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Comparative Effectiveness of the Nicotine Lozenge and Tobacco-Free Snuff for Smokeless Tobacco Reduction

Jon O. Ebbert, MD, MSc[a], **Herbert H. Severson, PhD**[b], **Ivana T. Croghan, PhD**[a], **Brian G. Danaher, PhD**[b], and **Darrell R. Schroeder, MS**[a]

[a]Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[b]Oregon Research Institute, 1715 Franklin Boulevard, Eugene, OR 97403, USA

Abstract

Long-term smokeless tobacco (ST) use is associated with cardiovascular disease and cancer, but not all ST users want to quit. Previous studies have evaluated the effectiveness of nicotine lozenges and tobacco-free snuff for reducing ST use among ST users not ready to quit, but no comparative effectiveness trials of these two products have been conducted. We conducted a multicenter, randomized clinical pilot study evaluating the comparative effectiveness of the 4-mg nicotine lozenge and tobacco-free snuff for reducing ST use and increasing tobacco abstinence among ST users with no intention of quitting in the next 30 days. Participants received 8 weeks of treatment and behavioral counseling on tobacco reduction strategies with follow-up to 26 weeks. We randomized 81 participants (40 nicotine lozenges, 41 tobacco-free snuff). No significant differences in reduction were observed between the two groups at weeks 8, 12, and 26. No signficant differences were observed between groups in nicotine withdrawal or tobacco craving. However, both groups significantly reduced ($p < .001$) ST use in cans/week and dips/day from baseline which was sustained through the end-of-study. The observed biochemically-confirmed abstinence rates at week 26 were similar between groups (12% vs. 12%, one-tailed $p = .615$). The 4-mg nicotine lozenge and the tobacco-free snuff both appear to be effective and comparable for reducing ST use among ST users not ready to quit in the next 30 days.

1. Introduction

In 2010, 3.5% of the U.S. population ≥ 12 years of age reported past month use of smokeless tobacco (ST) (Substance Abuse and Mental Health Services Administration, 2011). ST use may increase the risk for oral cancer (Stockwell & Lyman, 1986) and cancer of the kidney (Goodman, Morgenstern, & Wynder, 1986; Muscat, Hoffmann, & Wynder, 1995), pancreas (Muscat, Stellman, Hoffmann, & Wynder, 1997), and digestive system (Henley, Thun,

Corresponding Author: Jon O. Ebbert, MD, MSc, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA;, Telephone: (507) 266-1944; Facsimile: (507) 266-7900; ebbert.jon@mayo.edu.

Conflict of Interest

Dr. Jon O. Ebbert has received consulting fees from GlaxoSmithKline, manufacturer of the nicotine lozenge.

Contributors

JOE, HHS, ITC, BGD, and DRS designed the study, wrote the protocol and secured funding for the study. DRS conducted the statistical analysis. JOE and DRS wrote the first draft of the manuscript and HHS, ITC, and BGD provided critical review and edits. All authors have contributed to and approved the final manuscript.

Connell, & Calle, 2005). ST use is also associated with death from coronary heart disease and stroke (Henley, et al., 2005).

Not all ST users are ready to quit tobacco (Severson, 1992). Among cigarette smokers not ready to quit, tobacco reduction interventions incorporating pharmacotherapy (e.g., nicotine replacement therapy [NRT]) (Batra, et al., 2005; Rennard, et al., 2006; Wennike, Danielsson, Landfeldt, Westin, & Tonnesen, 2003) and combined behavioral and pharmacologic interventions (Carpenter, Hughes, Solomon, & Callas, 2004) have been shown to be effective for decreasing the number of cigarettes smoked and for increasing abstinence rates (Moore, et al., 2009; Wang, et al., 2008).

Three studies have been conducted examining the efficacy of ST reduction among ST users not ready to quit. One study evaluated the effects of switching to ST brands with lower nicotine concentrations (Hatsukami, et al., 2007), one evaluated substituting ST with tobacco-free snuff (Hatsukami, et al., 2008), and the third evaluated the effectiveness of the nicotine lozenge (Ebbert, Edmonds, Luo, Jensen, & Hatsukami, 2010). All three studies demonstrated significant reductions in nicotine and toxicant (i.e., tobacco carcinogens) exposure reduction. Nonsignificant trends were observed toward increased abstinence rates with these three approaches. However, the nicotine lozenge and tobacco-free snuff have not been directly compared.

We conducted a multicenter, randomized clinical pilot study to evaluate the comparative effectiveness of the 4-mg nicotine lozenge and tobacco-free snuff for ST reduction and tobacco abstinence among ST users not ready to quit. All participants received a behavioral intervention for ST reduction.

2. Methods

2.1. Study Design

Our study was a randomized, two-group, multicenter pilot clinical trial with a 12-week medication phase and follow-up through 6 months after randomization. Participants were randomized to receive either the 4-mg nicotine lozenge or tobacco-free snuff. All participants received behavioral tobacco reduction counseling. The study was conducted at Mayo Clinic (Rochester, MN) and the Oregon Research Institute (Eugene, OR). Enrollment took place between February 2010 and September 2011. The Institutional Review Boards at each study site approved the study protocol prior to subject recruitment.

2.2. Study Population

ST users were recruited from the local communities. A marketing campaign was used to encourage calls from ST users who wished to reduce their ST use but who had no intention of quitting in the next 30 days. Participants were eligible for inclusion if they were ≥ 18 years of age, reported ST as their primary tobacco used (i.e., occasional use of other forms of tobacco was not exclusionary), used ST daily for ≥ 12 months, and had no plans to quit in the next 30 days. Participants were excluded if they: (1) were currently using pharmacologic or behavioral treatments for ST use (past 30 days) or were enrolled in another research study; (2) had acute coronary syndrome in the past 6 months; (3) had phenylketonuria (PKU) [nicotine lozenges contain aspartame which is metabolized to phenylalanine and not processed in individuals with PKU]; (4) had a score of ≥ 15 on the Patient Health Questionnaire (PHQ-8) (Kroenke, et al., 2009); (5) had another household member participating in the study; (6) were currently pregnant or trying to become pregnant; and (7) were currently breast-feeding and unwilling to stop during this study.

2.3. Screening and Enrollment

Potential participants who satisfied a subset of study eligibility criteria over the phone were invited to attend a study visit at which time the study was explained, informed consent was obtained, and a medical screening and physical examination were completed. ST users who satisfied all eligibility criteria were then randomized to condition and asked to complete baseline measures.

2.4. Baseline Measures

Baseline measures included a tobacco use history, the Fagerström Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST) (Ebbert, Patten, & Schroeder, 2006) and the Severson Smokeless Tobacco Dependence Scale (SSTDS) (Akers, Severson, Yovanoff, & Boles, 2011; Severson, Akers, Andrews, & Boles, 2003).

2.5. Study Procedures

Study procedures replicated those of previous ST reduction trials using the nicotine lozenge (Ebbert, et al., 2010) and tobacco-free snuff (Hatsukami, et al., 2008). All participants received behavioral rate reduction counseling. The nicotine lozenge and tobacco-free snuff were provided for 8 weeks. At 8 weeks, participants were asked if they would like to quit ST. If interested in quitting, they were encouraged to do so and received a copy of an ST cessation intervention manual ("Skip the Dip, Lose the Chew"). Participants not interested in quitting at that time were encouraged to maintain their current level of ST reduction or to reduce even further. At 8 weeks, participants who chose to continue with the study were offered an additional 2-week supply of either lozenge or tobacco-free snuff based upon their experimental condition. At 10 weeks, participants were once again offered an additional 2-week supply of either lozenge or tobacco-free snuff. No additional lozenges or snuff were dispensed after week 12. Participants received remuneration for their participation independently of whether they reduced or quit ST use.

2.5.1. Behavioral tobacco reduction counseling—Participants received face-to-face and written instructions on ST reduction. Behavioral reduction methods included extending dip intervals, eliminating use in certain situations, and delaying morning use. They were encouraged to achieve a general goal of a reduction of ST use by 50% by week 4 and 75% by week 8 using a regimen alternating the use of their usual brand of ST and their assigned product (nicotine lozenge, tobacco-free snuff). Participants received a "Smokeless Reduction Diary" which served as a resource in which to record their ST use and to act as a visible reminder of their reduction goals.

2.5.2. Nicotine lozenge—The 4-mg nicotine lozenge was used. At each visit, participants were provided with a quantity sufficient to cover each day until their next study visit. We distributed 8 lozenges per day for weeks 1 to 6, 6 lozenges per day for weeks 7 to 8, and 4 lozenges per day for weeks 9 to 12 if participants requested additional medication beyond week 8.

2.5.3. Tobacco-free snuff—We provided participants with a choice of Smokey Mountain™ tobacco-free snuff products in either pouch or loose-leaf form in flavors of regular, wintergreen, mint, cherry, grape, and peach. This product contains no pharmacologically active ingredients and consists of organic material such as molasses, semolina, corn silk, red clover, ginseng, guarana, and cayenne pepper (Smokey Mountain Chew, 2009). At their baseline visit, participants sampled snuff products and chose the form and flavor they wanted to use. Participants were provided the number of tins of tobacco-free snuff per week based upon their baseline ST use pattern and their reduction goal.

2.6. Study Endpoints

2.6.1. Tobacco outcomes—The selected primary outcome was the percentage of participants who reduced their baseline ST use by ≥ 50% at week 4. Secondary endpoints included the mean percentage ST reduction; ST reduction of ≥ 50% and ≥ 75% at weeks 8, 12, and 26; and biochemically-confirmed tobacco abstinence at weeks 12 and 26. Although cotinine is the traditional measurement for the adjudication of self-reported tobacco abstinence (Benowitz, et al., 2002), cotinine cannot be used to biochemically validate tobacco abstinence during the use of NRT. Since nicotine replacement products do not contain the tobacco alkaloid anabasine and anatabine like tobacco does, urinary anabasine and anatabine are the preferred biomarkers of tobacco consumption in subjects using NRT (Jacob, Yu, Shulgin, & Benowitz, 1999). We used urinary anabasine and anatabine concentrations of < 2 ng/mL as our cut-off concentration to indicate abstinence from all tobacco (Jacob, et al., 2002; Jacob, et al., 1999). Biochemical analyses were conducted at the University of California, San Francisco.

2.6.2. Withdrawal and craving—Participants were asked to keep a daily diary of tobacco withdrawal symptoms for 6 weeks starting at the information session. The daily diary included the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes, 2007; Hughes & Hatsukami, 1998) modified for ST users. The MNWS is a 9-item measure consisting of the following symptoms rated on a 5-point Likert scale ranging from 0 (not present) to 4 (severe): desire to use tobacco (i.e., craving); anger, irritability, or frustration; anxiety or nervousness; difficulty concentrating; impatience; restlessness; hunger; awakening at night; and depression. We modified the item “desire to smoke” with “desire to use tobacco.”

2.6.3. Adverse events—At each clinic visit, adverse events either observed by study staff or mentioned by participants were documented on case report forms. Adverse events were managed according to a written Safety Management protocol until resolved or the subject completed the study.

2.7. Statistical Analyses

The purpose of this clinical pilot study was to obtain preliminary data regarding the potential effectiveness of nicotine lozenges compared to tobacco-free snuff for ST reduction and tobacco abstinence. Although debate exists regarding the value of formal statistical comparisons in phase II trials, formal comparisons are appropriate under the caveat that phase II studies are not expected to provide reliable definitive comparisons using a traditional two-sided type I error rate of 0.05 (Ratain & Sargent, 2009; Rubinstein, et al., 2005). Changes from baseline ST use were calculated at each follow-up visit with participants who discontinued study participation assumed to be using tobacco at the same rate as baseline. For the primary analysis, a dichotomous “success criterion” was defined as a reduction in the self-reported ST cans per week to ≤ 50% of baseline use at week 4. The percentage of participants meeting this criterion was compared between groups using the Fisher exact test with the *a priori* criteria being that a one-tailed p value of < .20 would be considered sufficient evidence to suggest that additional studies of the nicotine lozenge for the reduction of ST use may be warranted. Additional analyses were performed comparing the percentage of participants who met criteria for 75% reduction of ST use and biochemically-confirmed tobacco abstinence at other time points.

Daily diaries were used to assess nicotine withdrawal symptoms and cravings. A composite nicotine withdrawal score was calculated as the mean of the individual withdrawal symptoms. Desire to use tobacco (i.e., craving) was analyzed separately. Withdrawal and craving scores were analyzed using mixed linear models with a lag-1 autoregressive covariance structure used to take into account multiple observations for each subject. The

models included main effects for treatment group (nicotine lozenge vs. tobacco-free snuff) and time in days treated as a continuous variable as well as the time-by-treatment interaction effect. The frequency of adverse events considered to be possibly, probably, or definitely related to the study drug was compared between treatment groups using the Fisher exact test. For all treatment comparisons of tobacco reduction and abstinence outcomes, one-tailed p values were determined. For all other analyses two-tailed p values were determined.

3. Results

3.1. Participants

Of 130 individuals screened, 81 were randomized (40 nicotine lozenge, 41 tobacco-free snuff) and included in the final analysis (Figure 1). No significant differences were observed between the two groups at baseline. A total of 17 participants (9 nicotine lozenge, 8 tobacco-free snuff) discontinued study participation during the initial 8-week medication phase, and an additional 6 participants (5 nicotine lozenges, 1 tobacco-free snuff) discontinued during follow-up.

3.2. ST Reduction

The primary endpoint for the current investigation was the percentage of participants who self-reported reducing ST use by at least 50% in cans per week at week 4. For this endpoint, evidence suggested increased success among participants who used nicotine lozenges compared to tobacco-free snuff (62% vs. 46%; one-tailed $p = .108$). However, no evidence of a difference between treatment groups was observed for secondary reduction endpoints at weeks 8, 12, and 26 (Table 2). Both groups, however, significantly reduced ST use in cans per week (Figure 2) and dips per day (Figure 3) from baseline, which was sustained through the end of the study.

3.3. ST Abstinence

At 12 weeks, 8 participants in the nicotine lozenge group and 6 participants in the tobacco-free snuff group self-reported tobacco abstinence. Of these, one participant in the tobacco-free snuff group failed to provide a urine sample for biochemical confirmation. All other participants who self-reported abstinence at week 12 were biochemically-confirmed abstinent (20% vs 12%, one-tailed $p = .257$ for nicotine lozenge vs. tobacco-free snuff). At week 26, 8 participants in the nicotine lozenge group and 6 participants in the tobacco-free snuff group self-reported tobacco abstinence. Of these, one participant in each group failed biochemical confirmation due to elevated anabasine/anatabine and two participants in the nicotine lozenge group did not provide a urine sample. Thus, the **observed** biochemically-confirmed abstinence rates at week 26 were similar between groups (12% vs. 12%, one-tailed $p = .615$).

3.4. Nicotine Withdrawal and Desire to Use Tobacco

Composite nicotine withdrawal scores decreased with time (time effect = –0.010, SE = 0.005, $p = .007$) but did not differ significantly between the nicotine lozenge and tobacco-free snuff groups (nicotine effect = 0.159, SE = 0.117, $p = .184$). No evidence of a time-by-nicotine interaction was observed (interaction effect = 0.001, SE = 0.007, $p = .925$). Desire to use tobacco was also found to decrease with time (time effect = –0.036, SE = 0.012, $p = .004$) but did not differ significantly between the nicotine lozenge and tobacco-free snuff groups (nicotine effect = 0.444, SE = 0.297, $p = .144$). No evidence of a time-by-nicotine interaction was observed (interaction effect = 0.013, SE = 0.018, $p = .478$).

3.5. Use of Assigned Product

Of the 40 participants assigned to nicotine lozenges, 29 (72%) remained in the study through the end of the initial 8-week medication phase, and 26 (65%) requested and received additional medication for weeks 9 to 12. Of the 41 participants assigned to tobacco-free snuff, 33 (80%) remained in the study through weeks 8, and 29 (71%) requested and received additional medication for weeks 9 to 12.

3.6. Adverse Events

Four subjects (3 nicotine lozenge, 1 tobacco-free snuff) experienced adverse events considered to be possibly, probably, or definitely related to the study drug. These events included sore throat (1 nicotine lozenge, 1 tobacco-free snuff); dizziness (1 nicotine lozenge); and insomnia (1 nicotine lozenge).

4. Discussion

The results of our pilot clinical trial suggest that, among ST users not interested in quitting, both the nicotine lozenge and tobacco-free snuff facilitate ST reduction. In both groups at 26 weeks, almost one-third of participants achieved ≥ 75% ST reduction in cans/week and dips/day and 12% achieved biochemically-confirmed tobacco abstinence.

Our results are reasonably similar to those of previously published trials of tobacco-free snuff for reduction among ST users not ready to quit (Hatsukami, et al., 2008). In the Hatsukami et al. (2008) study, 23.1% of participants receiving tobacco-free snuff (N = 52) achieved a ≥ 75% reduction in cans/week at week 8, and we observed that 32% achieved this goal. At week 12, Hatsukami et al. (2008) observed that 19.2% of participants in the tobacco-free snuff group were biochemically-confirmed abstinent from tobacco while we observed that 12% were abstinent. Our results are very similar to another study evaluating the 4-mg nicotine lozenge for ST reduction (Ebbert, et al., 2010) in which 32.1% of the nicotine lozenge group (N = 57) achieved a ≥ 75% reduction in dips per day at week 8, and we observed a rate of 33%. Ebbert et al. (2010) also observed that the self-reported abstinence at week 8 was 14% while we observed a rate of 15% (n = 6) (data not shown).

Composite nicotine withdrawal scores and desire to use tobacco decreased with time in both groups. We were surprised that we did not observe a greater effect with nicotine lozenges for decreasing withdrawal and craving. Although we may have been underpowered for this analysis, this finding suggests that relief of withdrawal and craving among ST users may not be exclusively related to nicotine. Both psychological conditioning and sensorimotor aspects of tobacco use may be alleviated through the use of oral products. Among cigarette smokers, neither pure nicotine nor denicotinized cigarettes alone completely abolish cravings or provide the subjective satisfaction of smoking regular cigarettes (Rose, Behm, Westman, Bates, & Salley, 2003; Rose, Behm, Westman, & Johnson, 2000). Although these types of studies have not been conducted among ST users, they emphasize the role of sensorimotor factors in mediating the immediate subjective response to tobacco and the potential role of nonnicotine-containing products in the treatment of ST users.

Our results also provide additional support to the potential role of tobacco reduction as a treatment approach for tobacco users who are not ready to quit. Cigarette smokers who reduce daily cigarettes by greater than 50% are nearly twice as likely to be abstinent from smoking after six years (Falba, Jofre-Bonet, Busch, Duchovny, & Sindelar, 2004). Studies evaluating smoking reduction with NRT reveal significant and sustained decreases in the number of daily cigarettes smoked and an increased odds for quitting at long-term follow-up compared to placebo (odds ratio = 1.90; 95% CI 1.46, 2.47) (Stead & Lancaster, 2007). Importantly, none of the smoking reduction studies were observed to undermine future

tobacco abstinence (Hughes & Carpenter, 2006). Furthermore, no serious adverse events attributable to nicotine toxicity caused by concomitant use of NRT and smoking have been reported (Stead & Lancaster, 2007). In the present study, no serious adverse events were reported or observed associated with the concomitant use of NRT and ST.

5. Conclusions

Our study suggests that the nicotine lozenge and tobacco-free snuff can facilitate the reduction of ST use among ST users not ready to quit ST. Future studies could evaluate the combination of tobacco-free snuff and other forms of NRT such as the nicotine patch to further increase abstinence rates among ST users not ready to quit.

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Highlights

- Among ST users not wanting to quit, the lozenge and tobacco-free snuff reduced use.
- No reduction differences were observed between the lozenge and tobacco-free snuff.
- 12% of ST users were tobacco-abstinent at 6 months with both products.

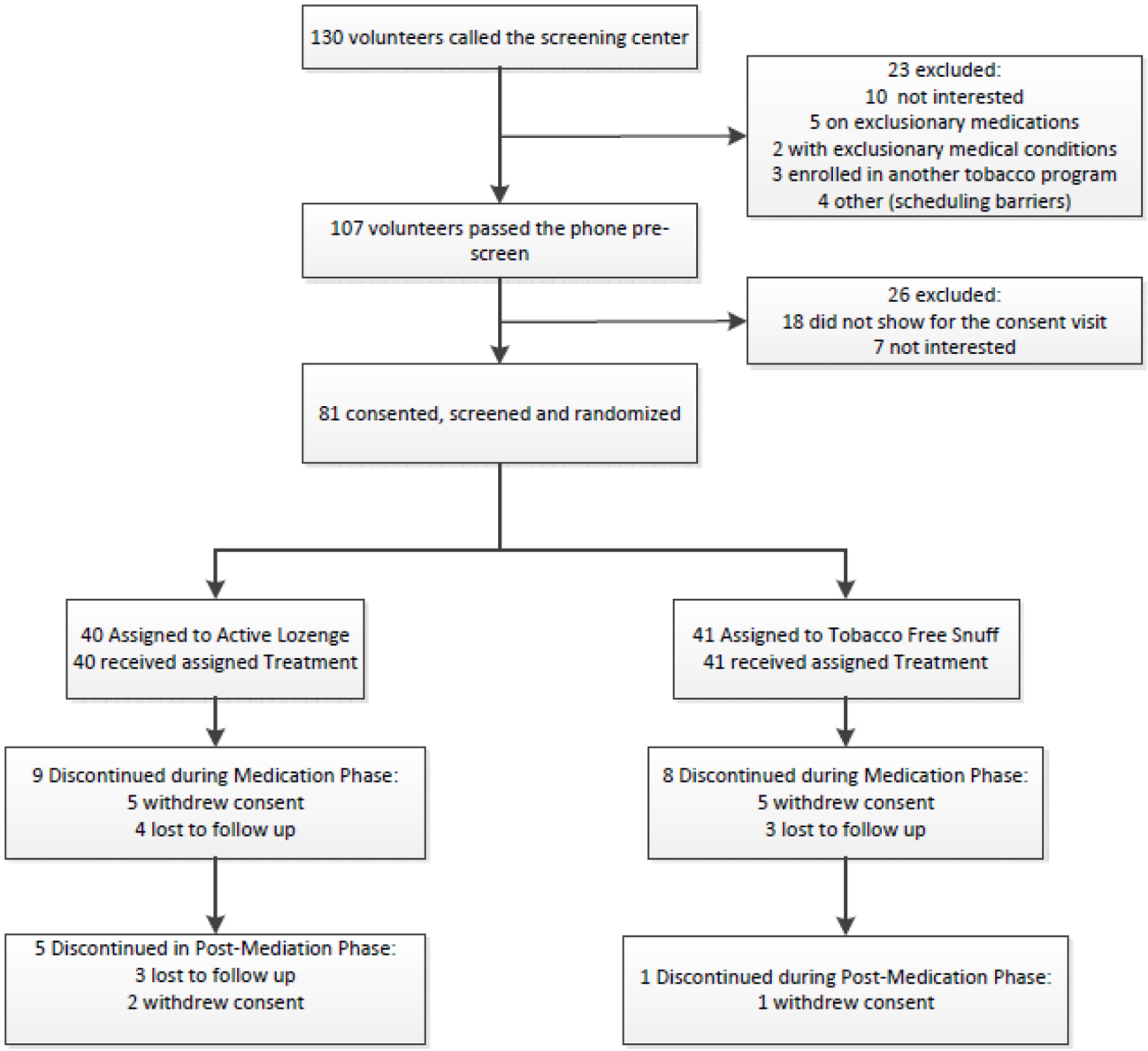

Figure 1.
Study Diagram.

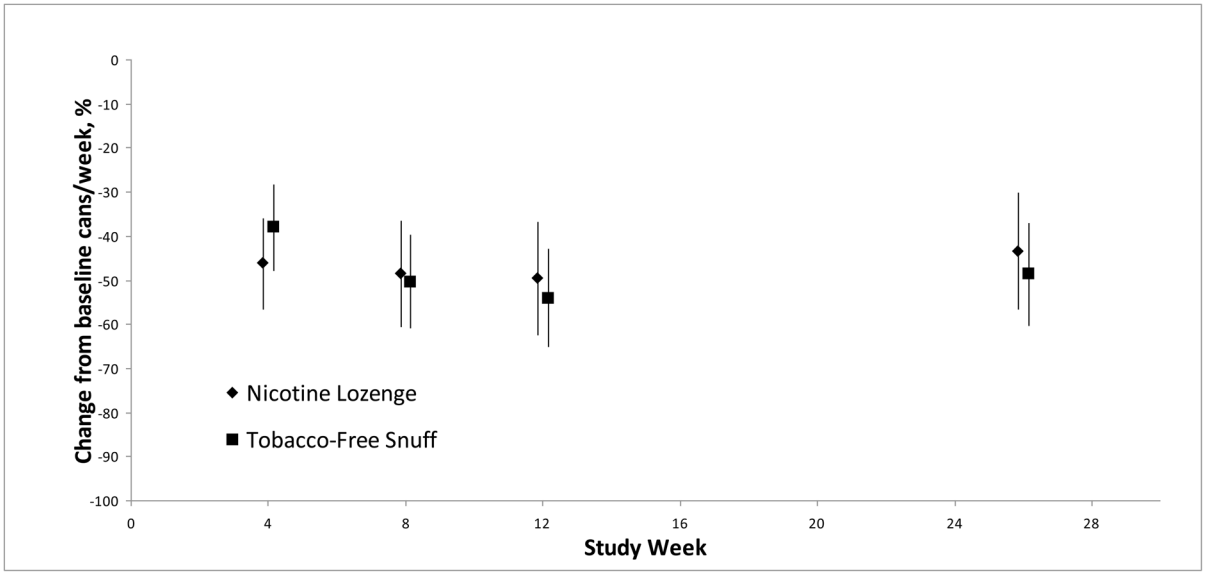

Figure 2.
Data represent mean percentage change (cans/week) with bars representing 95% confidence intervals.

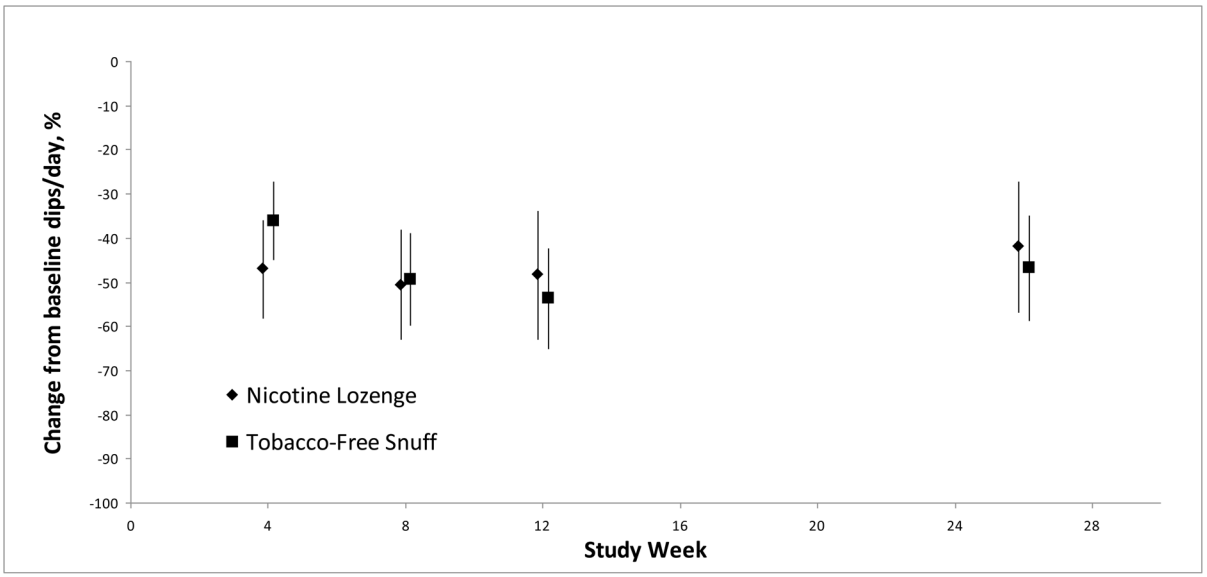

Figure 3.
Data represent mean percentage change (dips/day) with bars representing 95% confidence intervals.

Table 1

Baseline Characteristics of ST Users Enrolled in a ST Reduction Study[a]

Characteristic	Nicotine Lozenge (N=40)	Tobacco-Free Snuff (N=41)
Age, years	37.8 ± 15.9	37.5 ± 12.7
Male, n (%)	40 (100)	38 (93)
Caucasian, n (%)	40 (100)	37 (90)
Marital status, n (%)		
Married/living as married	20 (50)	25 (61)
Never married	15 (30)	13 (32)
Separated/divorced	5 (10)	3 (7)
Highest level of education, n (%)		
< High school graduate	2 (5)	2 (5)
High school graduate	10 (25)	9 (22)
Some college	19 (48)	22 (54)
College graduate	9 (22)	8 (19)
Current type of smokeless tobacco used, n (%)		
Snuff	39 (95)	41 (100)
Chewing tobacco	1 (5)	0 (0)
Smokeless tobacco use		
Cans/pouches per week	3.2 ± 2.1	4.0 ± 2.7
Dips per day[b]	7.6 ± 4.2	9.7 ± 3.7
Years of regular smokeless tobacco use, years	14.1 ± 10.9	15.3 ± 9.4
Current use of other tobacco products[c], n (%)	4 (10)	3 (7)
Other users of tobacco in household, n (%)	14 (35)	13 (32)
Number of closest friends who use ST, n (%)		
None	8 (21)	14 (34)
1	4 (10)	6 (15)
2	10 (26)	7 (17)
3 or more	17 (43)	14 (34)
Fagerström Test for Nicotine Dependence – ST	4.6 ± 2.3	4.9 ± 2.1
Severson Smokeless Tobacco Dependence Scale (SSTDS)	10.6 ± 3.8	9.7 ± 3.7
Ever made serious attempt to quit ST use, n (%)	32 (80)	30 (73)
Ever made serious attempt to reduce ST use, n (%)	34 (85)	37 (90)

[a] Data are presented as mean ± SD or n (%).

[b] Data were missing for 1 subject in the nicotine lozenge group.

[c] In the nicotine group 1 subject used cigars (< 1 per day), 2 participants used cigarettes (4 cpd and < 1 cpd), and 1 subject used hookah (< 1 per day). In the tobacco-free snuff group 3 participants used cigarettes (all < 1 cpd).

Table 2

Smokeless Tobacco Reduction and Abstinence Outcomes[a]

	Dips/day			Cans/week		
Timepoint % Reduction	**Nicotine Lozenge N=39[b]**	**Tobacco-Free Snuff N=41**	***p* Value[c]**	**Nicotine Lozenge N=40**	**Tobacco-Free Snuff N=41**	***p* Value[c]**
4 weeks						
Percent change from baseline, mean ± SD	−47 ± 35	−36 ± 29	0.086	−46 ± 33	−38 ± 32	0.149
Reduced ≥ 50%, n (%)	22 (56)	18 (44)	0.186	25 (62)	19 (46)	0.108
8 weeks						
Percent change from baseline, mean ± SD	−51 ± 39	−49 ± 34	0.365	−49 ± 38	−50 ± 34	0.526
Reduced ≥ 50%, n (%)	24 (62)	25 (61)	0.571	24 (60)	25 (61)	0.624
Reduced ≥ 75%, n (%)	13 (33)	12 (29)	0.440	11 (28)	13 (32)	0.744
12 weeks						
Percent change from baseline, mean ± SD	−48 ± 46	−54 ± 37	0.552	−50 ± 40	−54 ± 36	0.648
Reduced ≥ 50%, n (%)	23 (59)	27 (66)	0.809	22 (55)	27 (66)	0.890
Reduced ≥ 75%, n (%)	15 (38)	15 (37)	0.523	15 (38)	16 (39)	0.644
26 weeks						
Percent change from baseline, mean ± SD	−42 ± 46	−47 ± 38	0.655	−43 ± 41	−49 ± 38	0.716
Reduced ≥ 50%, n (%)	20 (51)	21 (51)	0.586	20 (50)	22 (54)	0.709
Reduced ≥ 75%, n (%)	12 (31)	12 (29)	0.538	12 (30)	13 (32)	0.658

[a] Participants with missing information at a given follow-up visit are assumed to be using tobacco at the same rate as baseline.

[b] One subject in the nicotine lozenge group is excluded from the dips/day analysis due to missing baseline information.

[c] Dichotomous endpoints are compared between groups using the Fisher exact test and the percentage change from baseline is compared between groups using the rank sum test. In all cases, one-tailed *p* values are reported.