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Short communication

Gender differences in snus versus nicotine gum for cigarette avoidance among a sample of US smokers

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ABSTRACT

Introduction: Women are more susceptible to the harmful effects of cigarette smoking. Thus, identifying effective harm reduction approaches for women is necessary. The goal of this project was to examine gender differences in response to snus versus nicotine gum for cigarette avoidance, as a means of harm reduction.
Methods: Participants were randomly assigned to use snus or nicotine gum as a method to avoid cigarette smoking. Participants attended clinic visits to receive study product, as well as provide biological samples to assess smoking avoidance and biomarkers and report on use of study product and cigarettes. A secondary analysis comparing men and women by randomization to study product was conducted.
Results: Participants (n = 391; 47% women) were randomized into the snus group (n = 196; 45% women) and the gum group (n = 195; 49% women). Men used more snus whereas women used more gum (p = 0.02). During treatment, men in the snus group had higher total nicotine equivalent values whereas women did not vary by group (p = 0.03). Overall, fewer men in the snus group completely avoided cigarettes compared to men in the gum group (e.g., continuous abstinence at Week 12: odds ratio = 0.43, 95% confidence interval = 0.20–0.93). Among women, there were no differences by randomization in cigarette avoidance.
Conclusions: Despite a number of gender differences in response to snus versus nicotine gum, these data suggest that snus may not be an optimal harm reduction approach for either gender.

1. Introduction

Although cigarette smoking is more prevalent in men (Jamal et al., 2015), women are at an increased risk of experiencing smoking-related morbidity and mortality (Allen et al., 2014; CDC, 2001). Women smokers are less likely to successfully quit smoking (Allen et al., 2014; Wetter et al., 1999). Therefore, identifying an effective harm reduction approach for women is of critical public health importance.

Snus, a moist form of smokeless tobacco, originated in Sweden and has a relatively low cancer-causing risk profile compared to cigarettes; likely due to its lower concentrations of carcinogenic tobacco-specific nitrosamines (TSNAs) and lack of combustion (Bates et al., 2003; Osterdahl et al., 2004; Ramström and Foulds, 2006). Given that TSNAs and combustion products are major contributors to smoking-related health problems, snus may serve as an effective harm reduction approach (Levy et al., 2004). Indeed, the use of snus is not related to increased risk of several types of cancer and non-fatal cardiovascular diseases (Lee, 2011). Cigarettes smokers who have switched to snus experience a reduced risk of oral and stomach cancer, as well as cardiovascular disease (Lee, 2013).

Two published studies have observed promising rates of cessation or complete cigarette substitution with snus. Fagerström and colleagues enrolled 250 smokers motivated to quit into a double-blind randomized control trial comparing active snus to placebo snus for smoking cessation (Fagerstrom et al., 2012). They observed 18% point prevalence abstinence at Week 6 in their active snus group compared to 9% in the placebo snus group. In contrast, we

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enrolled 391 smokers interested in switching to snus or nicotine gum as a substitution for cigarettes (Hatsukami et al., 2016). At Week 12, we observed 22% point prevalence complete substitution rate in the snus group compared to 24% in the nicotine gum group. Given women tend to respond differently to a variety of nicotine containing products (Perkins and Scott, 2008; Perkins, 2001; Vogel et al., 2014), it is important to understand how women may differentially respond to snus as a harm reduction tool.

The goal of this secondary analysis was to explore gender differences in responses to snus and nicotine gum in smokers. Utilizing data from a recently completed randomized trial (Hatsukami et al., 2016) we compared men and women in terms of product use, biomarkers of toxicant exposure, and complete avoidance (e.g., complete substitution) of cigarettes.

2. Methods

2.1. Participants

Study details are published elsewhere (Hatsukami et al., 2016). In brief, a convenience sample of healthy men and women was recruited at two sites (Minneapolis/St. Paul, Minnesota and Eugene, Oregon). Eligible participants were between the ages of 18 and 70, self-reported smoking ≥10 cigarettes/day for the past year and were willing to switch from their cigarettes to snus or nicotine gum. Exclusion criteria included contraindications to medicinal nicotine, regular use of other nicotine containing products and, for women, pregnancy or nursing.

2.2. Protocol

At screening, eligibility was determined and informed consent was obtained. After a one-week baseline smoking period, participants entered the 12-week treatment period. Participants were randomized separately at each site (1:1 ratio with block sizes of 10) to one of two products: Camel Snus (Reynolds American Inc.), offered in two flavors – Winterchill (2.5 mg nicotine/pouch) or Robust (2.6 mg nicotine/pouch) or 4 mg Nicorette brand nicotine gum (GlaxoSmithKline).

During the treatment period, all participants were encouraged to use at least 6–8 pieces of assigned study product per day for 30 min each and abstain from their cigarettes. Participants were asked to reduce their study product use with a 50% reduction between weeks 6–9 and a 75% reduction between weeks 10–12. Participants attended nine clinic visits (Weeks 0, 1, 2, 4, 6, 8, 12, 26, 52). Each clinic visit consisted of brief behavioral counseling, completion of study questionnaires, and bio-specimen collection. Participants earned up to $360 for their compliance.

2.3. Measures

Use of study product (pieces/day) and cigarettes (cigarettes/day) was obtained via daily Interactive Voice Response (IVR) calls during the treatment period. Any missing data from the IVR calls was collected at each clinic visit. Complete cigarette avoidance was assessed at Week 12 (end of treatment) and Week 26 via self-report using the timeline follow-back procedure (Sobell et al., 1996) and verified with an expired carbon monoxide level. Two definitions were used to classify participants as avoiding cigarettes. Point-prevalence avoidance was defined as self-report of not smoking a puff or more on the seven days preceding the Week 12 and Week 26 clinic visits with a carbon monoxide level of <6 ppm at each respective time point. The second definition was continuous cigarette avoidance; a self-report of no smoking at any time during treatment or follow-up and confirmed by a carbon monoxide level of <6 ppm at each clinic visit. Biomarkers of exposure were assessed at baseline and Week 4 via a urine sample and included three specific measures – cotinine, total nicotine equivalents (TNE; Scherer et al., 2007) and urinary 4-methylnitrosamino-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL) (Carmella et al., 2013).

2.4. Statistical analysis

Comparisons of baseline demographics and smoking behaviors by gender were assessed with χ^2 or Fisher's exact tests for categorical data and *t*-tests or Wilcoxon Rank Sum tests for continuous data, as appropriate. Analyses were conducted using intention-to-treat methods for randomized condition. Comparisons of baseline biomarkers (on the log scale to ensure normality) by gender were conducted using linear regression models, adjusting for treatment, site, and baseline cigarettes/day. Comparisons of Week 4 biomarkers were similarly conducted, additionally exploring a gender by randomization effect and adjusting for baseline biomarker levels. Effect sizes (Cohen's D) and their 95% confidence intervals (CI) are presented for comparisons between treatments within gender. Finally, the differences in the carbon monoxide-verified abstinence rates at Weeks 12 and 26 were compared by gender and randomization using logistic regression models adjusting for gender, randomization, and baseline cigarette use. P-values < 0.05 were considered statistically significant and data were analyzed using SAS 9.3 (Cary, NC).

3. Results

3.1. Participants

Participants (n = 391) included 53% men (107 snus, 100 gum) and 47% women (89 snus, 95 gum). Participants were, on average, 43.9 ± 12.5 years old with a Fagerstrom Test of Nicotine Dependence (Heatherton et al., 1991) score of 5.1 ± 2.0 and motivated to quit smoking (9.1 ± 1.1 on a 10-point likert-type scale). At baseline, women smoked significantly fewer cigarettes/week than men (119.9 ± 39.9 versus 132.1 ± 49.8, p = 0.01). No other significant gender differences were noted at baseline.

3.2. Product use

A significant gender by randomization interaction was observed ($F_{1,3248} = 4.92$, p = 0.03), with men in the snus group using more study product than men in the gum group (*d* = 0.11 [0.03–0.20]; Fig. 1). Women used more study product if they were assigned to the gum group versus the snus group (*d* = 0.22 [0.12–0.31]). While overall product use decreased over time ($F_{11,3248} = 145.86$, p < 0.001), the interaction between gender and randomization assignment did not vary over time ($F_{22,3248} = 0.92$, p = 0.56).

Women were more likely than men to report adverse events during the study. Within the gum group, more women than men reported a stomach ache (15.8% versus 7.0%; p = 0.05). Within the snus group, more women than men reported vomiting (6.7% versus 0.9%; p = 0.05), nausea (40.4% versus 23.4%; p = 0.03) and stomach ache (18.0% versus 5.6%, p = 0.02).

Regardless of randomization, women smoked significantly more cigarettes per week than men during treatment ($F_{1,3266} = 8.85$, p = 0.003, *d* = 0.22 [0.16–0.28]). The gender by randomization interaction was not statistically significant ($F_{1,3266} = 0.43$, p = 0.51); among men, those assigned to the snus group smoked slightly more cigarettes (*d* = 0.10 [−0.02 to 0.19]) whereas women were similar in both groups (*d* = 0.02 [−0.08, 0.11]). Overall the prevalence of dual use (i.e., using study product and cigarette smoking) declined during the study with the highest use among women assigned to gum at Week 1 (Women: gum = 85.9%, snus = 79.5%; Men: gum = 70.7%, snus = 74.0%) and Week 12 (Women: gum = 74.6%, snus = 49.2%; Men: gum = 43.2%, snus = 55.8%).