

Efficacy of a Nicotine Lozenge for Smoking Cessation

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Background: Since nicotine gum was introduced in the 1980s, nicotine replacement therapy has become the most widely used pharmacological smoking cessation treatment. Some smokers prefer acute oral forms, but many smokers reject chewing gum. We tested the safety and efficacy of a new nicotine polacrilex lozenge for smoking cessation.

Methods: Double-blind, placebo-controlled, randomized clinical trial with parallel arms testing 2- and 4-mg nicotine lozenges. Smokers (n=1818) were assigned to a lozenge dose on the basis of nicotine dependence, assessed by time to the first cigarette of the day. Low-dependence smokers were randomized to receive the 2-mg nicotine (n=459) or placebo (n=458) lozenge; high-dependence smokers, the 4-mg nicotine (n=450) or placebo (n=451) lozenge. We assessed abstinence at 6, 12, 24, and 52 weeks and analyzed craving and withdrawal symptoms.

Results: Treatment with the nicotine lozenge resulted in significantly greater 28-day abstinence at 6 weeks, for the 2-mg (46.0% vs 29.7%; odds ratio [OR], 2.10; 95% confidence interval [CI], 1.59-2.79; $P<.001$) and the 4-mg (48.7% vs 20.8%; OR, 3.69; 95% CI, 2.74-4.96; $P<.001$) lozenges, compared with placebo. Significant treatment effects were maintained for a full year. Smokers who used more lozenges achieved significantly better treatment effects. Use of the active lozenge also resulted in reduced craving and withdrawal. Most adverse events were moderate and resembled those seen with nicotine gum.

Conclusion: The nicotine lozenge is a safe and effective new treatment for smoking cessation in low- and high-dependence smokers.

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SMOKING IS the leading preventable cause of death and disease in the Western world.¹ Accordingly, clinical guidelines call for physicians to provide counseling and treatment for all smokers.^{2,3} Nicotine replacement therapy (NRT) is the most widely used pharmacological therapy for smoking cessation.⁴ The efficacy of NRT has been proven in many clinical trials, approximately doubling the success rates for quitting compared with placebo.⁵ Nevertheless, most smoking cessation efforts are attempted without benefit of treatment,^{6,7} and only about 28% of US and 11% of European smokers have tried NRT⁷ (Katie Kemper, MBA, unpublished data, 1998; available from GlaxoSmithKline, GSK House, 980 Great West Rd, Brentford, Middlesex TW8 9GS, England). Introducing new dosage forms and more effective therapy may help bring more smokers into treatment, thus enhancing cessation rates and improving public health.

Nicotine replacement therapy is available in several forms—patches, nasal spray, inhalator, sublingual tablets, 1-mg lozenges, and chewing gum. Nicotine patches

provide a steady transdermal infusion of nicotine⁸ and are preferred by many smokers who are trying to quit. However, acute administration of nicotine (orally or intranasally) has potential advantages, notably in allowing the smoker to control the amount and timing of dosing. This may allow smokers to self-titrate therapy to an appropriate dosage and to use acute dosing as a rescue medication to combat acute episodes of craving.^{9,10}

Unfortunately, the current forms of NRT available for acute administration also present significant barriers to patient acceptance and use.¹¹ The nasal spray, available only by prescription in the United States, is initially very irritating,¹² and its use may carry some stigma. The nicotine inhalator¹³ (which deposits nicotine in the oropharynx) may raise similar concerns, as it is shaped like a cigarette holder; it also delivers very modest doses of nicotine. Nicotine gum is available without a prescription in many countries, but also presents some barriers to acceptance and use. People with dentures or temporomandibular joint pain may be unable to use gum. Some individuals and some cultures are uncomfort-

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SUBJECTS AND METHODS

PARTICIPANTS

One thousand eight hundred eighteen smokers were randomized to treatment, 965 at 4 sites in the United Kingdom and 853 at 11 sites in the United States. Participants were solicited via advertisements and underwent initial screening by telephone before screening at the research sites. To qualify for the study, smokers had to be 18 years or older and interested in quitting smoking during the next 30 days. Smokers were excluded if, during the past 30 days, they had used other smoking cessation aids or forms of nicotine or tobacco other than cigarettes, had smoked other substances, or had been in a clinical trial. Other exclusion criteria included pregnancy, heart disease (within the previous 3 months), stomach ulcer, uncontrolled hypertension, insulin-dependent diabetes, or difficulty metabolizing aspartame (for patients with phenylketonuria, aspartame metabolizes to phenylalanine). Initially, 2168 volunteers underwent screening and 75 were excluded; the most common reason for exclusion was smoking of other substances (no other reason accounted for $\geq 10\%$ of exclusions). Thus, 2093 participants entered baseline monitoring, 275 withdrew before randomization, and 1818 were randomized (**Figure 1**).

DESIGN

We conducted a randomized, double-blind, placebo-controlled parallel clinical trial of nicotine lozenges for smoking cessation. The study procedures were reviewed and approved by the appropriate ethics committees, and participants provided written informed consent. Smokers were assigned to a lozenge dose based on their reported TTFC of the day, ie, those who reported smoking within 30 minutes of waking were assigned to the 4-mg dose ($n=901$), and the others to the 2-mg dose ($n=917$). (Recruiting low-dependency smokers for this cessation trial proved more difficult, and the high-dependency arm was filled and closed to new entries for a time while recruitment of low-dependency smokers was completed. This resulted in some high-dependency volunteers being turned away because that arm of the study was full.) Within these groups, smokers were randomized to receive the active or the placebo lozenge. These sample sizes were designed to be adequate to detect treatment effects independently for each dose.

After enrolling, participants provided baseline assessment of craving and withdrawal symptoms for 1 week. After a week of baseline monitoring, smokers returned to the study site and were randomized to receive the active or the placebo lozenges, dispensed a supply of medication, and directed to quit smoking. Visits were scheduled at 2, 4, and 6 weeks (± 3 days), 12 weeks (± 7 days), 24 weeks (± 7 days),

and 52 weeks (± 14 days) after randomization. At each visit, participants who failed to maintain abstinence (assessed by self-report or results of carbon monoxide verification) were discontinued from the study; only abstainers were continued and followed up. At visits up to week 4, methods for quitting smoking were discussed briefly. At visits up to week 24, lozenges were distributed. At each visit, participants were asked about any adverse events (AEs) they may have experienced; these were coded in accordance with the World Health Organization Adverse Reaction Terms system. Study personnel judged the seriousness of the AEs and their relationship to the study medication (not related, unlikely to be related, possibly related, probably related, or highly probably related).

OUTCOME MEASURES

Following a standard defined by the US Food and Drug Administration,³⁰ the primary efficacy measure was complete, continuous abstinence from smoking for at least 4 weeks before the 6-week visit. To count as abstinent, participants had to report abstinence at the 2-week visit and 4 weeks of continuous abstinence at the 6-week visit. Participants' reports of abstinence were subject to verification by an exhaled carbon monoxide level of no greater than 10 ppm. Continuous smoking abstinence (no slips allowed) was also assessed at 12, 24, and 52 weeks by self-report and confirmed by results of exhaled carbon monoxide monitoring. At each visit after week 2, participants who had smoked were discontinued; only continuous abstainers were retained and followed up. Participants who did not appear for a visit were counted as treatment failures.

ASSESSMENT OF WITHDRAWAL SYMPTOMS AND CRAVING

Weight was measured at each study visit. Data on subjective symptoms were collected via daily ratings that participants made using an automated telephone system (interactive voice response [IVR]). Starting 1 week before being directed to quit (for baseline data) and continuing for 6 weeks after the designated quit date, participants were instructed to call a toll-free telephone number and respond to 9 questions about withdrawal symptoms by using the telephone keypad. With the use of a 5-point scale (none, slight, mild, moderate, or severe), ratings were captured for craving; urge; anger, irritability, or frustration; anxiety; difficulty concentrating; restlessness; increased appetite; insomnia or awakening at night; and depressed mood. The questions on urge and craving were averaged to form a reliable craving index (Cronbach's α , 0.96). All other items were averaged to form a reliable withdrawal index (Cronbach's α , 0.90). The analysis examined ratings during the first 2 weeks (before smokers who failed to quit were systematically discontinued), with

able with chewing gum, whereas others may not view a gum as a serious medication. A substantial minority of smokers dislike chewing gum (Colin Baker, unpublished data, July 20, 2000). The dose of nicotine provided by nicotine gum might not be adequate for some smokers, particularly given smokers' tendency to underdose.² These limitations may keep current NRT medications from helping more smokers.

Two new oral forms of NRT have been recently introduced. A 2-mg nicotine bitartrate dihydrate sublingual tablet is available in some countries (eg, the United Kingdom, Sweden, and Denmark). The tablet delivers less nicotine than nicotine gum, and falls short of dose proportionality when 2 tablets are used simultaneously to mimic a 4-mg dose.¹⁴ It has been shown to be effective in highly dependent but not in less dependent smokers.¹⁵ A

baseline ratings used as a covariate. Compliance with the IVR system was poor, as less than 10% of eligible participants completed IVR ratings every day during baseline and the first 2 weeks. For analysis, ratings were averaged by week, and individual participants' data were included only when at least 3 daily ratings were available for the relevant week. About half (47.5%) of all subjects had adequate data for the first 3 weeks (baseline and weeks 1 and 2). Low-dependence smokers were less likely than high-dependence smokers to meet this compliance criterion (44.3% vs 50.7%; $P < .01$). As expected, because early drop-outs would be counted as failures and would also have failed to complete IVR telephone calls, smokers who were counted as failures (at 6 weeks) were more likely to have been non-compliant with IVR reporting (72.3% vs 33.3%; $P < .001$). However, within outcome groups, we found no differences in compliance by treatment group (active vs placebo) or interactions between lozenge treatment and IVR compliance. Treatment with the active lozenge was comparably effective in IVR-compliant and non-IVR-compliant smokers. Demographically, white smokers were more likely to be compliant (48.2% vs 36.9%; $P < .05$), as were smokers older than 40 years (53.3% vs 40.2%; $P < .001$). Otherwise, IRV-compliant and non-IRV-compliant smokers did not differ by sex or by smoking history (smoking rate, Fagerström Test for Nicotine Dependence score, and age at initiation), controlling for dosing group.

PHARMACOLOGICAL TREATMENT

Starting on the designated quit date, participants were provided with nicotine or placebo lozenges, per randomization. The 4-mg lozenge was assigned to those who smoked their first cigarette within 30 minutes of waking, and the 2-mg lozenge was assigned to all others. The active lozenge delivers nicotine into the mouth during a period of dissolution lasting approximately 30 minutes, depending on subject use. These lozenges provide 25% to 27% more nicotine than the corresponding nicotine gum doses.¹⁶

Participants were instructed to place the lozenge in their mouth and allow it to dissolve, periodically to move the lozenge in the mouth, and to avoid chewing or swallowing the lozenge. During the first 6 weeks of lozenge use, the instructions recommended using a lozenge every 1 to 2 hours, with a recommended minimum of 9 lozenges per day, and decreasing the dosage to 1 every 2 to 4 hours in weeks 7 to 9, and to 1 every 4 to 8 hours in weeks 10 to 12. From weeks 12 to 24, participants were instructed to keep the lozenges available and to use them occasionally in situations when they might be tempted to smoke. At each visit, participants were provided with sufficient lozenges for the labeled maximum use of 20 per day. Lozenge use was to stop after 6 months. During the first 6 months, participants were to report the number of lozenges used each

day during daily telephone calls to the IVR system. Compliance with IVR system was less than optimal and dropped over time. During the first 2 weeks, participants called an average (\pm SD) of 4.4 (\pm 2.6) of 7 days. During the last 12 weeks of lozenge use, this had dropped to 3.1 (\pm 2.7) calls per week. Lozenge use was estimated from the average of completed IVR telephone calls and was not imputed for missing days.

BEHAVIORAL SUPPORT

Participants were provided with a written user's guide that included behavioral guidance for smoking cessation and instructions on lozenge use. At each of the first 4 visits (through week 4 after randomization), study coordinators spent 5 to 10 minutes reviewing these behavioral tips and directing participants' attention to the user's guide. No other behavioral intervention was permitted.

STATISTICAL ANALYSIS

Analyses were performed separately for smokers assigned to the 2- and the 4-mg lozenges. We analyzed abstinence rates using the χ^2 test, controlling for country (United States vs the United Kingdom). A logistic regression model adjusted for site; we found no interaction between site and treatment. The primary outcome variable was 28-day abstinence at the 6-week visit. To assess the relation between outcome and use of lozenges, abstinence rates were compared between participants who used less than or greater than the median number of lozenges per day in the first 2 weeks of treatment (before any participants were dropped as treatment failures) within dependence groups. The effects of treatment on abstinence were analyzed at weeks 12, 24, and 52 and by survival analysis (which takes into account the duration of abstinence). Participants who presented at the site and reported smoking were asked to give a date of first smoking, which was used in the analysis. If no date was given, the midpoint between the previous and the current visit was used. Those participants unavailable for follow-up or those who remained smoke-free during the entire study were considered censored as of the time of last observation.

We compared craving and withdrawal symptoms of the active-treatment and placebo groups by analysis of covariance while adjusting for baseline symptom scores. The analysis focused on symptoms in the first 2 weeks of treatment; after this time, participants who smoked were discontinued for lack of efficacy, biasing the remaining sample. (Because the withdrawal measure was not normally distributed among the recipients of the 2-mg dose, a nonparametric analysis of median differences was used for this group.) We examined weight gain by analysis of variance at 6, 12, 24, and 52 weeks. We also compared the percentage of participants in the active-treatment and placebo groups who reported any AEs.

1-mg nicotine bitartrate salt lozenge (Nicotinell) has also been introduced in the United Kingdom and Sweden, but no pharmacokinetic or efficacy data have been published, so very little is known about the product.

Thus, there is a need for an alternate oral form of NRT that delivers more effective doses of nicotine and demonstrable efficacy across a broad spectrum of smokers. Increasing the reach and appeal of NRT and enhancing the

use of smoking cessation treatment is a matter of public health urgency. The current study presents clinical data on a new nicotine polacrilex lozenge designed to meet these objectives. We tested 2-mg and 4-mg doses. Compared with 2-mg or 4-mg nicotine gum, the nicotine lozenges deliver 25% to 27% more nicotine (based on the area under the curve),¹⁶ because some nicotine is retained in the gum, whereas the lozenges dissolve completely and deliver their

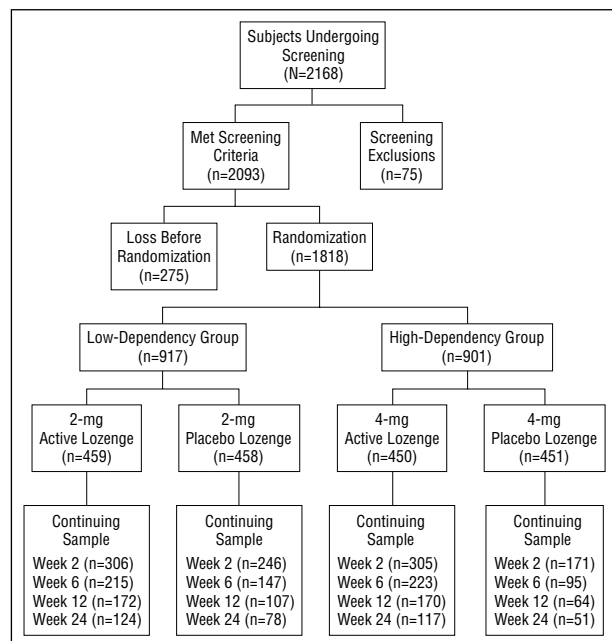


Figure 1. Disposition of subjects. Sample sizes for the continuing samples represent the number of participants who continued in the study after each study visit. At each visit, participants who were smoking or who failed to appear were discontinued. High- and low-dependency groups are described in the “Design” subsection of the “Subjects and Methods” section.

full dose. The 2- and 4-mg lozenges were intended for different groups of smokers. The higher dose was designed for more nicotine-dependent smokers, who are thought to need a higher level of nicotine. Studies of nicotine gum indicate that, for highly dependent smokers, the 4-mg dose achieves significantly better success rates than does the 2-mg dose¹⁷⁻¹⁹; indeed, for these smokers, the efficacy of 2-mg gum is roughly equivalent to that of placebo.^{17,18} Conversely, some evidence suggests that the 4-mg dose may actually be detrimental to smokers who are not highly nicotine dependent.²⁰ Thus, it is important to select the right dose for different smokers.

At present, smokers who use nicotine gum are typically instructed to self-select the higher dose based on their smoking rate. Although this method has the advantage of simplicity, smoking rate is a poor marker of nicotine dependence, especially as smoking restrictions force smokers to smoke fewer cigarettes^{21,22} and as smoking rates vary by cultural and ethnic groups.²³ A better measure of nicotine dependence is needed to assist smokers in choosing an effective nicotine dosage. The most widely used measure of nicotine dependence is the Fagerström Tolerance Questionnaire (FTQ^{24,25}). The FTQ predicts the efficacy of NRT treatment^{26,27} and has been used in clinical trials to assign smokers to a 4-mg dose of gum treatment.^{17,18} However, the FTQ is scored from an 8-item written test, and thus is unsuitable for simple patient selection or self-selection. Within the FTQ, the single best indicator of nicotine dependence is the item that asks whether the smoker has the first cigarette of the day within 30 minutes of waking.²⁸ This is an important indicator, because all smokers wake up in a state of nicotine deprivation, and the drive to self-administer nicotine is a good marker of nicotine dependence. Moreover, this single item on time to first ciga-

rette (TTFC) correlates highly with the full Fagerström Test for Nicotine Dependence test.²⁹ Accordingly, in this study, we allocated smokers to the following doses of nicotine lozenge based on their TTFC: those who normally smoke their first cigarette within 30 minutes of waking were assigned to the 4-mg lozenge, and those who waited longer were assigned to the 2-mg lozenge.

This study was an international, multicenter, placebo-controlled, double-blind, randomized clinical trial of nicotine lozenges for smoking cessation. Parallel arms were run with highly dependent and less dependent smokers assigned to the 4- and 2-mg nicotine lozenge (or placebo), respectively. The primary end point was 28-day continuous abstinence from smoking at 6 weeks. Participants also underwent assessment after 12, 24, and 52 weeks. We also evaluated the safety of the nicotine lozenge and its effects on nicotine craving and withdrawal.

RESULTS

Figure 1 shows the treatment assignment and disposition of all participants undergoing recruitment and screening in the study. A total of 1818 smokers were randomized to treatment. Of these, 901 were considered high-dependency smokers (TTFC, ≤ 30 minutes) and were assigned to the 4-mg lozenge (450 to the active and 451 to the placebo form). The remaining 917 were considered low-dependency smokers (TTFC, > 30 minutes) and were assigned to the 2-mg lozenge (459 to the active and 458 to the placebo form). **Table 1** shows the demographic profile and smoking history of the samples, which match those typically seen in smoking cessation trials. Participants' average age was 42 years, with more than 20 years of smoking. Most had previously tried and failed to quit smoking, and most had previously used pharmacological treatment. Women were slightly overrepresented. Differences between the 2- and the 4-mg lozenge groups were consistent with their selection for low vs high nicotine dependence. Within dependence groups, active-treatment and placebo groups were well matched, with no significant differences between them. Most participants (65.5%) reported having 1 or more preexisting medical conditions (not shown), with respiratory, cardiovascular, digestive, and genitourinary conditions accounting for almost two thirds of the stated conditions. Almost two thirds of participants were taking concomitant medication, most often for gastrointestinal tract or central nervous system conditions.

ABSTINENCE RATES

Table 2 summarizes abstinence rates and results of comparisons at 6, 12, 24, and 52 weeks. For the primary efficacy measure at 6 weeks, the odds of being abstinent were 2.10 (for the 2-mg lozenge) or 3.69 (for the 4-mg lozenge) times greater for those receiving the active lozenge vs placebo. Smokers receiving the active lozenge at either dose continued to demonstrate significantly higher abstinence rates at 12, 24, and 52 weeks. Even after 1 year, the odds of being abstinent were more than doubled by treatment with active lozenge.

We also analyzed the abstinence data by using survival analysis and contrasted active treatment and placebo

Table 1. Demographic and Smoking Characteristics of Randomized Participants*

	Treatment Group				Total Population (N = 1818)
	2-mg Lozenge		4-mg Lozenge		
	Active (n = 459)	Placebo (n = 458)	Active (n = 450)	Placebo (n = 451)	
Age, mean ± SD, y	41.11 ± 12.06	40.48 ± 11.94	44.28 ± 11.78	44.51 ± 11.92	42.58 ± 12.06
Sex, %					
Male	42.9	40.2	43.3	47.0	43.3
Female	57.1	59.8	56.7	53.0	56.7
Race, %					
White	92.8	93.4	93.6	95.8	93.9
Black	4.6	3.5	3.3	1.8	3.3
Asian	1.1	1.3	0.4	0.2	0.8
Other	1.5	1.7	2.7	2.2	2.0
Baseline weight, mean ± SD, kg	75.6 ± 17.2	74.6 ± 15.4	78.0 ± 21.1	75.7 ± 17.9	76.0 ± 18.0
Smoking rate, mean ± SD, cigarettes/d	17.7 ± 8.2	17.2 ± 9.4	26.3 ± 11.2	26.9 ± 10.1	22.0 ± 10.8
Average age of initiation, mean ± SD, y	17.3 ± 4.5	17.1 ± 3.9	16.6 ± 5.1	16.1 ± 4.0	16.8 ± 4.4
Made previous quit attempts, %	89.1	86.5	88.4	87.4	87.8
No. of previous quit attempts, mean ± SD	4.0 ± 6.0	5.1 ± 9.8	3.9 ± 4.3	4.4 ± 8.2	4.3 ± 7.4
No. of quit attempts in past year, mean ± SD	0.6 ± 1.4	0.8 ± 2.0	0.5 ± 0.8	0.6 ± 1.0	0.6 ± 1.4
Previous use of pharmacological treatment, %†	56.2	54.6	72.9	68.7	63.0
FTND score, mean ± SD‡	2.6 ± 1.8	2.6 ± 1.9	6.1 ± 1.8	6.2 ± 1.8	4.4 ± 2.5
Baseline CO, mean ± SD, ppm	19.36 ± 12.02	19.59 ± 12.38	27.16 ± 13.83	26.83 ± 14.13	23.20 ± 13.63

*FTND indicates Fagerström Test for Nicotine Dependence; CO, carbon monoxide.

†Includes nicotine gum, patch, nasal spray, inhalator, sublingual tablet, and bupropion hydrochloride.

‡Scores range from 0 to 10, with a higher score indicating greater dependence.

Table 2. Continuous Abstinence Rates*

Time, wk	Low Dependence, % of Participants		OR (95% CI)	High Dependence, % of Participants		OR (95% CI)
	Active (n = 459)	Placebo (n = 458)		Active (n = 450)	Placebo (n = 451)	
6	46.0	29.7	2.10 (1.59-2.79)	48.7	20.8	3.69 (2.74-4.96)
12	34.4	21.6	1.97 (1.45-2.66)	35.3	14.0	3.42 (2.45-4.76)
24	24.2	14.4	1.96 (1.39-2.78)	23.6	10.2	2.76 (1.89-4.02)
52	17.9	9.6	2.14 (1.43-3.22)	14.9	6.2	2.69 (1.69-4.29)

*Low-dependence groups received the 2-mg placebo or active lozenge; high-dependence groups, the 4-mg lozenge. OR indicates odds ratio; CI, confidence interval.

within each dependence group by using the log-rank test. **Figure 2** shows the resulting Kaplan-Meier survival curves. Among low-dependency smokers, treatment with the active lozenge significantly improved abstinence ($P < .01$). Median abstinence duration (survival) while receiving the active 2-mg lozenge was almost 3 times as long (266 days; 95% confidence interval [CI], 141-304 days) as that for subjects receiving placebo (95 days; 95% CI, 77-174 days). Similarly, for high-dependency smokers, treatment with the active 4-mg lozenge significantly prolonged abstinence, resulting in median survival times almost 6 times as long as those for placebo treatment (median, 182 vs 32 days; 95% CI, 158-275 vs 27-52 days; $P < .001$). **Figure 2** shows that, whereas high-dependency smokers treated with placebo had poor outcomes relative to those of low-dependency smokers treated with placebo, treatment with active 4-mg lozenges allowed high-dependency smokers to achieve outcomes comparable to those of the low-dependency smokers receiving 2-mg active lozenges, thus eliminating the excess risk due to high dependence.

CRAVING, WITHDRAWAL, AND WEIGHT GAIN

As shown in **Table 3**, treatment with the active lozenge significantly reduced baseline-adjusted craving in groups receiving the 2- and the 4-mg lozenges in weeks 1 and 2. In a parallel analysis of withdrawal symptoms, the active 4-mg lozenge yielded significantly lower withdrawal symptom scores in weeks 1 and 2; for the 2-mg lozenge, using nonparametric analysis, the reduction in symptoms was significant in week 1, but not in week 2. Similar outcomes were observed when we restricted the analysis to those who were abstinent at week 2.

All groups gained weight after smoking cessation. As shown in **Table 4**, compared with placebo, treatment with the active 4-mg lozenge significantly reduced weight gain by 45% (1.03 kg) at week 6 and by 21% (0.73 kg) at week 12. By 6 months, the differences between active and placebo treatment were no longer significant. In the group assigned to the 2-mg lozenge, treatment assignment had no reliable effect on weight gain.

ADVERSE EVENTS

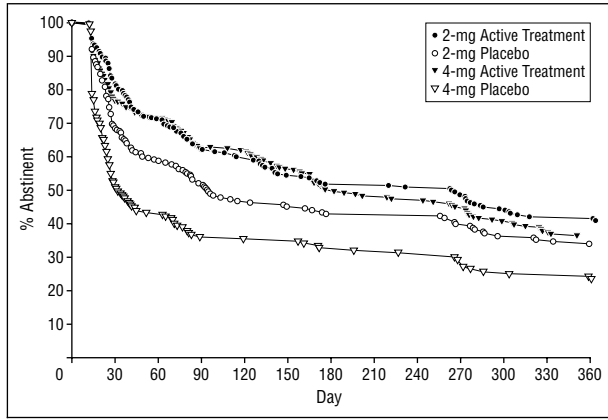


Figure 2. Survival curves for the treatment groups over time show the percentage of participants in each group who were abstinent, accounting for censoring. The curves include all participants randomized to treatment. When participants who had previously been abstinent failed to appear for a visit, their data were censored as of the last visit. If a participant was counted as smoking (based on self-report or results of carbon monoxide monitoring), but a lapse day was not known, the lapse day was assigned halfway between the present and the previous visit. Participants who did not appear for the visit at 2 weeks were censored at 7 days after randomization (halfway between randomization and the 2-week visit). Participants who remained abstinent for the duration of the study were censored at their final visit.

Table 5 shows that 61.8% of participants reported 1 or more AEs during the 6 months when lozenges were dispensed. Smokers assigned to the 2- ($P<.001$) and the 4-mg ($P<.001$) active lozenges were more likely than those assigned to placebo to report AEs.

The pattern for AEs with some putative relation to study drug was similar to that seen for all events, although the incidence was lower. Seventeen percent of participants experienced an AE classified as severe. Among those who experienced AEs, the risk for severe AEs did not differ for active vs placebo lozenge (2-mg group, $P=.11$; 4-mg group, $P=.57$). A total of 7.1% of participants withdrew from the study because of AEs. For participants receiving the 2-mg lozenge, withdrawal was more common among those receiving the active form ($P=.03$, vs placebo form), but this trend was reversed for the 4-mg lozenge ($P=.08$). Nonfatal, serious AEs were rare (1.6% of all participants) and were not more common among those receiving active medication (2-mg group, $P=.27$; 4-mg group, $P=.08$). Three deaths occurred during the study; all were among high-dependency smokers assigned to the placebo lozenge.

Table 3. Withdrawal and Craving Scores in Weeks 1 and 2, by Treatment and Dose*

	2-mg Lozenge			P Value	4-mg Lozenge			P Value
	Active	Placebo	No. of Participants		Active	Placebo	No. of Participants	
Withdrawal scores								
Week 1								
Mean (median)	1.04 (0.97)	1.13 (1.14)	732	.02	1.10 (1.00)	1.32 (1.29)	593	<.001
SE	0.04	0.04			0.04	0.04		
Week 2								
Mean (median)	0.89 (0.76)	1.02 (0.83)	548	.18	0.87 (0.79)	1.09 (1.00)	463	<.001
SE	0.04	0.04			0.05	0.05		
Craving scores								
Week 1								
Mean (median)	2.35 (2.43)	2.50 (2.60)	533	.02	2.50 (2.58)	2.96 (3.13)	596	<.001
SE	0.06	0.06			0.05	0.05		
Week 2								
Mean (median)	1.84 (1.79)	2.05 (1.89)	414	.03	1.91 (1.83)	2.47 (2.50)	464	<.001
SE	0.08	0.08			0.07	0.08		

*Scores are explained in the "Assessment of Withdrawal Symptoms and Cravings" subsection of the "Subjects and Methods" section. Median scores were the basis of the nonparametric analyses of the withdrawal data in the 2-mg group.

Table 4. Analysis of Weight Gain*

	Low-Dependency Group					High-Dependency Group				
	No. of Participants Observed	Mean Change in Body Weight, kg (No. of Participants)		Treatment Difference Between Groups (95% CI)†	P Value	No. of Participants Observed	Mean Change in Body Weight, kg (No. of Participants)		Treatment Difference Between Groups (95% CI)†	P Value
		Active	Placebo				Active	Placebo		
Week 6	394	1.43 (n = 235)	1.54 (n = 159)	-0.1 (-0.52 to 0.30)	.59	344	1.27 (n = 237)	2.30 (n = 107)	-1.03 (-1.48 to -0.57)	<.001
Week 12	324	2.25 (n = 198)	2.31 (n = 126)	-0.006 (-0.64 to 0.53)	.85	271	2.67 (n = 192)	3.40 (n = 79)	-0.73 (-1.43 to -0.03)	.04
Week 24	229	3.17 (n = 142)	3.15 (n = 87)	0.02 (-0.95 to 0.99)	.97	199	4.30 (n = 143)	4.74 (n = 56)	-0.44 (-1.68 to 0.80)	.49
Week 52	172	4.26 (n = 105)	3.84 (n = 67)	0.41 (-1.17 to 2.00)	.61	134	5.78 (n = 92)	4.88 (n = 42)	0.89 (-1.36 to 3.15)	.43

*To test the effect on abstinent participants, we also analyzed the week 2 data among those who reported abstinence at the week 2 visit. The results were substantially unchanged. Results were almost identical when the analysis was limited to those abstinent at each weight assessment. Dependency groups are described in the footnote to Table 2. CI indicates confidence interval.

†A negative score signifies a higher body weight in the placebo group compared with the active group.

Table 5. Treatment-Emergent Adverse Events Occurring in at Least 5% of Participants in Any Treatment Group (Intent-to-Treat Population)

	% of Participants			
	2-mg Lozenge		4-mg Lozenge	
	Nicotine (n = 459)	Placebo (n = 458)	Nicotine (n = 450)	Placebo (n = 451)
Any adverse event*	67.8	55.9	71.1	52.3
Using more than median No. of lozenges	73.1	53.4	75.6	51.2
Using median No. of lozenges or fewer	63.3	58.2	67.1	53.4
Experienced a severe adverse event†	27.3	21.1	31.9	29.2
Any related adverse event‡	46.4	36.2	51.6	32.8
Deaths	0.0	0.0	0.0	0.6
Nonfatal serious adverse event	2.0	0.9	2.7	0.9
Adverse event leading to discontinuation*	6.8	3.5	7.3	10.6
Adverse events reported by ≥5% of participants				
Central and peripheral nervous system disorders				
Headache	5.0	5.9	8.0§	3.3
Gastrointestinal tract disorders				
Diarrhea	3.5	2.2	5.3	3.8
Flatulence	9.8	8.5	10.4	7.8
Heartburn	5.0§	2.2	5.8§	0.9
Hiccup	3.5§	0.0	8.4§	0.0
Nausea	12.2§	4.8	15.1§	5.3
Respiratory tract disorders				
Coughing	4.1	2.8	5.6§	2.7
Sore throat	2.6	2.6	5.1	4.0
Upper respiratory tract infection	12.0	9.8	9.8	6.4

*Indicates treatment-emergent adverse event.

†Indicates among those experiencing adverse events.

‡Related indicates possibly, probably, or highly probably related to treatment.

§Statistically significantly different from placebo ($P < .05$).

Table 6. Lozenge Use by Week*

Week	Low-Dependency Group		High-Dependency Group	
	Active	Placebo	Active	Placebo
2				
No. of participants†	347	305	358	288
No. (%) using lozenge	334 (96.3)	299 (98.0)	354 (98.9)	279 (96.9)
Mean No. of lozenges (SD)	7.4 (4.0)	7.5 (4.1)	9.1 (3.8)	9.2 (4.5)
6				
No. of participants†	206	138	225	93
No. (%) using lozenge	188 (91.3)	123 (89.1)	222 (98.7)	86 (92.5)
Mean No. of lozenges (SD)	6.3 (4.1)	5.5 (4.0)	8.6 (4.0)	6.8 (4.9)
12				
No. of participants†	144	91	177	64
No. (%) using lozenge	119 (82.6)	69 (75.8)	164 (92.7)	44 (68.8)
Mean No. of lozenges (SD)	3.5 (3.3)	3.1 (3.2)	5.2 (3.6)	3.7 (3.7)
24				
No. of participants†	80	43	100	36
No. (%) using lozenge	17 (21.3)	8 (18.6)	42 (42.0)	10 (27.8)
Mean No. of lozenges (SD)	0.2 (0.5)	0.5 (1.4)	0.7 (1.3)	0.6 (1.6)

*Dependency groups are described in the footnote to Table 2.

†Indicates the number of participants still in the study and making reports of lozenge use (including those reporting no lozenge use) via the interactive voice response system.

Table 5 also shows the most common events (those reported by ≥5% in any group) by body system. Gastrointestinal and respiratory tract complaints were most frequent. Only heartburn, hiccup, and nausea occurred significantly more often in the active-treatment than in the placebo groups at both doses. Among respiratory tract events, upper respiratory tract infections (9.5%), coughing (3.8%), and sore throat (3.6%) were more often re-

ported; only coughing showed any relationship to nicotine dosing, and then only in the 4-mg group.

LOZENGE USE

Table 6 shows the reported lozenge use at weeks 2, 6, 12, and 24 of the study, as reported by those who were still in the study and providing reports via IVR reporting.

Table 7. Smoking Cessation Rate at 6 Weeks Stratified by Lozenge Use*

	2-mg Lozenge		Risk Ratio (95% CI)†	P Value‡	4-mg Lozenge		Risk Ratio (95% CI)†	P Value‡
	Active	Placebo			Active	Placebo		
High-level users, % (n = 855)§	57.7	29.9	2.34 (1.34-4.10)	.004	56.8	19.2	2.31 (1.27-4.21)	.006
Low-level users, % (n = 858)	40.6	33.5			44.2	24.6		

* For the study population, n = 1713 (intent to treat excluding those participants who did not provide reports of lozenge use). CI indicates confidence interval.

†Indicates ratio of odds ratios for the high- vs low-level lozenge user subgroups (95% CI).

‡Test for difference in active vs placebo treatment effect in high- vs low-level lozenge users.

§Indicates those who used greater than the median number of lozenges per day in the first 2 weeks of treatment (median was 6.7 lozenges per day in the 2-mg group and 8.2 per day in the 4-mg group).

||Indicates those who used less than or equal to the median number of lozenges per day in the first 2 weeks of treatment.

At week 2, almost all participants in all groups were using lozenges. By week 12, use of lozenges had diminished and varied by group and treatment, with the greatest use among high-dependence smokers receiving the active 4-mg lozenge. Finally, at week 24, only a minority of the remaining participants (<15% of the initial sample) reported using lozenges, and there were no differences between active-treatment and placebo groups at either dose. The number of lozenges used per day also dropped over time for active and placebo groups, as shown in Table 6.

It was hypothesized that the use of more lozenges might improve treatment effects. To test this, groups with high- and low-level lozenge use were formed by splitting participants at the median number of lozenges used per day during the first 2 weeks. As **Table 7** shows, the lozenge had significantly greater effect among those who used more lozenges. Using more than the median number of lozenges more than doubled the effect of lozenge treatment on abstinence. Finally, we assessed whether participants who used more lozenges were more likely to experience AEs. The character and pattern of AEs were similar among high- and low-level lozenge users, but high-level lozenge users were slightly more likely to report AEs (Table 5).

SEGMENTING SMOKERS BY NICOTINE DEPENDENCE AND SMOKING RATE

Although this trial allocated smokers to nicotine dose on the basis of TTFC, an indicator of nicotine dependence, current indications for nicotine gum allocate dose on the basis of smoking rate (divided at 25 cigarettes per day in the United States and 20 in other jurisdictions). Allocating smokers to dose by TTFC results in more smokers receiving the 4-mg dose. To test the safety of this changed dose allocation, we examined AEs among light smokers who were assigned to the 4-mg lozenge. Their AE reports were similar to those of heavy smokers receiving the 4-mg lozenge. To assess the efficacy implications, we examined treatment efficacy among heavy smokers assigned to the 2-mg lozenge and among light smokers assigned to the 4-mg lozenge. The lozenge showed significant efficacy in both groups.

COMMENT

This study demonstrated the efficacy and safety of 2- and 4-mg nicotine lozenges for smoking cessation. The odds of being abstinent after 6 weeks of treatment were 2.1 to

3.7 times greater among those receiving the active lozenge (2- and 4-mg doses, respectively) than among those receiving placebo. Increased abstinence was maintained even after 1 year since quitting and at least 6 months without lozenges. These data demonstrate the efficacy of the nicotine lozenges and thus add to the database demonstrating NRT efficacy.

The absolute success rates and the odds ratios achieved by use of the nicotine lozenge were in the upper range of those observed in previous studies of other forms of NRT,⁵ suggesting that this NRT may be particularly effective. The present success rates were achieved among smokers who had failed to quit smoking while receiving previous pharmacological treatment (Table 1). Piece for piece, the nicotine lozenge delivers approximately 25% more nicotine than the comparable dose of nicotine gum,¹⁶ which may help enhance efficacy. The nicotine lozenge achieved good efficacy even among low-dependency smokers, which was not the case for the sublingual tablet.¹⁵ Definitive conclusions about comparative efficacy require a randomized head-to-head comparison.

Many smokers in the trial used the number of lozenges recommended by the product label. The average number of lozenges used peaked at an average of 7 to 9 per day in the first few weeks and dropped over time. In this study, lozenge use data were only obtained from the subset who provided IVR reports, which may limit generalizability. Within this sample, those who used more lozenges achieved significantly higher success rates and derived more benefit from the active lozenge treatment. This finding is consistent with those on compliance with NRT and with the expected dose-response function. It also suggests that smokers should be encouraged to use at least 7 to 8 lozenges per day. Use of more lozenges slightly increased AEs, but the increase was not substantial and the events were not serious, and thus this increase does not present a safety concern. Physicians and other health care professionals should encourage patients to avoid underdosing, encourage use of sufficient medication, and dispel patients' unwarranted concerns about the safety of nicotine medications.

One could argue that the high absolute quit rates in this study may also have been enhanced by contacts with the research sites. However, this cannot account for the robust differences between the active-treatment and placebo groups, since all participants received similar treatment at the sites. In any case, smokers in this study were given very little face-to-face behavioral support. The pri-

mary vehicle of behavioral advice and support was a written user's guide that provided structure and techniques for quitting smoking. The face-to-face contacts smokers had with research personnel (who were not behavioral specialists) were focused on directing their attention to the user's guide and reinforcing it, rather than delivering formal behavioral therapy or introducing additional techniques. Thus, the results suggest that the nicotine lozenge is suitable for use without adjunctive behavioral treatment. Although the addition of behavioral treatment can boost quit rates, NRT efficacy is independent of the degree of support provided.³¹

The use of a simple patient-reported measure of nicotine dependence—TTFC—to allocate smokers to NRT dose may also have helped optimize the treatment. Research has suggested that treating highly dependent smokers with 2 mg of oral nicotine is ineffective,^{17,18} and one study found that giving low-dependency smokers the 4-mg gum may actually lower their quit rates.²⁰ In the present study, light smokers who were allocated to the 4-mg dose by TTFC showed good quit rates, strong lozenge efficacy, and no excess AEs, suggesting that they had been appropriately assigned to that dose. Smokers who smoked heavily but appeared less dependent based on TTFC and were thus assigned to receive the 2-mg lozenge also showed good quit rates and differences between the active-treatment and placebo groups, again implying appropriate dose allocation. The study did not compare dose allocation based on TTFC with dose allocation based on smoking rate, and thus cannot establish the relative strengths of one regimen over another. Nevertheless, in the context of other studies of oral NRT dosing,^{17,20} the data suggest that allocating smokers to the nicotine lozenge dose on the basis of TTFC is an appropriate regimen and may provide better dosing for some smokers.

Assigning smokers to lozenge dose on the basis of TTFC, rather than smoking rate, is likely to result in more smokers being assigned to the 4-mg dose. For example, for smokers in the United States, a recent survey found that although only 29% smoke at least 25 cigarettes per day (qualifying for the 4-mg dose under the current nicotine gum indication), 72% smoke their first cigarette within 30 minutes of waking, thus qualifying for the 4-mg lozenge.³² Similarly, in the United Kingdom, 25% of smokers smoke more than 20 cigarettes per day, but 67% smoke their first cigarette within 30 minutes of waking (Katie Kemper, MBA, unpublished data, 1998; available from GlaxoSmithKline). Thus, this new regimen will provide higher doses of medication to a substantial subset of smokers who appear to be nicotine dependent, although they are not heavy smokers. With the slightly increased level of delivery of nicotine by the nicotine lozenge (vs nicotine gum), this method may enhance treatment efficacy.

The nicotine lozenge also proved to be effective for relief of craving and partially effective for relief of withdrawal. Among low- and high-dependency smokers, treatment with the active lozenge resulted in lower craving within the first 2 weeks of quitting, when craving is at its peak.^{33,34} This finding contrasts with that for the sublingual tablet, which affected craving and withdrawal only among highly or moderately dependent smokers.^{15,35} Among high-dependency smokers, the 4-mg lozenge also

suppressed withdrawal symptoms in the second week of abstinence and suppressed weight gain during a 12-week period. The latter result is consistent with other findings that oral NRT suppresses weight gain while being used, but does not have lasting effects.² The withdrawal results were less robust among low-dependency smokers treated with the 2-mg nicotine lozenge, for whom withdrawal suppression did not reach significance in week 2,¹⁵ and no suppression of weight gain was observed. The fact that many participants did not comply with IVR reporting, and thus did not provide data (or complete data) on craving and withdrawal, may have biased the data and masked the effect of treatment. Among low-dependency smokers, symptoms may be modest and thus difficult to further suppress. Less dependent smokers, too, may benefit from higher doses of nicotine than 2 mg. In any case, robust enhancement of cessation was seen in the 2-mg group, even in the absence of documented lasting suppression of withdrawal, in contrast to findings by Wallström et al.¹⁵ Additional mechanisms beyond suppression of craving and withdrawal may underlie the efficacy of NRT.

In general, the clinical outcomes seen with the 4-mg lozenge were particularly robust, showing high quit rates, a favorable difference between active-treatment and placebo groups, and suppression of craving, withdrawal, and weight gain. The data show that although highly nicotine-dependent smokers were less successful at abstaining when treated with placebo, treatment with the active lozenge eliminated the excess failure due to dependence and helped high-dependency smokers achieve outcomes comparable to those of low-dependency smokers²⁷ (Figure 2 and Table 2). These data are consistent with the notion that more dependent smokers particularly need nicotine replacement and require higher doses. Only a modest increase in AEs associated with the 4-mg dose was found, despite the fact that participants assigned to the active 4-mg lozenge tended to use more lozenges. This finding suggests that future studies should explore the possibility of using this dose with all but the least nicotine-tolerant and -dependent smokers.

Our study demonstrated the safety of the nicotine lozenges tested in this study. The AEs experienced by smokers using the lozenge were generally moderate and transient and were similar in character and frequency to those observed in trials of other oral NRT medications,^{36,37} most involving minor discomforts such as nausea, hiccups, and heartburn. We found only a modest increase in AEs among smokers who used more lozenges. Thus, the lozenge is safe when used as directed.

The study's most notable limitation was poor compliance with daily IVR reports of craving and withdrawal symptoms. Non-IVR-compliant participants differed from compliant ones on several factors. Thus, the data collected by means of the telephone may be biased, and conclusions about those variables may be limited to subjects who complied with reporting.

CONCLUSIONS

The new nicotine lozenge is an effective and safe treatment for smoking. Physicians should counsel smokers to quit and suggest the nicotine lozenge as an option for

effective treatment. The nicotine lozenge provides smokers and practitioners with an additional effective tool for smoking cessation.

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