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Short Communication

# A pilot study of mailed nicotine lozenges with assisted self-help for the treatment of smokeless tobacco users

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ABSTRACT

Smokeless tobacco (ST) is associated with adverse health consequences yet treatment resources for ST are not widely available. Cost-effective behavioral interventions incorporating self-help materials and counseling calls have been demonstrated to reduce ST use rates and can be easily disseminated, but the feasibility and effectiveness of incorporating pharmacotherapy into this approach have not been evaluated. We conducted a clinical pilot study randomizing 60 patients to 12 weeks of the 4-mg nicotine lozenge or placebo delivered through the mail. All subjects received an assisted self-help intervention (ASH) with telephone support. At the end of the medication phase, lozenges were being used by 63% of subjects in the 4-mg nicotine lozenge group and 43% in placebo. The nicotine lozenge decreased composite withdrawal symptoms and adverse events were minimal. No significant differences were observed in abstinence rates between the two groups at 3 or 6 months. We conclude that the mailing of nicotine lozenges to ST users is a feasible and safe strategy the efficacy of which needs to be evaluated.



## 1. Introduction

Long-term use of smokeless tobacco (ST) may increase the risk for oral (Stockwell & Lyman, 1986), kidney (Muscat, Hoffmann, & Wynder, 1995) and pancreatic (Muscat, Stellman, Hoffmann, & Wynder, 1997) cancer. Long-term ST use is associated with death from coronary heart disease (CHD) and stroke (Henley, Thun, Connell, & Calle, 2005). However, few cessation resources are available for ST users. Clinic-based resources are not widely available and may not be accessed by ST users who tend to be young, rural males rarely seeking routine medical care (Ebbert, Carr, & Dale, 2004). Given the lower prevalence of past month ST use compared to cigarette smoking among individuals ≥12 years of age (3.5% vs. 23.9%) (Substance Abuse and Mental Health Services Administration, 2009) and the unique nature of this population of tobacco users, affordable, effective and disseminable interventions for ST users are needed.

In our previous work, subjects receiving a self-help manual plus two support phone calls [i.e., assisted self-help (ASH)] had significantly higher rates of abstinence at 6 months from ST and all tobacco compared to subjects who received only a self-help manual (Severson et al., 2000). In a different study, nicotine lozenge was observed to be effective for increasing ST abstinence rates and decreasing withdrawal and craving (Ebbert et al., 2007). The combination of an ASH intervention with mailed nicotine lozenge may provide the public health community with a cost-effective intervention combining behavioral and pharmacologic approaches for treating ST use.

We conducted a clinical pilot study to assess the feasibility and safety of mailed nicotine lozenges with an ASH intervention for ST users.

## 2. Methods

### 2.1. Study design

This study was a randomized, placebo-controlled clinical trial enrolling 60 ST users. Subjects were randomized to the 4-mg nicotine lozenge or placebo for 12 weeks with follow-up to 6 months. All subjects also received an assisted self-help (ASH) intervention.

The study was conducted at the Mayo Clinic in Rochester, MN, and the Oregon Research Institute (ORI) in Eugene. The Institutional Review Boards at each study site approved the study protocol prior to subject recruitment. Enrollment took place between June 24, 2008 and September 30, 2008.

### 2.2. Study population

ST users were recruited through press releases and advertising. Subjects were screened by phone and were eligible for inclusion if they were male ≥18 years of age, reported ST use as their primary tobacco of use, had used ST daily for at least 6 months and wanted to quit. Subjects were excluded if they: 1) previously enrolled in a nicotine lozenge study; 2) were currently using any treatment for ST use; 3) were currently enrolled in another research study; 4) had a

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history of unstable angina, myocardial infarction (past 6 months), cardiac dysrhythmia, or medically-treated or untreated hypertension with BP≥180 systolic or ≥100 diastolic; 5) had a significant medical or psychiatric history; 6) had a score of ≥15 on the Patient Health Questionnaire (PHQ-8) (Kroenke et al., 2009; Pinto-Meza, Serrano-Blanco, Penarrubia, Blanco, & Haro, 2005); 7) had another member of their household participating in the study; or 8) had phenylketonuria (PKU). Nicotine lozenges contain aspartame which is metabolized to phenylalanine and not metabolized in individuals with PKU.

### 2.3. Enrollment and randomization

After initial screening by telephone, potential subjects were invited to attend a single clinic visit. During this baseline visit, study staff explained study details and completed a physical exam. Eligible subjects provided informed consent and were randomized to the 4-mg nicotine lozenge or matching placebo.

### 2.4. Intervention

The medication phase was 12 weeks in duration. For weeks 1 through 6, subjects were instructed to use one lozenge orally every 1 to 2 h with a maximum of 16 lozenges per day. For weeks 7 through 9, subjects were told to use 8 lozenges per day (one every 2 to 4 h). For weeks 10 through 12, subjects were told to use 4 lozenges per day (one every 4 to 8 h). The target quit date was the day after the baseline visit. Medication was distributed at four different times (Table 1).

The assisted self-help intervention (ASH) included a self-help quitting guide (Severson, 1999) and telephone counseling. The guide presented best-practices topics including: health effects of ST, preparing for quit day, dealing with withdrawal, avoiding relapse, stress and time management, weight management, and wellness and exercise. Counseling support was tailored to the quitting status of the participant with reference to the self-help quitting guide. Nine study assistants provided the counseling using an empathetic, nonjudgmental listening style to encourage subjects in their quitting efforts. Counseling calls lasted 5 to 15 min. Study assistants were trained on the behavioral intervention.

### 2.5. Measures

Subjects were asked to keep a daily diary to record symptoms of nicotine withdrawal and medication use. Daily diaries were completed for three weeks after the start of medication. The daily diary included the Minnesota Nicotine Withdrawal Scale [MNWS] (Hughes & Hatsukami, 1986, 1998). The MNWS is an 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 smoke (i.e., craving); anger, irritability, or frustration; anxiety or nervousness; difficulty concentrating; impatience; restlessness; hunger; awakening at night; and depression. We modified the MNWS for ST users by replacing "desire to smoke" with "desire to use tobacco."

**Table 1**
Study schedule.

| | Phone screen | Baseline visit | Treatment phase | | | | Follow-up phase |
|---|---|---|---|---|---|---|---|
| Contact # | | 1 | 2 | 3 | 4 | 5 | 6 |
| Program week | | 0 | 1 | 3 | 7 | 12 | 24 |
| Phone pre-screen | X | | | | | | |
| Informed consent | | X | | | | | |
| Inclusion/exclusion | | X | | | | | |
| Study questionnaires completed | | X | | | | | |
| Daily diary dispensed | | X[a] | | | | | |
| Study medication dispensed | | X | | | | | |
| Study medication mailed | | | X[b] | X | X | | |
| Self-help book and video distributed | | X | | | | | |
| Support calls | | | X | X | | | |
| Assessment calls[c] | | | X | X | X | X | X |
| End-of-study interview | | | | | | | X |

[a] Subjects asked to complete daily diaries for 3 weeks after they start using medication (day after their baseline visit) and asked to mail them to research offices in pre-paid stamped envelopes. Subjects were reminded to return their daily diaries during the week 1 and week 3 phone calls.
[b] Mailed the remaining first month of medication if subjects were tolerating it and agreed to continue.
[c] Assessment calls included tobacco use, adverse events, and use of concomitant medications.

### 2.6. Abstinence

The efficacy endpoint was the self-reported 7-day point prevalence all tobacco abstinence rate at end-of-treatment (week 12), defined as self-reported all tobacco abstinence in the last 7 days. ST abstinence was a secondary endpoint. Prolonged abstinence from ST was also assessed. Subjects were classified as failing criteria for prolonged ST abstinence if they reported using ST on 7 consecutive days or at least once per week for 2 consecutive weeks following a two-week grace period after the target quit date (Hughes et al., 2003). Point prevalence and prolonged abstinence rates were also analyzed at 6 months.

### 2.7. Adverse events

All self-reported adverse events were recorded over the phone and documented on case report forms and followed until resolved. Adverse events were handled according to a standard protocol which specified that severe adverse events were handled by study investigators. Subjects discontinuing the use of medication were encouraged to stay in the study.

### 2.8. Statistical analyses

Average daily lozenge use was calculated by dividing the total number of lozenges used between study visits divided by the interval, in days, between visits. Lozenge use was compared between groups using the rank sum test.

Withdrawal symptoms and craving were assessed daily using the MNWS modified for ST users. For analysis purposes, a composite withdrawal score was computed as the mean of the ratings assigned to each of the 8 individual withdrawal symptoms with the craving item analyzed separately. The repeated measures of withdrawal and craving for the first 2 weeks following TQD were analyzed using generalized estimating equations (GEEs). For these models, the explanatory variables were treatment group (4-mg lozenge vs. placebo) and time. The time-by-treatment interaction effect was included to assess whether changes in withdrawal or craving over time differed by treatment group. To supplement the repeated measures analyses, daily scores were compared between groups using the two-sample *t*-test.

For tobacco abstinence endpoints, we used an intent-to-treat imputation in which any subjects who missed a visit were considered to be using tobacco (Hughes et al., 2003). Tobacco abstinence endpoints were summarized and compared using the Chi-Square test.

## 3. Results

### 3.1. Subjects

Of 60 individuals screened, 60 subjects were eligible and randomized to receive treatment (30 lozenge, 30 placebo) and included in the final analysis. Subjects were similar at baseline (Table 2). The overall study drop-out rate was 22% at 6 months.

### 3.2. Lozenge use

During the first week there were 2 subjects (1 in each treatment group) who reported using more than 16 lozenges per day. No