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Original Investigation

Nicotine Delivery and Subjective Effects of Swedish Portion Snus Compared With 4 mg Nicotine Polacrilex Chewing Gum

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Abstract

Introduction: Snus availability has been claimed to have contributed to the low rates of smoking among Swedish men and made possible the transfer to a less harmful form of nicotine dependence.

Methods: Fourteen cigarette smokers were randomly assigned to 2 types of 1 g Swedish portion snus and 4 mg nicotine polacrilex (NP) chewing gum in open-label, single-dose crossover study. Nicotine delivery and pharmacokinetics were estimated, and self-reports of subjective effects were obtained using Visual Analogue Scales (VASs).

Results: Extracted dose from the NP gum averaged 2.56 mg compared with 2.12 and 2.18 mg, respectively, for Swedish portion snus. This resulted in a slightly larger area under the curve (AUC) for the NP chewing gum. The rise of the nicotine plasma concentration was faster for Swedish snus. Median T_{max} was shorter, 30 min for snus compared with 45 min for the NP gum. The lower C_{max} of NP gum compared with the snus products in spite of larger AUC may be explained by slower absorption from the chewing gum. The faster absorption of nicotine from Swedish portion snus was mirrored in a higher VAS score for "head rush." Craving/urges to smoke decreased similarly for all treatments. Salivation and throat burn were rated higher for the 4 mg NP gum compared with both types of snus.

Conclusions: Swedish snus produced higher maximum blood nicotine concentration in shorter time and with a quicker onset of "head rush" compared with 4 mg NP chewing gum in spite of a smaller extracted dose. The quicker onset of "head rush" and supposedly higher satisfaction from snus may partly explain the widespread use of snus for stopping smoking in Sweden.

Introduction

Background

Cigarette smoking produces more negative health consequences, may have higher addiction potential and more severe withdrawal symptoms, and may lead to a higher relapse rate after cessation than some potential reduced exposure products (PREPs), for example, smokeless tobacco (ST; Hatsukami, Lemmonds, & Tomar, 2004). There has been a debate about whether snus products may be more satisfactory than nicotine replacement therapy products for smoking cessation since they are capable of rapid delivery of nicotine to the blood circulation (Gilljam & Galanti, 2003). Snus availability has been claimed to have contributed to the low prevalence of smoking among Swedish men by aiding the transfer to a less harmful form of nicotine dependence. Fifty percent of Swedish snus users are ex-smokers (Foulds, Ramstrom, Burke, & Fagerstrom, 2003).

American brands of moist snuff showed fast delivery of nicotine to the bloodstream and fast onset of pharmacological effects that were also dose dependent (Fant, Henningfeld, Nelson, & Pickworth, 1999). In a recent randomized crossover trial on heavy smokers, it was shown that nicotine polacrilex (NP) gum, Swedish snus, and an oral nicotine sachet (Zonnic) reduced smoking by 33%, 37%, and 42 %, respectively. The smokers had fewer cravings with snus and Zonnic, while NP gum caused more adverse effects (Caldwell, Burgess, & Crane, 2010). We demonstrated elevated nicotine plasma concentrations following repeated doses of Swedish snus compared with 2 mg NP chewing gum (Lunell & Lunell, 2005). Swedish snus typically has a pH of about 8.5 (Andersson, Bjornberg, & Curvall, 1994) and therefore is expected to give a fast delivery of the lipophilic nicotine base through the oral mucosa. However, single-dose pharmacokinetics of Swedish snus and a comparison with high-dose (4 mg) NP chewing gum have not been published.

Rationale

PREPs, such as ST, have been proposed for smoking cessation or harm reduction. Hatsukami et al. (2004), however, concluded that more research was necessary before considering ST for harm reduction. Swedish snus may also be an alternative for buccal nicotine administration to smokers who cannot use the gum because of problems with dentures (Christen, Young, Beiswanger, Jackson, & Potter, 1989) and dyspepsia (Summary of product characteristics Nicorette 4 mg gum, Pfzer). A comparison

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of the blood nicotine curves and subjective effects between the high-dose (4 mg) NP chewing gum and Swedish snus therefore seemed justifed.

Objectives

Primary objective was to compare the nicotine delivery (in vivo extraction) and plasma concentrations of nicotine after administration of one single pouch of two strengths of Swedish portion snus, Snus 1 and Snus 2, respectively, versus one piece of 4 mg NP chewing gum. A secondary objective was to compare the $C_{max,}$ T_{max}, and area under the curve $(AUC)_{inf}$ of portion snus to NP chewing gum. We also compared each subject's rating of subjective effects on Visual Analogue Scales (VASs).

Methods

Study Design

The study had an open-label, randomized three-way crossover design. The preparations were given as single oral administrations on three separate occasions. Washout between sessions was at least six days. Approval of the study was obtained from the Ethics Committee of the University of Lund, Sweden. The study adhered to the International Conference of Harmonization principles of Good Clinical Practice.

Subjects

Fifteen regular cigarette smokers, 9 males/6 females and 19–49 years of age, participated in the study. They were smoking 15.3 ± 4.9 cigarettes/day since 14.3 ± 10.5 years and had a Fagerström Tolerance Questionnaire score of 4.1 ± 1.8. Ever users of ST or NP gum were excluded. Signed informed consent was obtained from all subjects prior to inclusion. Subjects were fasting and abstinent overnight (12 hr) from cigarette smoking. Baseline levels of exhaled carbon monoxide up to 11 ppm were considered compatible with abstinence (Foulds et al., 2003). Our previous experience has shown that subjects who have abstained from smoking for 12 hr have a plasma nicotine value <4 ng/ml. One subject was excluded from statistical analysis due to baseline nicotine plasma concentration exceeding 4 ng/ml. Consequently, data for 14 subjects are presented.

Procedures

Two strengths of portion snus, Snus 1 and Snus 2 with the same pH (8.7), and NP chewing gum buffered to an alkaline pH, respectively, were used over 30 min. The subject kept the pouch of snus between the upper lip and the gum for 30 min. The gum was chewed over 30 min (one chew per 2 s, metronome was used). Drinking coffee and carbonated beverages was not permitted since it blocks absorption of nicotine (Henningfeld, Radzius, Cooper, & Clayton, 1990).

Assay and Calculation of Nicotine Delivery

The residual nicotine contents of Snus 1 and Snus 2, respectively, per portion of used snus were estimated. The mean nicotine content in six portions of unused snus was estimated. Nicotine was extracted using sodium hydroxide and methyl-tert-butyl ether containing quinoline as an internal standard. The nicotine content was determined using a gas chromatograph equipped with a fame ionization detector (CORESTA Recommended Method No 62, 2005). The NP chewing gum was assayed using a similar procedure. The nicotine extracted amount was calculated as the mean content of six portions of unused snus and chewing gum, respectively, minus the residual nicotine content.

Blood Sampling and Nicotine Assay

Venous blood samples (5 ml) were collected in sodium heparinized Venoject glass tubes at the following timepoints: before (0), 2, 4, 8, 16, 24, 30, 45, 60 min, 1.5, 2, 4, 6, and 8 hr after administration of each preparation. The determination of nicotine in plasma was performed using capillary gas chromatography with nitrogen phosphorous detection after a single liquid–liquid extraction of a basifed plasma sample (Feyerabend, 1990). The precision of the method above the 0.6 ng/ml level of nicotine was better than 12% coeffcient of variation (CV) and above 4 ng/ml better than 6% CV. The level of quantifcation was 0.6 ng/ml.

Treatments

Snus 1, "General Onyx Portion Snus White Large," 1 g portion, and containing 9.9 mg nicotine, and Snus 2, "General Portion Snus White Large," 1 g portion, and containing 8.7 mg nicotine, manufactured according to the GothiaTek standard were stored in sealed plastic containers in a refrigerator until use. NP chewing gum was stored in its original blister pack. Each dose was taken under supervision of the staff.

Heart Rate

Supine heart rate was measured after 10-min rest before administration of trial products (timepoint 0) and at the timepoints 10, 20, and 30 min.

Subjective Effects

Each subject's rating of subjective effects was recorded using a 100 mm VAS anchored with "not at all" to "extremely." VAS scores were obtained at the timepoints 0, 5, 10, 20, and 30 min after each product was administered:

- overall "product strength" (head rush," buzz," "hit," feeling alert)
- craving intensity/urges to smoke
- increased salivation
- burning sensation in the mouth and/or throat

Adverse Events

Spontaneous reports were recorded, and an interview regarding adverse events was performed at the end of each session.

Pharmacokinetic Calculations

Pharmacokinetic parameters were calculated by model-independent methods using the WinNonlin Professional computer system (Pharsight Corporation). AUC_{inf}, C_{max}, and T_{max} were primary variables.

Statistics

Sample Size and Randomization

From a prestudy, a plasma nicotine concentration of about 6 ng/ml at 30 min after start of dosing was expected for the NP

chewing gum and about 13 ng/ml for the Snus 1. To detect a difference between the Snus 1 and the NP chewing gum of 7 ng/ml, with a power of 80% and = .05, 12 subjects were needed. Fifteen subjects were enrolled. The randomization was performed using latin squares approach.

Pharmacokinetics and Subjective Effects

A three-period crossover analysis of variance model accounted for the following sources of variation: sequence, subject, period, treatment, and carryover. No statistically signifcant carry over effect or period effect was present, and therefore, a pairwise comparison was performed. The differences between the Snus 1 and Snus 2, respectively, and the 4 mg NP chewing gum regarding the T_{max}, C_{max}, and AUC_{inf} were analyzed using Wilcoxon's Rank Sum test. Heart rate and subjective effects are presented using descriptive statistics.

Results

Nicotine Delivery

Unused portions of Snus 1, Snus 2, and NP chewing gum contained a mean (±*SD*) amount of 9.92, 8.65, and 3.80 mg nicotine/portion, respectively. The used pieces of Snus 1, Snus 2, and NP chewing gum contained a mean (±*SD*) residual nicotine amount/portion of 7.80 ± 0.93 mg (range: 5.02–8.83 mg), 6.47 ± 0.92 mg (range: 4.17–7.88 mg), and 1.24 ± 0.29 mg (range: 0.69–1.58 mg), respectively. Mean (±*SD*) extracted amount from Snus 1, Snus 2, and NP chewing gum consequently were estimated at 2.12 ± 0.93 mg (range: 1.09–4.90 mg), 2.18 ± 0.92 mg (range: 0.77–4.48 mg), and 2.56 ± 0.29 mg (range: 2.22–3.11 mg) nicotine/portion, respectively. The extracted amount of nicotine from NP chewing gum was signifcantly larger than that from Snus 1 (p = .0072) as well as Snus 2 (p = .0408).

Nicotine Plasma Concentration–Time Profles

The mean nicotine concentration at 30 min, that is just after stopping dosing, was signifcantly higher following Snus 1 compared with NP chewing gum (p = .0409). The corresponding concentration following Snus 2 was also higher compared with- NP chewing gum; however, it did not reach statistical signif - cance (p = .1753). The rise of the nicotine plasma concentration was faster for both strengths of portion snus compared with the NP chewing gum (non-signifcant). Mean ± *SD* nicotine concentration at 8 min was 7.2 ± 3.1 and 7.0 ± 2.7 ng/ml following Snus 1 and Snus 2, respectively, compared with 4.9 ± 2.0 ng/ml following NP chewing gum.

Maximum Nicotine Plasma Concentration (C_{max})

The mean (±*SD*) C_{max} after administration of Snus 1 snus was 14.8 ± 3.3 ng/ml (range: 7.9–19.8 ng/ml). C_{max} following Snus 2 was 13.7 ± 3.7 ng/ml (range: 6.8–19.9 ng/ml). C_{max} following NP chewing gum was 12.8 ± 2.96 ng/ml (range: 9.9–20.1 ng/ml). The C_{max} following Snus 1 was higher compared with NP chewing gum; the difference, however, not statistically signifcant (p = .0849). The mean time to maximum nicotine plasma concentration (T_{max}) was 37.1 ± 10.2 min (range: 24–60 min) for Snus 1 as well as for Snus 2. T_{max} for NP chewing gum was 46.1 ± 16.2 min (range: 30–90 min); the difference was not statistically signifcant.

Area Under the Nicotine Plasma Concentration–Time Curve (AUC_{inf})

AUC_{inf} after administration of Snus 1 was 3,062 ± 1,002 ng·min/ml (range: 1,841–5,242 ng·min/ml). AUC_{inf} after administration of Snus 2 was 2,829 ± 1,037 ng·min/ml (range: 1,848–5,115 ng·min/ml). AUC_{inf} after administration of NP chewing gum was 3,190 ± 1,310 ng·min/ml (range: 1,802–6,951 ng·min/ml).

Heart Rate

Heart rate increased rapidly to reach a maximum at 20 min. The mean 20-min increase of heart rate was 9.3 ± 9.6, 8.9 ± 6.4, and 9.9 ± 5.1 beats/min for Snus 1, Snus 2, and NP chewing gum, respectively. After 30 min, heart rate had levelled out at 7.5 ± 7.4, 9.3 ± 5.5, and 9.3 ± 6.3 beats/min, respectively, for Snus 1, Snus 2, and NP chewing gum.

Rating of Subjective Effects—VAS

Head Rush

The subjective ratings of "head rush" on the VAS were zero in the morning after overnight abstinence before any trial preparation had been given. The ratings increased rapidly to a

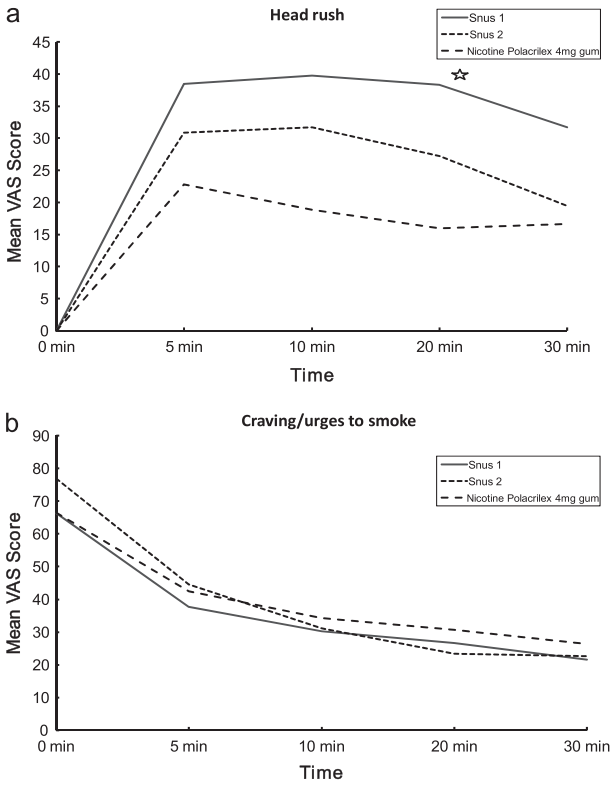

Figure 1. (a) Rating of "Head Rush" on Visual Analogue Scale (VAS) after administration of a single dose of two types of Swedish snus and 4 mg nicotine polacrilex chewing gum (N = 14). p = .0312 for the difference Snus 1 versus chewing gum. (b) Rating of craving/urges to smoke on VAS after administration of a single dose of two types of Swedish snus and 4 mg nicotine polacrilex chewing gum (N = 14).

maximum at 5 min. The mean 5-min value was 38.4 ± 31.7, 30.9 ± 26.5, and 22.8 ± 25.5 for Snus 1, Snus 2, and NP chewing gum, respectively. The corresponding values after 30 min were 31.6 ± 30.0, 19.5 ± 20.5, and 16.6 ± 20.6, respectively (Figure 1a). The difference between Snus 1 and NP chewing gum was statistically signifcant at 20 min ($p = .0312$).

Craving/Urges to Smoke

The subjective VAS ratings of craving/urges to smoke were highest in the morning after the overnight abstinence before administration of trial product (Figure 1b). They were similar for all products, 66.5 ± 21.4, 76.9 ± 9.0, and 62.5 ± 24.0 for Snus 1, Snus 2, and NP chewing gum, respectively. After 30 min, the ratings had decreased to 21.5 ± 15.7, 22.5 ± 25.5, and 26.3 ± 24.2 for Snus 1, Snus 2, and NP chewing gum, respectively. There was no signifcant difference between Snus 1, Snus 2, and NP chewing gum at any timepoint.

Salivation

The salivation score was signifcantly higher at 5 min following administration of NP chewing gum (Figure 2a) compared with Snus 2 ($p = .0066$), and the difference versus Snus 1 snus approached statistical signifcance ($p = .0618$).

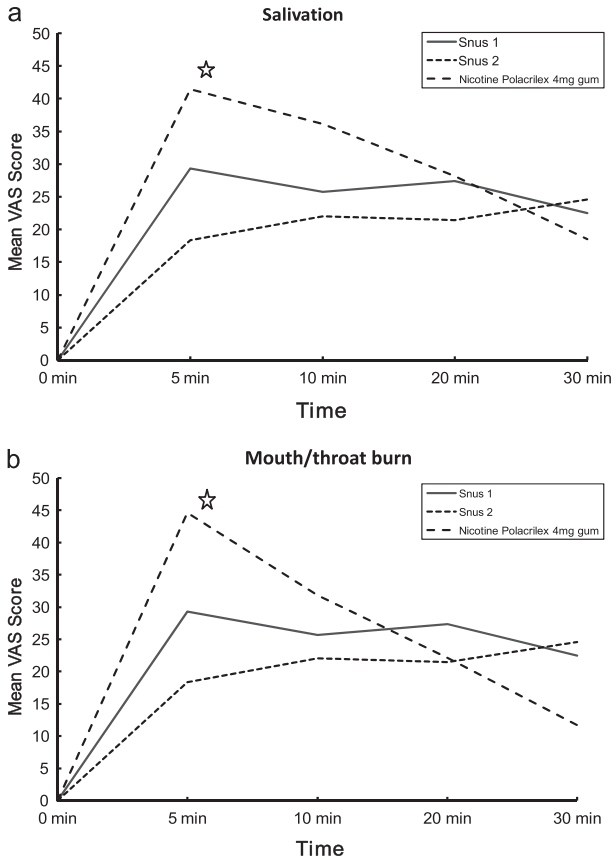

Figure 2. (a) Rating of salivation on Visual Analogue Scale (VAS) after administration of a single dose of two types of Swedish snus and 4 mg nicotine polacrilex chewing gum ($N = 14$). $p = .0066$ for the difference Snus 2 versus chewing gum. (b) Rating of mouth/throat burn on VAS after administration of a single dose of two types of Swedish snus and 4 mg nicotine polacrilex chewing gum ($N = 14$). $p = .0021$ for the difference Snus 1 versus chewing gum.

Burning Sensation

A majority of the participating subjects experienced a burning sensation in the mouth or throat of mild degree at some occasion during the testing of all preparations. The mean score for throat burn was higher at 5 min following administration of NP chewing gum compared with Snus 1 as well as Snus 2 (Figure 2b). The difference was statistically signifcant for Snus 2 ($p = .0021$).

Adverse Events

No subject withdrew from the study due to an adverse event. Two subjects experienced hiccups for about 10 min after start of the NP session. One subject experienced coughing for 5 min, 25 min after start of NP gum administration. The same subject experienced light headache for 15 min, 5 min after start of administration of Snus 1. No systemic effects such as nausea or dizziness were reported for any preparation.

Discussion and Conclusions

In the present study, we demonstrated a faster absorption of nicotine from the snus products and a corresponding faster rise to a higher score for "head rush" compared with the NP gum. Niaura et al. (2005) showed that a rapid-release nicotine gum reduced cue-provoked craving more rapidly compared with 2 mg NP chewing gum (Niaura et al., 2005). Furthermore, the novel pharmaceutical 4 mg oral nicotine sachet, Zonnic, reduced craving versus time AUC signifcantly more than placebo ($p = .002$; Thornley et al., 2009).

As seen in Figure 1b, the reduction of craving by Swedish snus did not differ from that of the NP chewing gum. The discrepancy between the subjective response for "head rush" and craving/urges to smoke in our study may be explained by the absence of provocative cues. Most smokers easily recognize the "head rush" from a cigarette. Craving/urges to smoke, the main acute nicotine "withdrawal" symptoms, constitute a more complex sensation, not as easily recognized, particularly in a laboratory setting.

American brands of moist snuff have shown fast delivery of nicotine to the blood circulation and fast onset of pharmacodynamic effects (Hatsukami et al., 2004). In contrast, PREPs including Ariva tobacco tablets and Camel Snus tobacco sachets showed ineffective withdrawal symptom suppression. One Ariva tablet increased mean ± *SD* nicotine plasma concentrations from 2.4 ± 0.9 to 3.4 ± 1.4 ng/ml 45 min posttablet. The authors concluded that administration of multiple tablets of Ariva may be necessary to attain a cigarette-like nicotine dose (Blank & Eissenberg, 2010).

Similarly, one clinical laboratory study showed that the PREPs Ariva tablets, Marlboro snus, Camel snus, Commit nicotine lozenge, and Quest cigarettes, delivered less nicotine than own brand cigarettes and failed to suppress tobacco withdrawal symptoms as effective as combustible products (Cobb, Weaver, & Eissenberg, 2010).

It has been debated whether PREPs, mainly ST, may constitute a harm reduction for smokers who cannot stop or an introduction to smoking for youth (Hatsukami et al., 2004). One Swedish (Ramström & Foulds, 2006) and one U.S. survey (Kozlowski, O'Connor, Edwards, & Flaherty, 2003) have shown

that ST was more often a gateway for smokers to quit smoking than a gateway for nonsmokers to become smokers.

We previously demonstrated elevated nicotine plasma concentrations following repeated doses of Swedish snus compared with 2 mg NP chewing gum (Lunell & Lunell, 2005). In the present study, the mean nicotine concentration at 30 min, that is, just after stopping dosing, was signifcantly higher following snus compared with 4 mg NP chewing gum.

More importantly, the rise of the nicotine plasma concentration was faster for both strengths of Swedish portion snus compared with the NP chewing gum. At 8 min after start of administration, the mean nicotine plasma concentration exceeded 7 ng/ml for both snus preparations compared with about 5 ng/ml for NP gum. Such a steep rise of the nicotine plasma concentration may have an impact on the smoker's satisfaction with respect to cigarette-like "head rush" and withdrawal reduction. The corresponding increase in plasma nicotine concentration after smoking a single cigarette is 5–14 ng/ml (Benowitz, Porchet, Sheiner, & Jacob, 1988; Breland, Kleykamp, & Eissenberg, 2006).

Interestingly, the mean amount extracted from the NP chewing gum, 2.56 mg, was signifcantly larger compared with that of Swedish snus, 2.12–2.18 mg. The mean extracted nicotine dose from Swedish snus in our previous study (Lunell & Lunell, 2005) was signifcantly larger, 2.74 mg/portion. The dis - crepancy may be explained by the experienced snus users participating in the former study in contrast to the present study, where all participants were smokers, naïve to snus use.

The larger dose extracted from the NP chewing gum compared with that of Swedish snus resulted in a higher dose absorbed into the systemic blood circulation and consequently a larger AUC. The lower C_{max} of NP gum compared with Swedish snus in spite of a larger AUC may be explained by a slower and more prolonged absorption from the chewing gum.

The faster absorption of nicotine from the snus products was mirrored in a higher score of the "head rush" on the VAS compared with the NP gum. The difference between Snus 1 and NP gum was statistically signifcant at 20 min ($p = .0312$). "Head rush" refects the pharmacological effect in the "reward" system of the brain and is of paramount importance for the smoker's liking of a nicotine-containing product. A similar difference was seen for heart rate increase, suggesting a faster onset of pharmacological effects in general for Swedish snus compared with nicotine gum. The importance of delivery kinetics for the abuse liability of nicotine preparations has been reported before (Henningfeld & Keenan, 1993) and snus undoubtedly has an addiction potential; however, there is a lack of controlled trials addressing this issue.

All products tested were well tolerated. The VAS ratings of salivation as well as burning sensation in the mouth or throat were higher for the 4 mg NP chewing gum compared with portion snus. For Swedish snus, the burning sensation was described as being located at the site of application in the mouth and only rarely involved the throat. In contrast, the burning sensation of the 4 mg NP chewing gum was located further back in the throat, more intense and harder to cope with. It should be noted that all subjects were smokers, and no subject had tried snus or nicotine chewing gum before. No adverse effects from snus were reported in this study. Long-term use of Swedish snus may lead to adverse health effects of which gingival recession is the most important (Andersson, 1991). There have been some suggestions of an increased risk of pancreatic cancer, cardiovascular disease, and diabetes, but the evidence is weak and some studies have found no associations (Eliasson, Asplund, Nasic, & Rodu, 2004; Hansson et al., 2009; Luo et al., 2007; Persson et al., 2000; Rodu, 2007; Roosaar, Johansson, Sandborg-Englund, Axéll, & Nyrén, 2008). Further research is required.

It is concluded that Swedish snus produces a higher maximum blood nicotine concentration, in shorter time and with a quicker onset of "head rush" in smokers naïve to snus, compared with the 4 mg NP chewing gum in spite of a smaller ingested dose. All products reduced craving/urges to smoke to the same extent. The quicker onset of "head rush" and supposedly higher satisfaction from snus may partly explain the widespread use of snus in Sweden in attempts to stop smoking.

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Declaration of Interests

Dr. EL has no appointments, consultancies, or stock ownership with Swedish Match AB.

References

Andersson, G. (1991). Snuff-induced changes associated with the use of loose and portion-bag-packed Swedish moist snuff—A clinical, histological and follow-up study. *Swedish Dental Journal Supplement*, *75*, 1–55.

Andersson, G., Bjornberg, G., & Curvall, M. (1994). Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: A comparative study. *Journal of Oral Pathology & Medicine*, *23*, 161–167. doi:10.1111/j.1600-0714.1994.tb01106.x

Benowitz, N. L., Porchet, H., Sheiner, L., & Jacob, P. (1988). Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. *Clinical Pharmacology and Therapeutics*, *44*, 23–28. doi:10.1038/clpt.1988.107

Blank, M. D., & Eissenberg, T. (2010). Evaluating oral noncombustible potential-reduced exposure products for smokers. *Nicotine & Tobacco Research*, *12*, 336–343. doi:10.1093/ntr/ntq003

Breland, A. B., Kleykamp, B. A., & Eissenberg, T. (2006). Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine & Tobacco Research*, *8*, 727–738. doi:10.1080/14622200600789585

Caldwell, B., Burgess, C., & Crane, J. (2010). Randomized crossover trial of the acceptability of snus, nicotine gum, and Zonnic therapy for smoking reduction in heavy smokers. *Nicotine & Tobacco Research*, *12*, 179–183. doi:10.1093/ntr/ntp189

Christen, A. G., Young, J. M., Beiswanger, B. B., Jackson, R. D., & Potter, R. H. (1989). Effects of nicotine chewing gum on complete dentures and their soft-tissue-bearing areas. *International Journal of Prosthodontics*, *2*, 155–162.

Cobb, C. O., Weaver, M. F., & Eissenberg, T. (2010). Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tobacco Control*, *19*, 367–373. doi:10.1136/tc.2008.028993

CORESTA Recommended Method No 62 (2005). *Determination of nicotine in tobacco and tobacco products by gas chromatographic analysis*. Retrieved from http://www.coresta.org

Eliasson, M., Asplund, K., Nasic, S., & Rodu, B. (2004). Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: The northern Sweden MONICA study. *Journal of Internal Medicine*, *256*, 101–110. doi:10.1111/j.1365-2796.2004.01344x

Fant, R. V., Henningfeld, J., Nelson, R. A., & Pickworth, W. B. (1999). Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tobacco Control*, *8*, 387–392. doi:10.1136/tc.8.4.387

Feyerabend, C. (1990). Determination of nicotine and cotinine in human plasma. *Journal of Pharmacy and Pharmacology*, *42*, 450–452.

Foulds, J., Ramstrom, L., Burke, M., & Fagerstrom, K. (2003). Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control*, *12*, 349–359. doi:10.1136/tc.12.4.349

Gilljam, H., & Galanti, M. R. (2003). Role of snus (oral moist snuff) in smoking cessation and smoking reduction in Sweden. *Addiction*, *9*, 1183–1189. doi:10.1046/j.1360-0443.2003.00379x

Hansson, J., Pedersen, N. L., Galanti, M. R., Andersson, T., Ahlbom, A., Hallqvist, J., et al. (2009). Use of snus and risk for cardiovascular disease: Results from the Swedish Twin Registry. *Journal of Internal Medicine*, *265*, 717–724. doi:10.1111/j.1365-2796-2009.02081x

Hatsukami, D. K., Lemmonds, C., & Tomar, S. L. (2004). Smokeless tobacco use: Harm reduction or induction approach? *Preventive Medicine*, *38*, 309–317. doi:10.1016/j.ypmed.2003.10.006

Henningfeld, J. E., & Keenan, R. (1993). Nicotine delivery kinetics and abuse liability. *Journal of Consulting and Clinical Psychology*, *61*, 743–750.

Henningfeld, J. E., Radzius, A., Cooper, T. M., & Clayton, R. R. (1990). Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *Journal of American Medical Association*, *264*, 1560–1564.

Kozlowski, L. T., O'Connor, R. J., Edwards, B. F., & Flaherty, B. F. (2003). Most smokeless tobacco is not a causal gateway to cigarettes: Using order of use to evaluate causation in a national U.S. sample. *Addiction*, *98*, 1077–1085.

Lunell, E., & Lunell, M. (2005). Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 4 mg nicotine polacrilex chewing gum. A cross-over study. *Nicotine & Tobacco Research*, *7*, 397–403. doi:10.1080/14622200500125468

Luo, J., Ye, W., Zendehdel, K., Adami, J., Adami, H-O, Boffetta, P., et al. (2007). Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: A retrospective cohort study. *Lancet*, *369*, 2015–2020. doi:10-1016/50140-6736(07)60677-1

Niaura, R., Sayette, M., Shiffman, S., Glover, E. D., Nides, M., Shelanski, M., et al. (2005). Comparative effcacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. *Addiction*, *100*, 1720–1730. doi:10.1111/j.1360-0443.2005.01218x

Persson, P-G, Carlsson, S., Svanström, L., Östenson, C-G, Efendic, S., & Grill, V. (2000). Cigarette smoking, oral moist snuff use and glucose intolerance. *Journal of Internal Medicine*, *248*, 103–110. doi:10-1046/j.1365-2796.2000.00708.x

Ramström, L. M., & Foulds, J. (2006). Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tobacco Control*, *15*, 210–214. doi:10.1136/tc.2005.014969

Rodu, B. (2007). Snus and risk of cancer of the mouth, lung and pancreas. *Lancet*, *370*, 1207–1208. author reply 1208. doi:S0140-6736(07)61533-5[pii]10.1016/S0140-6736(07)61533-5

Roosaar, A., Johansson, A. L. V., Sandborg-Englund, G., Axéll, T., & Nyrén, O. (2008). Cancer and mortality among users and nonusers of snus. *International Journal of Cancer*, *123*, 168–173. doi:10.1002/ije.23469

Summary of product characteristics Nicorette 4 mg gum, Pfzer (2011). Retrieved from www.Medicines.org.uk

Thornley, S., McRobbie, H., Lin, R. B., Bullen, C., Hajek, P., Laugesen, M., et al. (2009). A single-blind, randomized, cross-over trial of the effects of a nicotine pouch on the relief of tobacco withdrawal symptoms and user satisfaction. *Nicotine & Tobacco Research*, *11*, 715–721. doi:10.1093/ntr/ntp054