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Brief Report

Smokeless tobacco reduction with the nicotine lozenge and behavioral intervention

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Abstract

Introduction: Studies have evaluated smoking reduction with nicotine replacement therapy to reduce tobacco exposure and facilitate abstinence among cigarette smokers, but none have evaluated a reduction approach in smokeless tobacco (ST) users.

Methods: We conducted an open-label pilot study to determine if the 4-mg nicotine lozenge with a behavioral intervention could facilitate ST use reduction among ST users compared with a behavioral intervention alone. Eligible subjects were ST users not interested in quitting.

Results: One hundred and two subjects were randomized. Both interventions were associated with significant decreases in ST use and toxicant exposure and with increased abstinence, quit attempts, and duration of abstinence. However, no significant differences were observed between groups for these outcomes.

Discussion: A behavioral intervention with or without the nicotine lozenge may be effective for decreasing both ST use and toxicant exposure and for increasing tobacco abstinence, quit attempts, and duration of abstinence. The use of reduction strategies for ST users not interested in quitting deserves further evaluation as an intervention strategy.

Introduction

Numerous studies have evaluated cigarette smoking reduction as a method to reduce tobacco exposure and facilitate smoking abstinence (Stead & Lancaster, 2007), but only two have examined this approach in smokeless tobacco (ST) users. One study examined the effects of switching ST brands on nicotine and toxicant (i.e., tobacco carcinogens) exposure reduction and tobacco cessation (Hatsukami et al., 2007). The other study examined the effects of substituting ST with a tobacco-free snuff on nicotine and toxicant exposure reduction and tobacco cessation (Hatsukami et al., 2008). Significant reductions in nicotine and toxicant exposure were observed with both approaches.

Cigarette consumption reduction can be facilitated by the use of nicotine replacement therapy (NRT; Hughes & Carpenter, 2006). NRT can maintain serum concentrations of nicotine while reducing tobacco exposure (Shiffman, Mason, & Henningfield, 1998). No studies have examined the effects of NRT on ST reduction.

The nicotine lozenge is an attractive NRT option for ST users since it can provide oral sensory stimulation (Muramoto, Ranger-Moore, & Leischow, 2003) while providing more nicotine than the nicotine gum (Choi, Dresler, Norton, & Strahs, 2003). We conducted a pilot study to determine if the nicotine lozenge with a behavioral intervention would reduce ST use and toxicant exposure compared with a behavioral intervention alone. We were also interested in determining the potential impact of the lozenge for increasing ST abstinence, number of quit attempts, and duration of tobacco abstinence.

Methods

Subject recruitment

Subjects were recruited from the Minneapolis, MN, metropolitan area through news media advertisements and flyers. After telephone screening, potential subjects visited our research center to submit informed consent and complete baseline measures. Potential subjects were eligible for enrollment if they were (a) between the ages of 18 and 70 years, (b) interested in reducing ST use but not quitting (i.e., not having an established quit date within the next 90 days), and (c) using ST daily use (≥2 tins per week) for the past 6 months. Tobacco use rate as an inclusion criteria was used to target heavy ST users so that a reduction in toxicant exposure could be observed. Patients were excluded if they had an unstable medical condition or were taking psychotropic medications, other tobacco or nicotine products, or pregnant or lactating.

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Experimental procedures

After a 2-week baseline period, subjects were assigned to groups at the first treatment visit (Week 0) using a randomization list. Subjects were randomized to 8 weeks of the 4-mg nicotine lozenge with behavioral intervention (intervention) or behavioral intervention alone (control). Both groups were instructed that the goal was a percentage intake reduction of 50% for the first 4 weeks and 75% for the subsequent 4 weeks. The number of ST dips required to achieve this reduction was determined from baseline measurements. They were instructed on behavioral reduction methods, such as extending dip intervals, eliminating use in certain situations, and delaying morning use. The lozenge group subjects were instructed to alternate their usual ST brand with the lozenge to achieve targeted reduction and encouraged to use more nicotine lozenges if necessary to reduce ST use to the targeted goal.

Clinic visits and measurements occurred weekly during the 2-week baseline and the 8-week treatment period. At each clinic visit, ST use and lozenge use were determined by self-recorded data captured on daily diaries. Urine analyses were collected during baseline and at Weeks 4, 8, and 12 for cotinine, as a measure of tobacco exposure, and toxicants. The toxicant analyzed was the tobacco-specific carcinogen 4-(methylnitrosamino)-l-(3-pyridyl)-l-butanone (NNK) (Hecht et al., 1999). NNK metabolite measurements were analyzed and reported as total NNAL consisting of 4-(methylnitrosamino)-l-(3 pyridyl) l-butanol (NNAL) and its glucuronides (NNAL-Glucs; Hatsukami et al., 2003).

At 8 weeks, subjects were asked if they would like to quit ST. If interested, they set a quit date and follow-up calls were made at 1 week and 1 month after their quit date. If not, they were encouraged to maintain ST use reduction or reduce even further. Subjects in the lozenge condition were offered more if they chose to continue. Two weeks worth of products were dispensed. Subjects needing more nicotine lozenges reported at Week 10 to receive 2 additional weeks of medication. No lozenges were dispensed after Week 12.

Counseling

Subjects met with a counselor during the 8 weekly clinic visits for individual sessions lasting ≤10 min. A specific format was followed that included (a) asking about tobacco use status, (b) discussing motivations for tobacco reduction, (c) discussing encountered problems, (d) problem-solving difficult situations or compliance issues, and (e) providing support. For individuals wanting to quit after the 8-week period, counseling involved(a) discussing reasons for wanting to quit and potential obstacles; (b) discussing the content of the treatment manual, *Tough Enough to Quit Snuff*, including preparation for the quit day, identification of high risk situations, and strategies to deal with these situations; and (c) identifying sources of support.

Follow-up

A follow-up session occurred at Week 12. Subjects were asked to monitor ST and other tobacco use for the prior week using daily diary cards. They were also asked to provide first morning urine. Participants received $10 per each clinic visit during treatment, $25 per follow-up visit, and $150 bonus for attending all the visits and complying with the study requirements.

Statistical analysis

Baseline demographics were tabulated for treatment groups using summary statistics. Tins per week, dips per day, and mean concentrations of cotinine and NNAL through Week 12 were calculated with baseline values assumed for missing data.

Outcomes were analyzed using an intention-to-treat approach. The primary hypothesis tested was whether the treatment group had different effects on level of ST reduction at the end of 4 and 8 weeks and at the 12-week follow-up. Analysis of ST use and exposure measures used linear mixed models to investigate whether the two interventions had different effects on ST use reduction (Cnaan, Laird, & Slasor, 1997; Littell, Pendergast, & Natarajan, 2000; Schluchter, 1988). Analyses modeled the repeated measures in reported ST use and concentrations of total cotinine and NNAL at each visit (baseline and Weeks 4, 8, and 12). Covariates included main effects for the discrete time and the treatment group as well as interactions between treatment group and time. Models were fitted using restricted maximum likelihood to estimate covariance structure for within-subject responses.

The percentage of each group achieving targeted reduction level at the end of 4 (≥50%), 8 (≥75%), and 12 (≥50%) weeks was calculated and compared using chi-square test. The analysis of the percentage in each group that achieved the targeted reduction level at the end of 4 (≥50%), 8 (≥50% and ≥75%), and 12 (≥50%) weeks compared the success rates for the different treatment groups using a logistic regression model. We examined both ≥50% and ≥75% reduction at 8 weeks although the targeted reduction was 75% because 50% is the typical outcome of reduction studies. Generalized linear mixed model was used to model the probability of achieving the reduction target at each follow-up visit (Weeks 4, 8, and 12). The same covariates were included in this model as in the previous linear mixed model. In this analysis, the percent reduction for a subject who did not complete a particular visit was assumed to be less than the targeted reduction and coded as unsuccessful.

The two treatment groups were also compared on (a) 7-day point prevalence tobacco abstinence, (b) number of ≥24-hr quit attempts, and (c) mean duration of abstinence. The Fisher's exact test for comparing the two treatment groups at each week was conducted. For all analyses, p values ≤.05 were considered statistically significant.

We also summarized the mean ± *SD* lozenges used by week during the 8-week treatment period.

Results

Participants

Of 175 screened subjects, 102 were randomized. Among the 73 subjects who failed to enter the study, 61 subjects did not return after the initial screening visit, 8 were excluded for medical reasons (7 for hypertension and 1 for chest pain), and 4 did not meet the minimum tobacco use requirement. A total of 23 subjects dropped out of the study (12 were in the behavioral intervention only group and 11 were in the lozenge group). Brand use varied significantly between groups (Table 1).

Table 1. Demographics of ST users enrolled in study of ST reduction

Variables	Nicotine lozenge and behavioral intervention ($N = 57$)		Behavioral intervention only ($N = 45$)	
	Mean ± *SD* (or %)	*n*	Mean ± *SD* (or %)	*n*
Age (years)	35.0 ± 7.5	57	35.3 ± 9.7	45
Age of daily ST use (years)	19.9 ± 5.7	57	20.5 ± 7.4	45
Age of first ST use (years)	16.6 ± 4.9	57	17.4 ± 7.8	45
Tins/week	4.3 ± 1.9	57	4.1 ± 1.8	45
Dips/day	10.1 ± 5.2	57	9.3 ± 5.2	45
Total cotinine (ng/ml urine)	8,835 ± 6,652	57	7,249 (4,553)	45
Total NNAL (pmol/ml urine)	6.4 ± 5.7	48	5.5 (3.7)	35
Total NNAL (pmol/mg creatinine)	4.0 ± 3.3	48	4.8 (3.6)	35
Brand of smokeless [a]				
Copenhagen	38.6	22	11.1	5
Skoal	14.0	8	24.4	11
Kodiak	26.3	15	37.8	17
Red Man	0	0	2.2	1
Grizzly	19.3	11	20.0	9
Timber Wolf	1.8	1	2.2	1
Other	0	0	2.2	1

Note. NNAL = 4-(methylnitrosamino)-l-(3 pyridyl) l-butanol; ST = smokeless tobacco.

[a]Distribution of brand was different between the two groups, $p = .02$, Fisher's exact test. For all the other variables, there was no statistically significant difference between the two groups.

Reductions in ST and toxicant exposure

Both interventions produced decreases in ST use, tobacco exposure, and toxicants, but no significant differences were observed between groups (Figure 1).

For both groups, significant time effects were observed for tins per week ($p < .001$), dips per day ($p < .001$), cotinine ($p < .001$), and total NNAL (pmol/mg creatinine; $p = .03$, indicating a non-constant time trend in these variables over the baseline and follow-up visits. A time-by-treatment interaction effect was observed ($p = .03$) with significantly higher cotinine levels in the lozenge group at Week 4 (difference = 2,115, $p = .03$) and marginally significantly greater reduction in cotinine in the lozenge group at Week 12 (difference in reduction = −1,642, $p = .05$) compared with baseline. No other significant treatment or time-by-treatment effects were observed.

Percentage reduction

At Week 8, a greater but not statistically significant proportion of subjects in the lozenge group achieved a ≥75% reduction in dips per day (32.1%) compared with the behavioral intervention group (16.7%, $p = .08$). A higher proportion of subjects in the lozenge group also achieved a ≥75% reduction in total NNAL (pmol/mg creatinine) at Week 8 (18.8% vs. 5.7%, $p = .08$). As expected, a higher percentage of subjects in the behavioral intervention group achieved a ≥50% reduction in cotinine at Week 4 (31.1% vs. 15.8%, $p = .07$) and ≥75% reduction in cotinine at Week 8 (11.1% vs. 5.3%, $p = .28$) compared with the lozenge group.

Significant time effects were observed for dips per day in both groups ($p = .01$), for cotinine in the lozenge group ($p = .02$) and for total NNAL (pmol/mg creatinine) in the lozenge group ($p = .01$), indicating that the reduction in these variables are not constant over the three follow-up visits. No other significant time, treatment, or time-by-treatment effects were observed.

Abstinence, quit attempts, and duration of abstinence

Both groups showed significantly increased proportions of self-reported 7-day abstinence with time ($p < .001$ and $p = .01$ for lozenge and the behavioral intervention group, respectively). The lozenge group doubled the proportion of self-reported 7-day abstinence as compared with the behavioral intervention group at Week 8 although the difference was not significant (lozenge vs. counseling: 14.0% vs. 6.7%, respectively, $p = .34$). No treatment-by-time interactions were observed.

Both groups showed a significantly increased proportion of quit attempts with time ($p < .001$). Approximately one third of subjects in each group had made quit attempts by Week 12 (lozenge vs. behavioral: 33.3% vs. 28.9%, respectively, $p = .67$). No treatment-by-time interactions were observed.

Both groups showed significantly increased duration of abstinence with time ($p < .001$). A trend was observed toward a longer duration of abstinence in the lozenge group compared with the behavioral intervention group (9.9 ± 17.3 [*SD*] days vs. 6.6 ± 15.1 days, $p = .30$). No treatment-by-time interactions were observed.

Lozenge use

All subjects reported using lozenges from Weeks 1 to 7, and all subjects except one used lozenges during Week 8. At Weeks 1–4, subjects used a mean ± *SD* of 3.1 ± 1.6, 3.6 ± 2.0, 3.7 ± 1.8, and 4.1 ± 2.4 lozenges per day, respectively. At Weeks 5–8, subjects

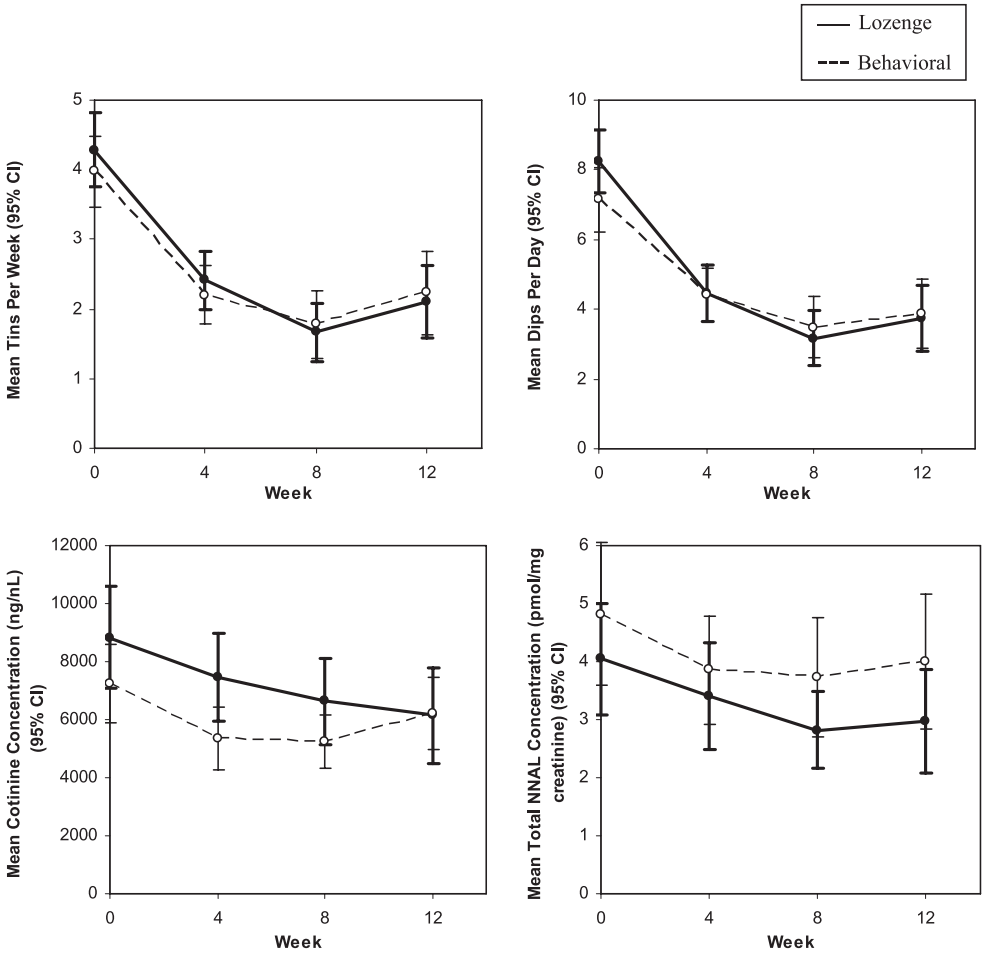

Figure 1. The effects of lozenge and a behavioral intervention on ST use, tobacco exposure (cotinine), and toxicants (total NNAL) during treatment period (baseline to Week 8) and at 12-week follow-up. Missing values are replaced by baseline values.

used a mean ± *SD* of 4.6 ± 2.7, 4.5 ± 2.4, 4.5 ± 2.6, and 5.1 ± 3.2 lozenges per day, respectively.

Discussion

We conclude that a behavioral intervention with or without the nicotine lozenge may be effective for decreasing both ST use and toxicant exposure. However, a trend toward more subjects achieving a ≥75% reduction in dips per day and toxicant exposure with the nicotine lozenge was observed. Both interventions were effective for increasing tobacco abstinence, number of quit attempts, and duration of abstinence over time.

In studies among cigarette smokers unable or unwilling to quit, NRT significantly increased the odds of cigarette reduction by ≥50% (odds ratio [*OR*] = 2.02, 95% *CI*: 1.55–2.62) and the odds of quitting (*OR* = 1.90, 95% *CI*: 1.46–2.47; Stead & Lancaster, 2007). Although we may have been underpowered for these analyses, the nicotine lozenge group demonstrated a higher proportion of subjects with a ≥75% reduction in dips per day (32.1% vs. 16.7%, $p = .08$) and higher 7-day self-reported tobacco abstinence rates (14.0% vs. 6.7%, $p = .34$) compared with the counseling group at Week 8. Larger trials are needed to assess the effect of the nicotine lozenge on ST reduction and tobacco abstinence rates among ST users unwilling or unable to quit.

Our study had several limitations. First, we were likely underpowered to detect important differences between groups because this was a pilot study, and we did not have previous literature upon which to base effect sizes. Second, we lacked a nicotine lozenge placebo. The use of an oral substitute may explain the trend toward a higher proportion of subjects achieving a ≥75% reduction in dips per day and toxicant exposure. We cannot make conclusions about the role of nicotine in this observed difference. Third, we lacked a "no counseling" control condition for the behavioral intervention. An ideal design for future trials assessing whether the nicotine lozenge or counseling or both increase the odds of abstinence among ST user unwilling or unable to quit would be a 2 × 2 design of active versus placebo lozenge and counseling versus no counseling. Finally, we did not adjust lozenge dosing according to patterns of ST use or use of different ST brands. Therefore, ST users with higher baseline levels of nicotine exposure may have not experienced as much symptom relief from the nicotine lozenge as those with lower levels, which may have compromised the efficacy of the lozenge. Future investigators could consider tailoring nicotine lozenge use based upon nicotine exposure (e.g., serum cotinine concentrations).

We provide novel information regarding ST reduction among ST users not interested in quitting (i.e., not having an established quit date within the next 90 days). This population is distinctly different from a population of ST users actively trying to achieve tobacco abstinence through reduction, frequently referred to "gradual cessation" (Hughes & Carpenter, 2005). Studies in smokers suggest that reduction programs increase the percentage of smokers willing to participate (Glasgow et al., 2006). Our study suggests that a behavioral intervention with or without the nicotine lozenge offered to ST users not interested in quitting may not only engage a larger population of ST users but may also decrease their tobacco exposure and risk of tobacco-related illnesses.

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Declaration of Interests

None declared.

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