Effect of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study

Michael Kotlyar,1-3 Louise A Hertsgaard,1 Bruce R Lindgren2, Joni A Jensen,1 Steven G Carmella,1,2 Irina Stepanov,2 Sharon E Murphy,1,2 Stephen S Hecht1,2 Dorothy K Hatsukami,1,2

University of Minnesota

1University of Minnesota Tobacco Use Research Center, 2University of Minnesota Masonic Comprehensive Cancer Center, 3Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota

Please address correspondence to:

Dorothy K. Hatsukami, 717 Delaware St. SE, Minneapolis, MN 55414, USA. E-mail: hatsu001@umn.edu.

Acknowledgements: This study was funded by P50 DA01333 and K23DA017307

We would like to thank Aleksandar Knezevich for technical support

Clinical Trials.gov #: NCT00469079

Running Title: Oral Snus effects on Toxicant Exposure
Key Words: Smokeless tobacco, medicinal nicotine, biomarkers, craving, withdrawal

ABSTRACT

**Background:** Smokeless, spitless tobacco products are being introduced and marketed as cigarette substitutes. Data are needed regarding how smokers interested in cessation would use these products, the levels of resultant toxicant exposure and the feasibility of using these products as aids for tobacco cessation.

**Methods:** Smokers were randomized to receive Camel Snus (n=51), Taboka (n=52) or medicinal nicotine (n=27) and required to quit smoking for 4 weeks. Measures of toxicant exposure and symptoms of craving and withdrawal were assessed prior to and during product use.

**Results:** Concentrations of exhaled carbon monoxide, urinary cotinine, urinary total NNAL and urinary total NNN were significantly (p values <0.05) lower at the end of treatment in each group except for total NNN in those receiving Camel Snus (p=0.066). A significant group x time effect was observed for total NNAL concentrations (p=0.002) with the decrease greatest in the medicinal nicotine group and smallest decrease in the Camel Snus group. No significant differences between groups were found in craving and withdrawal symptoms.

**Conclusions:** Enrolling smokers into a cessation study utilizing newer smokeless tobacco products is feasible. Camel Snus and Taboka use was not found to be superior to medicinal nicotine in reducing withdrawal symptoms but decreases in NNAL were smaller in users of Camel Snus.

**Impact:** This study demonstrates the feasibility of conducting a smoking cessation study utilizing these newer tobacco products. An appropriately powered study is needed assessing
smoking cessation rates using these newer products compared with established, safer products such as medicinal nicotine.
INTRODUCTION

The use of smokeless tobacco as a substitute for cigarette smoking has been suggested by some since it is considered to be a less harmful tobacco product (1-4). Smokeless tobacco lacks the toxicants associated with combustion and data suggest that for an individual, there is less risk of disease (e.g. cardiovascular disease, lung disease) compared with continued smoking (5). Additionally, secondhand smoke risks are eliminated when smokeless tobacco is used.

Smokeless tobacco products however are not harmless. Swedish moist snuff (i.e. snus) contains lower levels of carcinogens than most other brands of moist snuff but even these products have been found to contain nitrosamines (5, 6) and use of these products has been associated with increased risk of pancreatic cancer (7, 8). Some studies have suggested that use of Swedish snus also may be associated with a higher risk of oral or gastroesophageal cancer and cardiovascular disease (9-11).

In recent years, a number of spitless, smokeless tobacco products have been introduced in the United States. These products are among those broadly referred to as “potential reduced exposure tobacco products” (PREPs) or modified risk tobacco products (a term used in the U.S. Family Smoking Prevention and Tobacco Control Act) and are often marketed to be used when smoking bans prevent cigarette use or as a substitute for cigarettes. While dual use of oral tobacco and cigarettes may not significantly reduce exposure to toxicants, a complete switch to oral tobacco products may have promise for reducing individual risk for disease. Furthermore, some researchers have indicated that smokeless tobacco may be more effective for smoking cessation than the currently available products, particularly among smokers who have been unsuccessful in the past (12, 13). A cross-sectional survey of Norwegian men found that smoking cessation rates were higher for those who used snus compared to those who used...
nicotine gum but a larger proportion of snus users (relative to medicinal nicotine users) reporting continued long-term use (14). Large scale prospective studies are needed to determine if these products may be useful as aids to smoking cessation, particularly since there is the concern that these products may in fact undermine the smoking cessation attempt.

The goal of the current study is to determine if smokers interested in cessation would be willing to enroll in and complete a study in which they are required to switch to these newer products. This would determine the feasibility of conducting a larger study assessing smoking cessation. Since there is relatively little published data regarding these newer products, additional goals of this study were to evaluate extent of exposure to selected toxicants and severity of craving and withdrawal symptoms following the use of the smokeless tobacco products Camel Snus (produced by RJ Reynolds) and Taboka (produced by Phillip Morris, no longer on the market). These products are pasteurized rather than fermented, leading to lower tobacco specific nitrosamine levels, and they contain less moisture to eliminate spitting (15). These two products were selected since they have substantially different amounts of free nicotine and therefore may be used in different ways by smokers, with Camel Snus having higher amounts of nicotine than Taboka (15). Nicotine replacement therapy was included in this study as a comparison condition since it has proven efficacy in assisting smoking cessation and has few adverse health effects.

METHODS

Subjects

Cigarette smokers in generally good health between the ages of 18 and 70 who were interested in quitting smoking were recruited via advertisement. To be eligible, potential study
participants must have reported smoking an average of at least 10 cigarettes per day for at least one year. Subjects were excluded if they a) had uncontrolled or unstable medical or psychiatric conditions or conditions that would require medical attention during the course of the study; b) reported current or recent (within 6 months) alcohol or drug abuse; c) had any contraindications for nicotine replacement therapy; d) were using any medication that could interact with the products being tested or could affect the outcomes of interest in this study; or d) regularly used tobacco products other than cigarettes.

Study Design

Subjects were first screened via telephone to determine interest in participation and initial eligibility. Those interested and determined likely to qualify were invited to attend an orientation meeting where the study was explained in greater detail, informed consent was obtained and full screening evaluation occurred to ensure subject eligibility. Eligible subjects who were interested in continuing with the study were then asked to continue smoking at their normal rate for a two week period during which baseline measurements were obtained.

At the end of the two weeks of baseline data collection, smokers were randomly assigned to one of three conditions: a) quit smoking using either the 4 mg nicotine gum or 4 mg lozenge (subjects were given a choice of these products prior to assignment); b) switch to Camel Snus; or c) switch to Taboka. During a one week sampling period, smokers were given their assigned product and asked to use it as a substitute for smoking at times of their choosing but to use the product at least 1 to 2 times per day. Those assigned to nicotine replacement were given the choice of receiving the mint flavor of either nicotine gum or nicotine lozenge, those assigned to Taboka were given the choice of either Green (mint) or Regular flavor and those assigned to Camel Snus were given the choice of either Original, Frost or Spice flavor. Subjects were free to
choose either one flavor or a combination of flavored versions of each product at each study visit.

Taboka supplies for the study were purchased on three occasions (10/2006, 8/2007, 10/2007) in Indianapolis, IN. Camel Snus was purchased as needed every 1 to 2 months between 10/2006 and 10/2008 from Austin, Texas. Camel Snus was modified in June 2008 at which time the amount of nicotine and tobacco in each pouch increased, therefore subjects who received supplies after that point received the new formulation. Seventeen of the subjects receiving Camel Snus had completed the study by this point and therefore used the older formulation exclusively.

After the 1 week sampling period, smokers quit smoking cigarettes and used only their assigned product. During the 4 week intervention period, subjects were told to use their assigned product at least every 2 hours (i.e. a minimum of 6 to 8 doses per day) and to use additional doses when necessary. Starting in the 5th week following smoking cessation, subjects gradually reduced the amount of product used such that by the end of that week they would completely discontinue use of all nicotine and tobacco products.

Subjects were seen at weekly clinic visits during the study starting with the first baseline visit until the 1 week post cessation visit that occurred after subjects quit all nicotine and tobacco products (i.e. week 6 in Figure 1). An additional visit occurred 11 weeks after tobacco and nicotine cessation to determine smoking status. At each visit, subjects received standardized brief behavioral-supportive counseling of 10 minutes duration, first to prepare for smoking cessation and then to support use of the study products and finally to stop the use of all tobacco and nicotine products. Counseling was performed by an individual trained in tobacco cessation counseling and was based on topics suggested in the National Cancer Institute’s “Clearing the
Air” manual including identifying high risk situations for smoking and developing tools to deal with these situations. The counselor was not blind to the treatment assigned to the subject.

**Outcome measures**

Use of study products and cigarettes was determined by subject daily diaries which were reviewed at each of the weekly study visits. Subjects were encouraged to use only study products after the sampling week but were told that it is crucial for the study that they report use of any non-study products. They were not penalized for use of such products.

Exhaled carbon monoxide (CO) was measured at every visit using a Bedfont Micro Smokerlyzer® (Bedfont Scientific Limited, Kent, UK). Urinary cotinine (a metabolite of nicotine) was measured at baseline, during product use (i.e. weeks 2 and 4) and during follow-up. For purposes of analysis, baseline cotinine concentration was calculated using the measure obtained at the first visit (i.e. baseline 1 in Figure 1) since a subject’s smoking behavior is likely to start changing during the week prior to cessation (i.e. in anticipation of cessation). Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), which are metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were measured at baseline and during product use at weeks 2 and 4 (Figure 1) (16). Urinary $N'$-nitrosonornicotine and its glucuronide (total NNN), which are metabolites of the tobacco-specific carcinogen $N'$-nitrosonornicotine were measured at baseline and during product use at week 4 (Figure 1) (17).

Tobacco craving and withdrawal symptoms were measured at each visit using the Minnesota Nicotine Withdrawal Scale, which asked subjects to rate several withdrawal symptoms (i.e. craving, irritability / anger, anxiety / tension, difficulty concentrating, restlessness, impatience, problems with sleep, increased appetite, drowsiness, depressed mood) on a scale from 0 (i.e. not
present) to 4 (i.e. severe) (18, 19). This scale has been used in other studies examining withdrawal signs and symptoms from cigarettes, nicotine gum and smokeless tobacco (19-24).

**Statistical Analysis**

Baseline characteristics, including demographics and smoking history, were summarized by treatment groups. The three groups were compared by Fisher’s exact test for categorical variables and the non-parametric Kruskal-Wallis test for continuous variables. The baseline value of the outcome variables were measured on two consecutive weeks. The value from the first baseline week was used in the analysis, if available; otherwise the second baseline value was used. For biomarker concentrations below the lower limit of detection, a value of one-half of the lower level of detection was used (this occurred for 9% of the NNAL samples and 14% of NNN samples). A generalized linear mixed model was used for outcomes that had been repeatedly measured from baseline through the end of the treatment period. This model includes cases with missing data points due to dropouts or missed visits. As a result, all available data from each subject is included in the analysis. Each repeated measures model included the treatment effect, a visit effect, the interaction between treatment and visit, the between subject error and the within subject error terms. The variance/covariance structure for the data was estimated using restricted maximum likelihood (REML). The p-values reported for multiple comparisons were unadjusted. Due to a very skewed distribution to high values, the biomarkers total NNAL, total NNN and cotinine were analyzed in the natural logarithmic scale. The geometric means in the original units were used for constructing the graphs for these biomarkers. In addition to the drop-out rates, the 7 day point prevalence abstinence at end of treatment and at follow-up visits and the continuous abstinence rate (no smoking during the 4 week treatment period) were
compared between groups using Fisher’s exact test. SAS version 9.1 (SAS institute Inc., USA) was used for all analyses. A p-value < 0.05 indicated statistical significance.

RESULTS

Subjects

A total of 1159 smokers responded to advertisements placed to solicit interest in the study. The advertisements specifically stated that the study was assessing use of oral tobacco products and the study was described to subjects during that first phone call. Of the 801 subjects who were able to be reached and were screened over the telephone, 372 either did not qualify for the study or were not interested in participating. Of the 429 scheduled for orientation, 212 did not show up to the orientation meeting. Only 2 subjects volunteered that they were not interested in the study because they were not interested in using oral tobacco products, however this information was not systematically solicited from subjects.

A total of 217 subjects attended the orientation session of which 211 subjects were enrolled in the study and 130 were randomized to treatment (51 to Camel Snus; 52 to Taboka and 27 to nicotine replacement). One hundred twenty six subjects completed the one week sampling period and eighty subjects completed the 4 weeks of product use and 1 week taper period. Seventy-eight subjects completed the follow up period. The number of subjects dropping out of the study at various time-points and the reasons given are illustrated in Figure 2. No significant differences in drop-out rates were observed among the groups. The baseline demographics of the subjects are summarized in Table 1. There were no significant differences found among the groups except for score on the Fagerstrom Test for Nicotine Dependence (FTND) (p<0.01). Mean baseline FTND score in those receiving medicinal nicotine was 5.2 compared to 3.8 in
those randomized to Taboka and 4.4 in those randomized to Camel Snus. There were no significant differences in demographics between subjects who dropped out of the study after randomization and those who completed the entire study except in the number of previous quit attempts reported. The median number of quit attempts for completers was 5 and, for those who dropped out, it was 3 (p=0.013). Additionally, within each of the 3 groups, FTND score and number of cigarettes smoked were similar between those who completed the study and those who did not. FTND scores in those who completed the study were 4.4 ± 1.6 for those assigned to Camel Snus, 4.1 ± 1.3 for those assigned to Taboka and 5.1 ± 1.1 for those assigned to medicinal nicotine. For those who did not complete the study, FTND scores were 4.3 ± 1.6, 3.5 ± 0.8 and 5.2 ± 1.6 respectively. Cigarettes smoked per day for those who completed the study were 19.9 ± 6.4 for those assigned to Camel Snus, 19.1 ± 7.1 for those assigned to Taboka and 22.8 ± 8.3 for those assigned to medicinal nicotine. For those who did not complete the study, cigarettes smoked per day were 19.3 ± 3.5, 20.8 ± 4.4 and 25.2 ± 9.0 respectively.

**Product use during treatment**

For subjects receiving Taboka, 10% chose to use the Regular flavor exclusively, 33% chose the Mint flavor and the rest used both flavors. For subjects receiving Camel Snus, 16% used 1 flavor exclusively (i.e. Frost or Regular), 38% used the same 2 flavors throughout and 47% used multiple flavors. In those receiving medicinal nicotine, 44% chose to use the gum exclusively, 22% chose to use the lozenge exclusively and the rest used both products.

The average amount of assigned product and regular cigarettes used at baseline and during the treatment period is illustrated in Figure 3 (panels A and B). There was a significant group effect found for amount of product used (p=0.012) with smokers assigned to Taboka using fewer doses
per day than those assigned to either Camel Snus or medicinal nicotine. At the week 4 treatment visit, those assigned to Taboka used significantly less product and smoked significantly more of their usual brand cigarettes than those assigned to either of the other two conditions (all p values <0.05). The percentage of subjects smoking on average more than 3 cigarettes per day during the treatment weeks was 9.1% in the Camel Snus group, 13.6% in the medicinal nicotine group but 26.8% in the Taboka group. Fewer doses of Taboka (than of the other two products) were also used among subjects who reported being abstinent from cigarettes during weeks 2, 3 and 4 of the treatment period, although this difference did not reach statistical significance (6.9 pouches of Camel Snus per day vs. 5.8 pouches of Taboka per day vs. 7.4 pieces of medicinal nicotine per day; p=0.052).

**Effects of products on biomarkers of exposure**

Concentrations of exhaled CO, urinary cotinine, total NNAL and total NNN at baseline and during treatment are illustrated in Figure 4, panels A – D. Significant time effects were seen for all four biomarkers (all p values < 0.001). Concentrations of each of the biomarkers were significantly (all p values <0.05) lower at the end of treatment (i.e. week 4) compared to concentrations measured at baseline in each of the three treatment groups for all measures except for urinary NNN concentrations in those receiving Camel Snus (p=0.066). There were no significant group effects for any of the biomarkers measured, however a significant group x time effect was observed for urinary total NNAL concentrations (p=0.002). Thus, the decrease in total NNAL during treatment was greatest for those receiving NRT and smallest for those receiving Camel Snus. Analyzing biomarkers only in subjects who were abstinent from cigarettes at weeks 2 to 4 resulted in similar results for most biomarkers, however for total
NNAL there was a significant group effect (p=0.05) with a significant difference found between the Camel Snus and medicinal nicotine group (i.e. total NNAL concentrations were higher in the Camel Snus group) (p=0.032). The group x time interaction continued to be significant for total NNAL (p<0.001).

Effects of study products on craving and withdrawal symptoms

Nicotine craving and withdrawal symptom scores are illustrated in Figure 3 (panels C and D). Changes in craving and withdrawal symptoms were assessed at the time of discontinuation of usual brand cigarettes (i.e. baseline compared to week 1) and overall craving and withdrawal symptoms scores during treatment were compared. Upon discontinuation of cigarette smoking, significant increases in withdrawal symptoms were observed in the Camel Snus and Taboka groups (Camel Snus p=0.010; Taboka p=0.028; NRT p=0.113) while craving did not increase significantly in any of the groups (p>0.1). No significant differences in magnitude of symptom change were found among the groups (Craving p=0.492; Withdrawal p=0.971). Overall craving and withdrawal scores decreased during the 4 weeks of treatment (significant time effect for both measures; p<0.001), with no differences observed among the groups in either the overall levels of craving and withdrawal (no significant group effect for either measure) or in changes in craving or withdrawal symptoms during the treatment period (no significant group x time effects for either measure). Similar results were found when craving and withdrawal symptoms were analyzed only in those subjects who were abstinent from cigarettes at weeks 2 to 4.

Abstinence
This study was not powered to detect differences in smoking cessation rates between groups; however smoking status was collected at each visit to obtain preliminary data. Point prevalence (no smoking during the previous 7 days) cigarette abstinence rates were calculated at the week 4 visit and at each of the two follow up visits. Continuous abstinence rates were calculated for the four week period between the week 1 and week 4 visits. Abstinence at all visits was assessed by self-report (i.e. no cigarettes smoked) and confirmed by an exhaled CO of < 8 ppm. At the follow-up visits, abstinence was also confirmed by both exhaled CO concentrations and urinary cotinine concentration (< 35 ng/ml). One subject in whom exhaled CO data were missing but urinary cotinine was < 35 ng/ml was counted as abstinent. Since subjects used nicotine containing products during the treatment period, cotinine-confirmed abstinence rates were not calculated for those visits. No significant differences in abstinence rates were seen between groups at any of time-points calculated (table 2). Analyzing only subjects still remaining in the study after the sampling period (i.e. smokers interested in the products) resulted in similar results with no significant differences in quit rates found among groups. At the 1 week follow-up visit, NRT use was reported by 4 subjects in the Camel Snus group, 3 subjects in the Taboka group and 13 subjects in the NRT group. At the week 11 follow-up visit, NRT use was reported by 3 subjects in the Camel Snus group, 4 subjects in the Taboka group and 6 subjects in the NRT group. Five subjects reported oral tobacco use during the follow-up period (2 subjects in the Camel Snus group and 3 subjects in the Taboka group).

**DISCUSSION**

This study found that enrolling smokers in a cessation study utilizing newer smokeless tobacco products is feasible. The proportion of subject dropping out in those assigned to one of
two smokeless tobacco products (i.e. Camel Snus, Taboka) was similar to the proportion assigned to medicinal nicotine and the overall drop-out rate during the treatment period was comparable to other smoking cessation studies (25, 26). Although many of those who initially responded to advertisements did not subsequently enroll in the study, many of the reasons for not enrolling were not reasons that suggest a resistance to using the study products (e.g. some could not be reached by telephone, others did not meet inclusion / exclusion criteria). Overall, this study therefore found smokers were willing to enroll and complete a cessation study which used the newer tobacco products and did not find that smokeless tobacco was superior to nicotine replacement in decreasing craving or withdrawal symptoms; however nicotine replacement use resulted in larger decreases in total NNAL than Camel Snus.

Differences in how the three products were used may be related to the amount of nicotine in each of the products. Subjects used significantly fewer doses of Taboka than either Camel Snus or the nicotine replacement product. A recent study found that Taboka had 0.844 – 1.26 mg free (unprotonated) nicotine / gram dry weight and 19.9 – 21.1 mg total nicotine / gram dry weight, whereas Camel Snus had 6.09 – 9.16 mg free nicotine / gram dry weight and 23.7 – 28.2 mg total nicotine / gram dry weight (15). Products with similar amount of nicotine as Taboka (e.g. Revel) have been found to result in lower plasma nicotine concentrations than the nicotine lozenge (5, 27). Therefore, the nicotine concentrations obtained from Taboka may not have been sufficient to maintain product use. Very low nicotine cigarettes, or nicotine free cigarettes, have shown promise as potential aids for cessation but it is not clear that low nicotine smokeless products would be equally effective (28-30). Unlike the extra low nicotine or nicotine free cigarettes, low nicotine smokeless products are likely not as effective at substituting for the sensory and behavioral aspects of smoking. This is consistent with the finding that during the last week of
treatment those receiving Taboka smoked significantly more of their usual brand cigarettes than those assigned to either of the other two treatments. Our study therefore suggests that for smokeless products to be effective at substituting for cigarettes, nicotine concentrations likely have to surpass a certain threshold. Quit rates for Camel Snus were comparable to those obtained with nicotine replacement therapy, therefore a properly powered study is needed to determine if use of smokeless tobacco products with higher nicotine content can be an effective path to smoking cessation, perhaps especially among smokers who are not interested in or previously were not successful with using approved pharmacotherapies.

This study addressed the issue of whether switching smokers to smokeless tobacco offers any advantages relative to switching to medicinal nicotine. In the various outcomes assessed (i.e. craving, withdrawal symptoms, toxicant concentrations), no clear advantages were found for smokeless tobacco over medicinal nicotine. Previous studies similarly found few differences in subjective measures after use of a single dose or repeated doses of some of the newer smokeless tobacco products vs. nicotine lozenge and have shown no significant increases in craving after switching from cigarettes to medicinal nicotine or other newer products (27, 28, 31). However, studies assessing these measures are relatively small and may not be able to detect small differences between groups. In measures of toxicant exposure, switching to medicinal nicotine resulted in lower levels of NNAL than switching to one of the smokeless tobacco products. This is consistent with other studies demonstrating that many of the newer smokeless tobacco products, although having lower levels of toxicants than cigarette smoke, are not toxicant free (6, 15, 31-33). The lack of significant differences among groups in total NNN exposure was perhaps due (at least in part) to endogenous NNN production (from nicotine) in those receiving medicinal nicotine (34, 35). Further research is needed to determine the extent to which this
occurs. This study therefore suggests that for smokers interested in quitting, medicinal nicotine should be the first option recommended and barriers to medicinal nicotine use should be identified and removed if possible.

Several limitations are present in the current study. Smokeless tobacco products commercially available in the United States have been introduced, withdrawn or changed at a relatively rapid rate. As a result, one of the products tested in the current study (Taboka) is no longer commercially available and changes to the other product (Camel Snus) occurred during the time period that the study occurred. Nonetheless, the study provides important information regarding the feasibility of conducting studies with these products and information regarding toxicant exposure during their use. Lack of commercial availability of these products for most of the subjects during the follow-up period precludes evaluating if and how smokers introduced to these products would use them in a natural setting once these products were no longer provided by the study. An additional limitation is that in the measurement of toxicant exposure, it is not known how much of the exposure was contributed by the study products as compared to cigarettes that subjects were smoking during the study (i.e. since the amount of product used and the amount smoked differed significantly between groups). A strength of this approach, however, is that it more closely resembles toxicant exposure when these smokers are given these products in the natural environment. Furthermore, when examining smokers who were verified to be abstinent, those assigned to Camel Snus continued to have higher toxicant exposure compared to those assigned to medicinal nicotine. It should be noted that the results of this study are limited in applicability only to smokers who are interested in quitting smoking and willing to use nicotine replacement therapy. It is not known how these products would compare in smokers not
interested in cessation or smokers interested in cessation but not interested in using nicotine replacement therapy. Future studies are needed to address these issues.

In summary, this study demonstrated that smokers interested in quitting smoking were willing to enroll in and complete a study evaluating the newer smokeless tobacco products. Additionally, this study did not find that the “modified risk” smokeless tobacco products tested were superior to medicinal nicotine in decreasing subjective measures (i.e. craving, withdrawal) but resulted in greater exposure to one of the toxicants assessed. Further studies are needed to definitively determine if these products are effective at increasing cessation rates and to determine how smokeless tobacco products might be used in smokers not immediately interested in smoking cessation.
REFERENCES


Figure Legends

Figure 1: Diagram of the study design.

Figure 2: Flow of subjects through the study

Figure 3: Least squares (LS) mean (±SE) of amount of study product used per day (Panel A), number of cigarettes smoked per day (Panel B), craving (Panel C) and withdrawal symptoms (Panel D).

Figure 4: Least squares mean (±SE) of exhaled carbon monoxide concentrations (Panel A), Geometric Mean (95% confidence interval) of total cotinine (ng/mL) (Panel B), of total NNAL (pmol / mg creatinine) (Panel C) and of total NNN (pmol / mg creatinine) (Panel D).
211 signed informed consent form

130 smokers randomized

51 assigned Camel Snus
- 2 No Show
  - 1 Personal reason
- 48 completed sample week
- 5 No Show
  - 1 Personal reason
  - 1 Inefficacy
  - 2 Adverse events (HBP)
  - 1 Product dissatisfaction
- 40 completed 2 weeks of treatment period
- 5 No Show
  - 2 Inefficacy
- 32 completed 4 week treatment + taper week
- 2 No Show
- 30 completed follow-up period

52 assigned Taboka
- 1 No show
- 51 completed sample week
- 5 No show
  - 2 Personal reasons
  - 1 Inefficacy
  - 4 Product dissatisfaction
  - 1 ineligible miscellaneous
  - 3 Adverse events (2 mouth sores, 1 heartburn)
- 35 completed 2 weeks of treatment period
- 2 No Show
  - 3 Inefficacy
- 30 completed 4 week treatment + taper week
- 30 completed follow-up period

27 assigned nicotine replacement
- 27 completed sample week
- 4 No show
  - 1 Inefficacy
  - 2 Product dissatisfaction
- 4 No Show
- 1 Personal reason
- 1 Inefficacy
- 2 Adverse events (HBP)
- 1 Product dissatisfaction
- 32 completed 4 week treatment + taper week
- 1 Personal reason
  - 1 Adverse event (mouth sores)
- 18 completed 4 week treatment + taper week
- 18 completed follow-up period

40 lost to follow-up
- 14 ineligible
- 24 not interested / personal
- 3 don’t want to use oral tobacco

30 completed follow-up period

103 completed 2 weeks of treatment period

30 completed follow-up period

18 completed 4 week treatment + taper week

18 completed follow-up period
Table 1: Baseline demographics of subjects

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Camel Snus (n=51)</th>
<th>NRT (n=27)</th>
<th>Taboka (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>51 43.6±11.5</td>
<td>27 42.4±12.8</td>
<td>52 42.4±11.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Female</td>
<td>20 39.20%</td>
<td>12 44.40%</td>
<td>21 40.40%</td>
<td>0.92</td>
</tr>
<tr>
<td>Caucasian</td>
<td>44 86.30%</td>
<td>24 88.90%</td>
<td>40 76.90%</td>
<td>0.45</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Some high school</td>
<td>0 0%</td>
<td>1 3.70%</td>
<td>0 0%</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>15 29.40%</td>
<td>7 25.90%</td>
<td>13 25.00%</td>
<td></td>
</tr>
<tr>
<td>Some college/2-year degree</td>
<td>24 47.10%</td>
<td>15 55.60%</td>
<td>25 48.10%</td>
<td></td>
</tr>
<tr>
<td>College graduate/4-year degree</td>
<td>10 19.60%</td>
<td>3 11.10%</td>
<td>11 21.20%</td>
<td></td>
</tr>
<tr>
<td>Graduate / Professional</td>
<td>2 3.90%</td>
<td>1 3.70%</td>
<td>3 5.80%</td>
<td></td>
</tr>
<tr>
<td>Cigarettes per day (mean ± SD)</td>
<td>51 19.7±5.3</td>
<td>27 23.6±8.5</td>
<td>52 19.8±6.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Age becoming a regular smoker (yrs)</td>
<td>50 17.0±2.9</td>
<td>27 17.4±3.2</td>
<td>51 17.1±3.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Number of quit attempts (mean ± SD)</td>
<td>51 6.9±6.1</td>
<td>27 6.4±6.7</td>
<td>52 7.3±14.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Motivation to quit (0-10 scale) (mean ± SD)</td>
<td>51 9.3±1.0</td>
<td>27 9.2±1.0</td>
<td>52 8.6±1.8</td>
<td>0.1</td>
</tr>
<tr>
<td>FTND Score (mean ± SD)</td>
<td>50 4.4±1.6</td>
<td>25 5.2±1.2</td>
<td>52 3.8±1.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Table 2: Abstinence rates at follow-up

**Continuous Abstinence (weeks 1 – 4)**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Snus (n=51)</th>
<th>Taboka (n=52)</th>
<th>NRT (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td># abstinent</td>
<td>%</td>
<td># abstinent</td>
<td>%</td>
</tr>
<tr>
<td>22</td>
<td>43.1</td>
<td>17</td>
<td>32.7</td>
</tr>
<tr>
<td>14</td>
<td>27.5</td>
<td>15</td>
<td>55.6</td>
</tr>
</tbody>
</table>

1CO Verified

<table>
<thead>
<tr>
<th>Visit</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>29</td>
<td>56.9</td>
<td>22</td>
<td>42.3</td>
<td>15</td>
<td>55.6</td>
<td>0.299</td>
</tr>
<tr>
<td>Week 6 (1 week follow-up)</td>
<td>24</td>
<td>47.1</td>
<td>20</td>
<td>38.5</td>
<td>15</td>
<td>55.6</td>
<td>0.349</td>
</tr>
<tr>
<td>Week 16 (11 weeks follow-up)</td>
<td>16</td>
<td>31.4</td>
<td>12</td>
<td>23.1</td>
<td>9</td>
<td>33.3</td>
<td>0.537</td>
</tr>
</tbody>
</table>

**CO Verified Point Prevalence Abstinence**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Snus (n=51)</th>
<th>Taboka (n=52)</th>
<th>NRT (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td># abstinent</td>
<td>%</td>
<td># abstinent</td>
<td>%</td>
</tr>
<tr>
<td>20</td>
<td>38.5</td>
<td>17</td>
<td>32.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 (1 week follow-up)</td>
<td>14</td>
<td>27.5</td>
<td>12</td>
<td>23.1</td>
<td>8</td>
<td>29.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Week 16 (11 weeks follow-up)</td>
<td>10</td>
<td>19.6</td>
<td>7</td>
<td>13.5</td>
<td>4</td>
<td>14.8</td>
<td>0.712</td>
</tr>
</tbody>
</table>

**CO and Cotinine Verified Point Prevalence Abstinence**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Snus (n=51)</th>
<th>Taboka (n=52)</th>
<th>NRT (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td># abstinent</td>
<td>%</td>
<td># abstinent</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>32.7</td>
<td>11</td>
<td>29.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th># abstinent</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 (1 week follow-up)</td>
<td>14</td>
<td>27.5</td>
<td>12</td>
<td>23.1</td>
<td>8</td>
<td>29.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Week 16 (11 weeks follow-up)</td>
<td>10</td>
<td>19.6</td>
<td>7</td>
<td>13.5</td>
<td>4</td>
<td>14.8</td>
<td>0.712</td>
</tr>
</tbody>
</table>
Effects of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study

Michael Kotlyar, Louise A Hertsgaard, Bruce R Lindgren, et al.

Published OnlineFirst November 10, 2010.

doi: 10.1158/1055-9965.EPI-10-0349

Access the most recent version of this article at:

doi: 10.1158/1055-9965.EPI-10-0349

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.