Improving the Armamentarium for Smoking Cessation

Shiffman S, Dresler CM, Hajek P, et al. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 2002;162:1267–76.

Study Overview

Objective. To determine the efficacy and side-effect profile of nicotine lozenges for smoking cessation.

Design. Double-blind, placebo-controlled, randomized clinical trial with parallel arms to test 2- and 4-mg nicotine lozenges.

Setting and participants. A multicenter, international trial was conducted at 11 sites within the United States and 4 sites within the United Kingdom. 2168 volunteers were initially screened and 75 were excluded. 275 patients withdrew prior to randomization, resulting in 1818 participants. Eligibility criteria included age of 18 years or older and an interest in quitting smoking within the next 30 days. Patients were excluded if they had used other smoking cessation aids, including nicotine, or had used non-cigarette forms of tobacco in the prior 30 days. Patients also were excluded if they were pregnant or had heart disease, uncontrolled hypertension, peptic ulcer disease, insulin-dependent diabetes, or difficulty metabolizing aspartame.

Intervention. Participants initially were divided into low- and high-dependency groups based on self-reported nicotine dependency, with patients who smoked their first cigarette within 30 minutes of waking assigned to the high-dependency group. Participants were randomized to either 2-mg nicotine polacrilex lozenge or placebo (low-dependency group) or 4-mg nicotine polacrilex lozenge or placebo (high-dependency group). Participants were instructed to begin therapy with one lozenge every 1 to 2 hours, with a recommended minimum of 9 lozenges per day. After 6 weeks, the number of lozenges was tapered and discontinued at 6 months.

Main outcome measures. The primary endpoint was 28-day continuous abstinence from smoking. Continuous abstinence was defined as complete abstinence reported at week 2, and 4 weeks of continuous abstinence reported at week 6. Abstinence assessments also were made at weeks 12, 24, and 52. Self-reported abstinence was confirmed by the results of exhaled carbon monoxide monitoring. Secondary outcomes included subjective assessment of withdrawal symptoms, cravings, and weight gain assessed at clinical follow-up points.

Main results. There were no statistically significant differences seen in comparisons of patient characteristics between the active treatment and placebo groups. For the primary outcome measure, 46% of the 2-mg nicotine lozenge group versus 29.7% of the placebo group (odds ratio [OR], 2.10 [95% confidence interval {CI}, 1.59–2.79]; $P < 0.001$) and 48.7% of the 4-mg lozenge group versus 20.8% of the placebo group (OR, 3.69 [95% CI, 2.74–4.96]; $P < 0.001$) remained abstinent at 6 weeks. At 52 weeks, 17.9% of the 2-mg nicotine lozenge group versus 9.6% of the placebo group (OR, 2.14 [95% CI, 1.43–3.22]) and 14.9% of the 4-mg lozenge group versus 6.2% of the placebo group (OR, 2.69 [95% CI, 1.69–4.29]) remained abstinent. Using Kaplan-Meier survival curves, the median abstinence duration for the 2-mg nicotine lozenge group was 266 days (95% CI, 141–304) compared with 95 days (95% CI, 77–174 days) for the placebo group ($P < 0.01$). The median abstinence duration for the 4-mg nicotine lozenge group was 182 days (95% CI, 158–275) compared with 32 days (95% CI, 27–52 days) for the placebo group ($P < 0.001$). Craving scores were significantly lower for both the 2- and 4-mg active treatment groups versus placebo at weeks 1 and 2, while withdrawal scores were lower for both the 2- and 4-mg active treatment groups versus placebo at week 1 but only significantly lower for the 4-mg nicotine lozenge group at week 2. Participants assigned to active treatment were more likely to suffer an adverse event when compared with placebo ($P < 0.001$, both dosages). However, the risk of severe adverse events did not differ between the placebo and nicotine groups. Patients who used more than the median number of nicotine lozenges were more than twice as likely to remain abstinent.

Conclusion. The use of nicotine lozenges for smoking cessation is safe and effective. Nicotine lozenges were effective for both low- and high-dependency smokers.

Commentary

Despite widespread clinical guidelines and aggressive public advertising campaigns, smoking still remains the leading

cause of preventable death in the United States. Nicotine replacement therapy has been shown to improve smoking cessation success rates in clinical trials [1]. To improve the appeal of nicotine delivery systems, manufacturers have developed several alternative forms. Nicotine can be delivered as a nasal spray, patch, inhaler, sublingual tablet, and chewing gum. However, potential barriers to these delivery systems include the high visibility of the delivery systems, oral or nasal mucosa irritation, and poor nicotine absorption resulting in lower serum levels. A recently developed nicotine polacrilex lozenge appears to deliver more nicotine than chewing gums while being more discreet than inhalers.

Shiffman et al's well-designed randomized controlled trial suggests that the nicotine lozenge, like other forms of nicotine therapy, is effective and safe for smoking cessation. The authors minimized confounding behavioral interventions by only distributing a single written pamphlet describing behavioral interventions for smoking cessation to the participants and by not allowing any additional counseling. This more likely reflects actual clinical practice and is a strength of the study. One major limitation of the study was the extremely poor response rate with regard to withdrawal symptoms and cravings. With less than 10% of participants completing data on a daily basis, it is difficult to draw any conclusions from the withdrawal and cravings evaluations.

Applications for Clinical Practice

Compared with placebo, nicotine lozenges are efficacious and safe for maintaining smoking cessation at 1 year. Nicotine lozenges have some theoretical benefits over other nicotine delivery systems, but head-to-head comparisons are required.

–Review by Harvey J. Murff, MD, MPH

References

1. Silagy C, Mant D, Fowler G, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2000;(3):CD000146.