Nicotine Exposure and Subject Response Following Use of Two Smokeless, Spitless Tobacco Products and Medicinal Nicotine

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Abstract

Introduction: With smoking restrictions becoming increasingly common in the United States, alternative tobacco products are being introduced that can be used discreetly when smoking is not permitted. Many of these are smokeless tobacco products that do not require spitting and therefore may be more socially acceptable to use than the older smokeless products. There is currently limited information regarding the extent to which these products deliver nicotine or the effect that they have on nicotine craving and withdrawal symptoms

Methods: Eleven smokeless tobacco users completed three laboratory sessions in this cross-over study. At each session, they used either Camel Snus, Taboka or nicotine lozenge for a 30 minute period. Nicotine concentrations were measured over a 90 minute period and subjective measures (i.e. craving, withdrawal symptoms, product effects and liking measures) were assessed during product use and compared among products.

Results: Significant differences were found among products in maximal nicotine concentration (Cmax) and in the 90 minutes area under the concentration time curve (AUC_{90}) ($p<0.01$ for both). Both Cmax and AUC were highest when subjects received the nicotine lozenge. AUC was significantly higher during medicinal nicotine use than during use of Camel Snus which was significantly higher than during us of Taboka. Cmax was significantly higher during use of nicotine lozenge and Camel Snus than during Taboka use. No significant difference in time to reach maximal concentrations was observed among the three products. The decline in craving and withdrawal symptoms during product use did not differ among products (no significant time x

product interaction) and few differences were seen among products on measures of product effects or liking.

Conclusion: The two smokeless tobacco products tested resulted in less nicotine exposure than use of medicinal nicotine. These products had equivalent effects on craving and withdrawal symptoms and were equivalent on most measures assessing product effects and liking. Since the newer tobacco products are rapidly changing and long term studies with each formulation of each product is not feasible, short term laboratory studies are needed to determine if and how smokers are likely to use these products and to determine if they offer any advantages (in terms of overall effects on public health) over medicinal nicotine products that lack the toxicants that all tobacco products contain. The current study does not suggest that the products tested offer advantages over medicinal nicotine, however future studies are needed to determine if emerging products that contain higher nicotine levels are more effective at reducing craving and withdrawal symptoms or if they are more appealing to tobacco users based on other product characteristics. Based on current data however, smokers who are interested in switching to less harmful products should be encouraged to use medicinal nicotine.

Table of Contents

Section	Page
List of tables……	v
List of figures……..	vi
Introduction…….	1
Methods……..	6
Results……..	10
Discussion…….……	13
Bibliography…….	23

List of Tables

Table	**Page**
Table 1: Nicotine AUC_{0-90} and Cmax for three products tested	11

List of Figures

Figure	Page
Figure 1: Mean (± SE) nicotine concentrations during and after 30 minutes use of three smokeless products	11
Figure 2: Mean craving score during use of three smokeless products	12
Figure 3: Mean withdrawal scores during use of three smokeless products	13

INTRODUCTION

With smoking restrictions becoming increasingly common in the United States, alternative tobacco products are being introduced that can be used discreetly when smoking is not permitted. A variety of alternative tobacco products have been introduced, many of which are oral tobacco products which do not necessitate spitting like the older oral tobacco products did (Hatsukami *et al.*, 2007). Some of these products are packaged in pouches which are placed in the mouth and then discarded (with no spitting necessary while being used) whereas others dissolve in the mouth over time. Many of these products are available in a variety of flavors in order to further increase palatability for smokers that would normally not be interested in using smokeless tobacco products. These products have been broadly referred to as either "potential reduced tobacco products" (PREPs) or potential modified risk tobacco products.

The advertising for these newer smokeless, spitless tobacco products had initially been largely targeted at smokers looking for an alternative to smoking when in a smoke-free environment. For example, advertising for one of these products (i.e. Camel Snus) has used phrases such as "enjoy it anytime, anywhere", "pleasure for wherever", "No smoking? No problem" and "can be enjoyed virtually anywhere including places where smoking is banned or restricted" (Camel, 2010; Mejia and Ling, 2010; Samet and Wipfli, 2009; Timberlake *et al.*, 2011). Indeed, a paper analyzing tobacco company documents concludes that these products were introduced as a cigarette alternative in response to indoor smoking restrictions (Mejia and Ling, 2010) and this message is being successfully disseminated to smokers as indicated by an analysis of comments on the Camel Snus discussion board which found that smokers frequently thought the product

was great for use in places or situations in which they could not smoke (Wackowski *et al.*, 2011). Over time however, advertising has shifted to also target smokers interested in switching from cigarettes to one of these newer products. More recent advertising for Camel Snus has incorporated phrases such as "Tune in, Smoke out" with some advertising appearing to be targeted at smokers who are likely interested in quitting smoking. For example, seasonal promotional materials were used around the New Year in which Camel Snus was advertised as a way to maintain a "smoke-free resolution" (Trinkets and Trash, 2012). The marketing for these newer products is therefore targeting a broad range of smokers likely resulting in the number of smokers using these products to increase over time. Indeed, recent data suggests that a substantial number of smokers have heard of and tried these products. In the areas where these products were first test-marketed, the number of smokers who have tried these products is substantial. In the part of Indiana in which most smokers were aware of these newer products, 20% of male smokers had reported trying either Taboka or Camel Snus (two of the products tested in the area) (Biener and Bogen, 2009) and 29% of young adult male smokers had tried snus in three additional test markets (Portland, Kansas City, Columbus) for snus products (Biener *et al.*, 2011). National survey data demonstrates that these products are becoming increasingly known and used. A national survey of adults conducted in 2009 found that 44.2% of adults had heard of Camel or Marlboro snus and 5.4% had tried one of these products (Regan *et al.*, 2012). Another survey similarly found that 5.1% of adults in the United States and 2.7% of adults in the US who have never smoked have tried Snus (McMillen *et al.*, 2012). Of particular concern is that adolescents and young adults are especially likely to be familiar with these products. In the three test markets

for snus products described above, the rates of those who tried snus was highest in males between the ages of 18 and 24 (29%) and lowest in females over the age of 36 (1.1%). National surveys have reported that 61.9% of those between the ages of 18 and 24 had heard of and 8.0% have tried snus (McMillen *et al.*, 2012; Regan *et al.*, 2012). A survey conducted among Texas students attending 6th to 12th grades found that 7.1% reported ever trying snus (Loukas *et al.*, 2012).

The use of smokeless tobacco products may further be impacted by the suggestion by some that smokeless tobacco should be a recommended alternative for cigarette smoking since it is a less harmful tobacco product than cigarettes (Rodu, 1994; Rodu and Godshall, 2006; Russell *et al.*, 1980; Russell *et al.*, 1981). Smokeless tobacco lacks the toxicants associated with combustion and data suggest that for the individual tobacco user, smokeless tobacco use is associated with lower risk of disease development (e.g. lung disease, cardiovascular disease) compared with continued smoking (Hatsukami *et al.*, 2007). Indeed there is evidence, both from studies in which the amount of toxicants is measured in the smokeless tobacco product and from studies in which amount of toxicants are measured in tobacco users who are asked to use these products exclusively for a period of time, that the level of toxicants (specifically tobacco specific nitrosamines) is lower in these newer smokeless products when compared to either cigarettes or traditional moist snuff (Blank and Eissenberg, 2010; Gray *et al.*, 2008; Kotlyar *et al.*, 2011; Sarkar *et al.*, 2010; Stepanov *et al.*, 2006; Stepanov *et al.*, 2008). There is however significant controversy regarding using smokeless tobacco products in this manner since it is not known how promotion of such use will affect concurrent tobacco smoking in the individual or overall tobacco use at the population level. For example, it is not known if

by attempting to switch from cigarettes to smokeless products, smokers would be less likely to quit tobacco products entirely or would ultimately be more likely to use both cigarettes and smokeless tobacco products (i.e. dual-use). Furthermore, it is not known what effect promotion of smokeless tobacco products as less dangerous than cigarettes would have on tobacco use initiation, particularly given survey data suggesting that adolescents and young adults are the most likely groups to use these products.

The increased prevalence of smoking bans in public places, the development of smokeless tobacco products that can be used discreetly, the increasing marketing of these products to smokers and the promotion by some of smokeless tobacco as a safer alternative to continued smoking will all likely lead to a large number of smokers who are not interested in quitting to use these newer smokeless, spitless tobacco products. Current users of smokeless tobacco products are also likely to be interested in switching to a product that is more socially acceptable (since these newer products do not require spitting). Additionally, there is increasing interest in investigating if newer smokeless tobacco products can be used as a means to facilitate cessation by those who are interested in quitting tobacco use entirely with a recent study finding that point prevalence quit rates 6 weeks after cessation were higher in those receiving snus than in those receiving placebo (18.4% vs. 8.8%) (Fagerstrom *et al.*, 2012). If there is continued interest in using these products as aids to smoking cessation, that would suggest that the population of tobacco users potentially using these products would include current users of traditional smokeless tobacco products, smokers who are not interested in quitting tobacco products as well as smokers who are interested in cessation.

Despite the demonstrated increases in use of these products over the recent years and the potential for that increase to continue, there is relatively little information currently available about these products. Basic information such as the extent of nicotine exposure following use of these products and the effect of these products on severity of craving and withdrawal symptoms are lacking. Such information is necessary to determine the extent to which increased use of these products might maintain nicotine addiction and impact smoking behavior. In a recent report from the Institute of Medicine "Scientific Standards for Studies on Modified Risk Tobacco Products", among the twelve recommendations made is a call for studies assessing the effect of these newer products on addiction potential and on perception about the products' effects and likelihood of addiction (Institute of Medicine, 2012).

The purpose of this study was to assess nicotine exposure and subjective responses of tobacco users when using one of two smokeless, spitless tobacco products and compare them to the medicinal nicotine lozenge (4 mg Commit). The newer smokeless tobacco products studied were 1) Camel Snus (produced by RJ Reynolds) and Taboka (previously produced by Phillip Morris but no longer on the market). These products are pasteurized rather than fermented, leading to lower concentrations of the tobacco specific nitrosamines that have been found to be associated with cancer risk. These two specific products were chosen because they have substantially different amounts of nicotine and therefore could be expected to have different effects on subjective measures. A study analyzing the amount of nicotine in these products reported that Taboka had 0.171 mg free nicotine per pouch whereas Camel Snus had 1.35 mg free nicotine per pouch (Stepanov *et al.*, 2008). This study assessing nicotine exposure after a single dose was

done in parallel with a study evaluating the use of these products on tobacco specific nitrosamines and withdrawal symptoms when used as a substitute for cigarettes in subjects interested in cessation (Kotlyar *et al.*, 2011) . The data from this single dose study can therefore help inform the interpretation of the results obtained in that cigarette switching study.

METHODS

Study Design

A randomized cross-over study was conducted in which subjects at each laboratory session received either one pouch of Taboka, one pouch of Camel Snus or a 4 mg nicotine lozenge. Only current smokeless tobacco users were enrolled in order to collect information regarding product liking from a population that is familiar with these products. The order in which subjects received products was random and laboratory sessions were separated by at least 3 days. At each laboratory session nicotine concentrations were measured over a 90 minute period which included 30 minutes of product use and the 60 minute period following product use. Measures of craving, withdrawal, product effects and product liking were measured during and immediately after use of each product.

Subjects

Participants were recruited from the University of Minnesota and surrounding communities through flyers and advertisements in local media. Eligible subjects were those that were between the ages of 18 and 65 and were daily users of traditional

smokeless tobacco products for at least one year. Subjects were excluded if they reported any unstable medical or psychiatric conditions, were regularly using other tobacco products, had severe periodontal or other lesions or for other reasons that in the investigators' judgment could interfere with measures being assessed. The study was approved by the University of Minnesota Institutional Review Board and written informed consent was obtained from all subjects.

Laboratory sessions

Blood was drawn immediately prior to and at 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min after product placement with blood samples assayed for plasma nicotine concentrations. Subjects were instructed to refrain from using any tobacco products for at least 12 hours prior to each laboratory session and an additional 2 hours elapsed between the subjects' arrival and baseline measures to assure at least that length of abstinence. An indwelling catheter (to facilitate blood draws) was placed thirty minutes prior to product use.

Subjects completed baseline questionnaires, were then provided the study product which they were to use for 30 minutes after which the product was removed and subjects rinsed their mouths with water. Questionnaires assessing craving, withdrawal, product effects and liking were completed prior to product placement, 5 minutes and 15 minutes after product placement and immediately after the product was removed (i.e. 30 minutes after product placement). To assess craving and withdrawal, a modified version of the Minnesota Nicotine Withdrawal Scale was used. In this scale craving is determined via a single item on the scale, whereas withdrawal is determined by adding the scores of the

other 6 symptoms assessed (irritability/frustration/anger, anxiety/tension, difficulty concentrating, restlessness, depressed or sad mood and impatience). This scale has been widely used to assess craving and withdrawal after the use of cigarettes (Hatsukami *et al.*, 1991; Hughes and Hatsukami, 1986; Hughes *et al.*, 1991), medicinal nicotine (Hatsukami *et al.*, 1992; Hatsukami *et al.*, 1993) and smokeless tobacco products (including reduced exposure products) (Hatsukami *et al.*, 1987; Hatsukami *et al.*, 1992; Kotlyar *et al.*, 2007).

To assess products effects and liking, a 17 item questionnaire was used on which subjects rated each item on a 10 point scale. Items assessed the extent to which subjects 1) craved tobacco; 2) felt good effects from the product; 3) felt bad effects from the product; 4) found the product satisfying; 5) liked the product; 6) desired the product; 7) felt the product was strong. Additional items assessed the extent to which the product made subjects feel 8) good; 9) relaxed; 10) a head rush; 11) fast pounding heart; 12) tremor in hands, arms or face; 13) lightheaded / dizzy; 14) drowsy; 15) energetic; 16) jittery and 17) high. This scale was adapted from scales previously described (Hasenfratz *et al.*, 1993; Jaffe and Glaros, 1986; Kochhar and Warburton, 1990; Pritchard *et al.*, 1996; Schuh *et al.*, 2001) and has been used in a previous study assessing smokeless tobacco products (Kotlyar *et al.*, 2007).

Pharmacokinetic Analysis

Because six of the eleven subjects had quantifiable baseline (i.e. time 0) nicotine concentrations (suggesting that they did not abstain from using tobacco products as directed), the measured concentrations were adjusted using the following equation:

$$Ct(adj) = Ct - C_0 e^{-Kt}$$

Where Ct(adj) is the adjusted plasma concentration used for purposes of analysis; Ct is the observed plasma concentration (or one-half the lower limit of quantitation if concentrations were too low to be quantified); C_0 is the measured baseline plasma concentration (if the baseline was below the lower limit of quantitation, a value of 0 was substituted); K is the nicotine elimination rate constant of (0.693/120); and t is the time of the measured plasma concentration in minutes. The half-life used for the calculation of the elimination rate constant (i.e. 120 minutes) is based on previous reports of average nicotine elimination half-life (Benowitz *et al.*, 2006). This approach to adjusting nicotine concentrations has been used in previous studies (Shiffman *et al.*, 2009). In three instances, a baseline plasma concentration was not available. In those instances, the nicotine plasma concentration measured at 1 minute was used in the equation above for C_0. Adjusted nicotine concentrations were used to calculate each subject's area under the concentration-time curve during the sampling period ($AUC_{0\text{-}90}$), time to maximal concentration (Tmax) and maximal concentration observed (Cmax). AUC was calculated using noncompartmental methods (WinNonlin Professional, Pharmsight Corporation, Mountain View, CA).

Statistical Analysis

The three pharmacokinetic parameters were analyzed in the natural logarithmic scale and were reported as geometric means adjusted for the session the product was given at. Linear mixed models with random subject effects were used to determine differences in AUC, Cmax and Tmax between the three products (Commit, Camel Snus and Taboka). The subjective effects included craving, withdrawal and items on the effects and liking

questionnaire. To assess differences between products, the score for each response was analyzed with a linear mixed model with random subject effect and a repeated factor for time (0, 5, 15 and 30 minutes). Baseline values for craving and withdrawal were added as covariates. Interaction terms were included in the models if significant.

All statistical analyses were performed using SAS, version 9.3 (SAS Institute). P-values less than 0.05 were considered statistically significant. The Tukey method was used to adjust p-values for pair-wise comparison.

RESULTS

Subjects

Eleven subjects completed three laboratory session (i.e. used each of the products during the study) and were included in the analysis. All of the subjects were male. The average age of subjects was 34 (range: 20 - 51). Subjects on average used 4 tins of smokeless tobacco per week.

Nicotine pharmacokinetics

The nicotine concentration-time profile for each of the three products is illustrated in Figure 1. Significant differences among products were observed in the Cmax and in the 90 minute AUC (table 1) ($p<0.001$ for both). Both Cmax and AUC were highest when subjects received the nicotine lozenge. AUC was significantly higher during medicinal nicotine use than during use of Camel Snus which was significantly higher than during us of Taboka. Cmax was significantly higher during nicotine lozenge and Camel Snus use

than during Taboka use. No significant difference in time to reach maximal concentrations was observed among the three products (figure 1).

Table 1: Nicotine AUC_{0-90} and Cmax for three products tested			
	Nicotine Lozenge (4mg)	**Camel Snus**	**Taboka**
AUC (ng*min/ml)	397.38[a] (264.12, 597.89)	248.49[b] (163.43, 377.81)	153.30[c] (101.88, 230.65)
Cmax (ng/ml)	6.97[a] (5.05, 9.63)	4.83[a] (3.47, 6.73)	2.90[b] (2.10, 4.00)

Data are adjusted geometric mean (95% confidence interval). Products with different letters were significantly different ($p<0.05$).

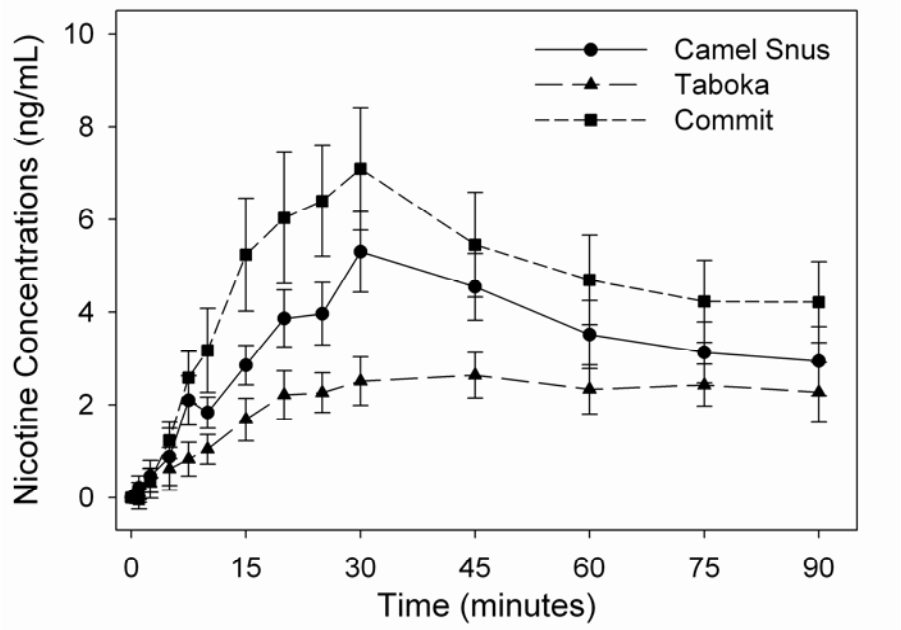

Figure 1: Mean (± SE) nicotine concentrations during and after 30 minutes use of three smokeless products

Subjective Effects

The time course of craving and withdrawal symptoms reported during the 30 minute period that the products were being used are illustrated in figures 2 and 3. There was a

main effect of time for both craving ($p<0.002$) and withdrawal ($p=0.008$) indicating that these symptoms declined during products use. There was however no time x product interaction for either craving or withdrawal indicating that there was no difference between products in the decline of withdrawal symptoms. Baseline values were not significantly different between products.

Among the items assessed on the drug effects and liking questionnaire, differences between products were found only in responses to how satisfying the product was and the extent to which the product made the subject feel energetic. The adjusted mean score for satisfaction was higher for Snus than for either Taboka ($p=0.016$) or medicinal nicotine ($p=0.018$). The score for feeling energetic was lower for Taboka than for either Snus ($p<0.001$) or medicinal nicotine ($p<0.001$).

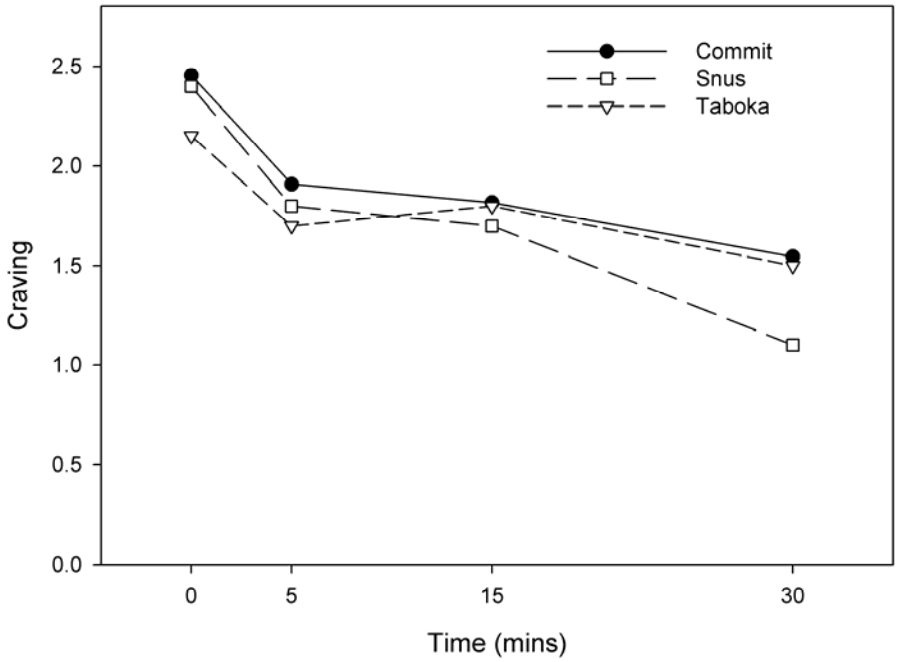

Figure 2: Mean craving score during use of three smokeless products

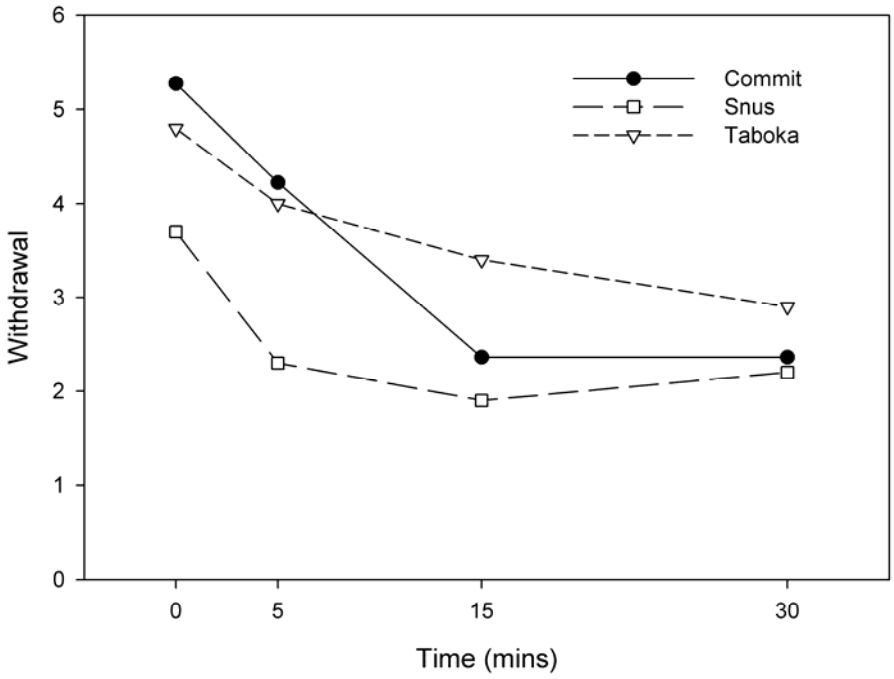

Figure 3: Mean withdrawal scores during use of three smokeless products

DISCUSSION

This study found that when compared to medicinal nicotine, the two smokeless, spitless tobacco products tested achieved lower nicotine exposure and had very similar effects on measures of craving and withdrawal. The products were similar in most measures on a product effect and liking scale, however Camel Snus had the highest ratings on a measure assessing how satisfying the product was and Taboka had the lowest scores on a measure assessing the extent to which subjects felt energetic.

This study adds to a growing body of literature examining the amount of nicotine that these products deliver and the effect they have on craving and withdrawal symptoms as

well as measures of product effects and liking. This information from single dose studies is needed in order to determine how these products are likely to be used once in the marketplace. Since nicotine is the primary addictive component in tobacco, the amount of nicotine that a new product delivers is likely to be a factor in how the product will be used. Products with low levels of nicotine should be less likely to be acceptable substitutes to tobacco users in place of their usual brands since they would not replace the nicotine from the tobacco products that they are currently using. Indeed, the current data demonstrates that Taboka delivered less nicotine than either Camel Snus or medicinal nicotine and a clinical study in which smokers were asked to substitute one of these products for their usual brand of cigarettes found that those assigned to Taboka used fewer doses (and smoked more cigarettes) than those assigned to either of the other two products (Kotlyar *et al.*, 2011). However, other product specific factors are likely to also contribute to how acceptable subjects find a particular product. For example, in a study in which smokers were asked to sample and then select one of five products (i.e. Camel Snus, Marlboro Snus, General Snus, Stonewall, Ariva) to use during a 2 week cigarette abstinence period, no smokers selected General Snus despite it being the highest nicotine product available to choose from (Hatsukami *et al.*, 2011). Among the four products that were selected by smokers for the abstinence phase of the study, those who selected Camel Snus (the highest nicotine content product of the four) tended to use more of the product and to smoke fewer cigarettes than those who selected one of the other products (Hatsukami *et al.*, 2011). It therefore appears likely that nicotine content as well as other product characteristics influence how a product is likely to be used. An analysis assessing the various components of the product effects and liking scale found that

measures of satisfaction are most associated with amount of the product that is used (Hatsukami et al., In Press). In our study, Camel Snus was associated with the highest measures of satisfaction.

A limitation of any study examining specific tobacco products is that they are frequently being introduced, withdrawn or reformulated. The Camel Snus that was used in the current study has since been reformulated into larger pouches and Taboka is no longer on the market. Additionally, there may also be regional differences in the composition of these products. For example, a study that evaluated the nicotine content in 36 samples of Camel Snus obtained from 5 different regions of the country found that there was an approximately 3 fold difference in unprotonated nicotine content (the biologically available form of nicotine) between products obtained in the regions with the highest nicotine content (i.e. west, south) relative to the region from which the products contained the lowest level of unprotonated nicotine (i.e. pacific northwest) (Stepanov *et al.*, 2012). Nonetheless, other studies examining nicotine concentrations achieved after use of these newer products have similarly found that for the products evaluated to date the maximal nicotine concentrations achieved after use are not generally higher than obtained from medicinal nicotine products such as nicotine gum and nicotine lozenge. For example, a study evaluating nicotine concentrations after use of two dissolvable products (i.e. Ariva, Stonewall) or a tobacco pouch product (i.e. Revel) found that maximal nicotine concentration obtained after the use of any of these three products was lower than after the use of the medicinal nicotine lozenge (Kotlyar *et al.*, 2007). A study that evaluated nicotine concentrations after use of a single dose of Ariva found similarly modest increases in nicotine concentrations (Blank and Eissenberg, 2010). A study in

which smokers used 2 doses (separated by 60 minutes) of three non-combustible products (i.e. Ariva, Camel Snus original flavor, Marlboro Snus mild flavor) and the 2 mg nicotine lozenge found that 15 minutes after the administration of the second dose only Camel Snus had significantly higher plasma nicotine concentrations relative to baseline (mean plasma concentration of 7.6 ng/ml). The increase in plasma concentration was next highest for those receiving nicotine lozenge (mean concentration of 4.6 ng/ml), followed by Ariva (mean concentration of 3.4 ng/ml) and Marlboro Snus (mean concentration of 2.9 ng/ml). Since the nicotine lozenge dose used was one-half of that used in our study (2 mg vs. 4 mg), the results are consistent with our findings that nicotine concentrations after use of these newer products tested to date are no higher than after use of medicinal nicotine (Cobb *et al.*, 2010). These data are in contrast to studies with older smokeless tobacco products (e.g. moist snuff) that demonstrated higher peak concentrations after use of those products when compared to medicinal nicotine (Benowitz *et al.*, 1988; Kotlyar *et al.*, 2007).

Of importance when evaluating newer smokeless tobacco products is what effect they have on craving and withdrawal symptoms since this may impact how likely the products are to be used as a substitute for usual brand cigarettes or traditional smokeless tobacco products. The products evaluated to date have generally found that medicinal nicotine and the newer products have comparable effects on nicotine craving and withdrawal symptoms, however the amount of nicotine that a product has does influence these measures. In a study comparing 3 of the newer tobacco products to medicinal nicotine, craving levels were highest in the product that delivered the lowest amount of nicotine (i.e. Revel) (Kotlyar *et al.*, 2007). In the current study, no differences were found among

products despite the observed differences in nicotine concentrations. There are several potential explanations for these findings. It is possible that product characteristics other than nicotine delivery influence the effects that the product has on subjective symptoms. Indeed in the current study, Camel Snus was rated as a more satisfying product than nicotine lozenge despite lower nicotine exposure. It is possible that these factors contributed to the lack of difference in craving and withdrawal symptoms score. Another potential explanation is that compared to their regular smokeless tobacco use, subjects taking any of the three products received so little nicotine that there was no discernible difference between them in subjective measures (i.e. there is a nicotine floor effect below which there are no differences in response). A third potential explanation is that the differences in nicotine concentrations seen between the products tested were not large enough to influence craving and withdrawal symptoms. Future studies are needed to determine if any of these explanations is accurate.

Our study is nonetheless generally consistent with other studies showing that medicinal nicotine and the newer smokeless tobacco products have similar effects on craving and withdrawal symptoms. A study comparing several products (including Camel Snus and nicotine lozenge) found similar effects of these products on urge to smoke (Cobb *et al.*, 2010). Although the Swedish Snus products are not very well accepted by smokers in the United States (Hatsukami *et al.*, 2011), several studies with these products also demonstrate that snus products do not seem to have substantial benefits over medicinal nicotine in decreasing withdrawal symptoms. For example, one study found both Swedish Snus and nicotine lozenges suppressed craving to a similar degree but that the lozenges suppressed craving for a longer time period (Barrett and

Wagner, 2011) and another study found that decreases in craving after use of either Swedish Snus or nicotine gum were equivalent (Lunell and Curvall, 2011). A study in which smokers not interested in quitting were asked to sample nicotine lozenge, Camel Snus, Marlboro Snus and Stonewall (three newer smokeless products) for a week found that smokers preferred the nicotine lozenges over the other products (O'Connor *et al.*, 2011). These studies demonstrate that medicinal nicotine delivers at least as much nicotine as the currently available newer smokeless products that have been tested, is as effective at reducing craving and withdrawal symptoms and may be preferred over the smokeless products.

Of particular importance when evaluating these tobacco products is the extent to which they expose smokers to toxicants associated with tobacco related disease. Medicinal nicotine results in no exposure to such toxicants whereas this is not the case of these newer tobacco products. In a study in which smokers were asked to quit smoking and were given 4 weeks of either Camel Snus, Taboka or medicinal nicotine, concentrations of NNAL decreased to a greater extent in those using medicinal nicotine relative to those using Camel Snus suggesting a lower health risk for medicinal nicotine (Kotlyar *et al.*, 2011). Other published studies also suggest that although smokeless tobacco products are substantially safer than cigarette smoking, they 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 (Hatsukami *et al.*, 2004; Hatsukami *et al.*, 2007) and use of these products has been associated with increased risk of pancreatic cancer (Boffetta *et al.*, 2005; Luo *et al.*, 2007). Some studies have suggested that use of Swedish Snus also may be associated

with a higher risk of oral or gastroesophageal cancer and fatal cardiovascular disease (particularly myocardial infarction) (Hergens *et al.*, 2007; Roosaar *et al.*, 2008; Zendehdel *et al.*, 2008). Therefore, use of these smokeless products should be recommended only if the health risk is lower than with continued smoking and there are no lower risk products available. The current data does not suggest that this is the case since medicinal nicotine appears to be equally effective as the currently tested products on subjective effects of smoking without exposing tobacco users to additional toxicants. Efforts are needed to educate the public regarding the health risks associated with the various smokeless products relative to the risk associated with medicinal nicotine. A survey of adults in which 22.1% indicated that they believe snus is as harmful as medicinal nicotine or non-nicotine medications and 51.9% were not sure if snus is more harmful than medicinal nicotine or non-nicotine medications suggests that smokers are currently lacking this information (Regan *et al.*, 2012).

Despite no clearly demonstrated advantages of these smokeless products over medicinal nicotine, marketing efforts by tobacco companies will likely lead to them being used extensively by smokers (and perhaps non-smokers). Although the health risks associated with smokeless tobacco use are lower than the health risks associated with cigarette smoking, risk to a smoker would only be lower if smokeless tobacco use doesn't undermine tobacco abstinence. To fully address this question, studies would need to be conducted in smokers interested in quitting as well as smokers not currently interested in quitting. For those who are currently interested in quitting, the primary concern would be that rather than complete cessation, use of these products would result in smokers either switching to smokeless products or of greatest concern to concurrently use both the

smokeless tobacco product and cigarettes (i.e. dual use). For those who are not currently interested in quitting, the primary concern is that use of smokeless tobacco products would decrease their future motivation to entirely quit tobacco use. Few studies have addressed these issues. A small study (n=31) found that 2 weeks of Ariva or Stonewall use (two of the newer smokeless tobacco products) in smokers not interested in quitting resulted in a significant increase in motivation to quit relative to continued smoking (Carpenter and Gray, 2010), however the study did not utilize a medicinal nicotine condition to determine if the same results could have been attained with medicinal nicotine nor did it follow smokers to determine if they had actually quit smoking. Clearly more research is needed to determine the consequences that increased marketing of the newer smokeless tobacco products will have on smoking behavior in current smokers as well as on smoking uptake by adolescents and young adults.

There are a number of limitations to this study. One limitation is that this study was conducted in users of traditional smokeless tobacco products rather than in cigarette smokers. The study was designed in this manner in order to assess subjects who are already familiar with and comfortable using oral tobacco products but this makes it difficult to generalize these results to cigarette smokers who are likely to be the main users of these products. It is unlikely that the nicotine concentration time profile after use of these products would be different in smokers than in users of smokeless tobacco products; therefore those data should be applicable to both populations. It is less clear that the results obtained on the subjective measures are also applicable to smokers and a study directly comparing the effects of these products in smokers and smokeless tobacco users would be needed to confirm if they are applicable to both populations. An

additional limitation is that based on baseline nicotine concentrations, a majority of smokers did not abstain from using tobacco products overnight prior to each laboratory session (despite being asked to do so). A mathematical correction was applied to the observed nicotine concentrations to address this issue; however the calculation assumes that the elimination rate constant is the same for all subjects despite known variability that exists between individuals in rate of nicotine metabolism (Benowitz *et al.*, 2006). Nevertheless, the adjusted values should result in a reasonable approximation of the nicotine concentration boost that occurred as a result of using the study product. The effect of noncompliance with tobacco abstinence is potentially more problematic in interpreting the results of the subjective measures since these cannot be corrected for. Abstinence at baseline did not significantly predict craving and withdrawal scores although separating those who abstained from those who did not resulted in an extremely small sample size and therefore that analysis does not yield interpretable data. The data on subjective effects is largely consistent with what was observed in other studies and with the nicotine concentration data, therefore although it should be interpreted with caution, it does add to the overall literature on the topic.

In summary, assessing pharmacokinetics of a product is an important component in evaluating tobacco products. The current study found that nicotine exposure (as measured by the 90 minute nicotine AUC) was higher after medicinal nicotine use than after the use of either Camel Snus or Taboka. Despite these differences in nicotine exposure, no differences were observed in craving and withdrawal symptoms and few differences were observed in measures of product effects and liking. This suggests that the subjective measures are either influenced by product characteristics other than

nicotine delivery or that bigger differences in nicotine delivery are needed in order to influence these measures. The factors that influence subjective response to tobacco products are important to determine as they are likely to be significant factors in how these products will be used by tobacco users. This study is consistent with the literature in suggesting that the newer smokeless tobacco products tested several years ago, although higher in toxicants than medicinal nicotine tend not to be more effective in decreasing craving or withdrawal symptoms. Unless data is generated suggesting that smokeless tobacco products offer some advantage over medicinal nicotine in decreasing overall tobacco related health risk, medicinal nicotine should be preferentially recommended for smokers looking for an alternative to their current tobacco product.

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