects, and greater strength or quality). The scales or items also distinguish between PREP products, with products having higher nicotine content rated more highly than products with lower nicotine content, with the exception of scales measuring product evaluations where the results are equivocal.

Items that showed a significant difference between PREPs compared with a placebo, usual brand, or other PREPs were examined in terms of the three aims for using the scales in PREP studies. It may be worthwhile including these items 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 in at least one study 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 among PREPs, usual brand, and 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 in at least one study 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 the characteristics of the product. The following items were most often significantly different among PREPs, usual brand, and 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 in at least one study were the following: 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 being tested.

Scales to evaluate responses to tobacco products are still at 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) with Marlboro Ultra Lights in 48-hour conditions, low subjective ratings for Marlboro UltraSmooth seemed to be associated with low levels of exposure (43). In another laboratory study conducted among ST users designed to assess nicotine levels and the physiologic and subjective effects of ST products, including Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits or nontobacco mint snuff, increases in the rating of product strength showed an association with plasma concentration during the first 10 to 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 seem to measure withdrawal symptoms and craving effectively. The scales are able to detect decreases in withdrawal symptoms and craving, differences between PREP product and usual

brand cigarettes or between PREP products based on nicotine content of the product. This review also showed that when studies used more than one scale, the results revealed 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. The second most used scale, the QSU, yields two factors, intention to smoke (factor 1) and anticipation of relief from withdrawal (factor 2), which provides a more thorough examination of urges to smoke. Therefore, at a minimum, these two 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 from a modified cigarette product with high levels of nicotine.

Another key area for 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 to lead to addiction, and the difficulty consumers may experience when trying to stop using the product.

When considering the three primary areas of tobacco product evaluation, most laboratory and clinical studies reported that when comparing PREPs with placebo or no tobacco condition or with the subjects' usual brand cigarettes, the results are in the anticipated direction; generally PREPs are rated more highly than placebo and usual brand more highly than PREPs. 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, assessing the three primary areas of tobacco product evaluation is critical. Development and validation of a product scale that measures these three 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 are important pieces of information to ascertain, particularly for novel designs. Validation of these scales can include examining how effective the scales are in predicting the amount of product self-administered,

product choice, and discrimination across products with different nicotine yields or sensory properties, sustained use of the product, and potential dependence and abstinence effects from the product. Future studies can also examine product marketing, messaging, and labeling, price, social norms, and attitudes towards the product effect responses to these scales.

The determination of the validity of these scales, which is the relationship between subjective responses to actual use, is a critical area of research. In addition, the 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 nontobacco 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 nicotine 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 Food and Drug Administration 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 the protection of public health.

Disclosure of Potential Conflicts of Interest

Dorothy Hatsukami received grant funding from Nabi Biopharmaceuticals to evaluate the nicotine vaccine. No other potential conflicts of interest were disclosed.

Acknowledgments

We thank Dr. Mark Parascandola for his valuable comments on the manuscript.

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