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Timing of nicotine lozenge administration to minimize trigger induced craving and withdrawal symptoms

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HIGHLIGHTS

- Smokers are often advised to use nicotine lozenge when craving or withdrawal symptoms occur
- Using nicotine lozenge after craving and withdrawal symptoms occur may be too late to prevent relapse
- This study compared the use of nicotine lozenge at various times before vs. immediately after exposure to a smoking trigger
- Using a lozenge before trigger exposure resulted in smaller increases in severity of withdrawal symptoms and urge to smoke

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ABSTRACT

Introduction: Smokers are often advised to use nicotine lozenge when craving or withdrawal symptoms occur. This may be too late to prevent lapses. This study assessed if nicotine lozenge use prior to a common smoking trigger can minimize trigger induced increases in craving and withdrawal symptoms.
Methods: Eighty-four smokers completed two laboratory sessions in random order. At one session, nicotine lozenge was given immediately after a stressor (to approximate current recommended use – i.e., after craving and withdrawal symptoms occur); at the other session subjects were randomized to receive nicotine lozenge at time points ranging from immediately to 30 min prior to the stressor. Withdrawal symptoms and urge to smoke were measured using the Minnesota Nicotine Withdrawal Scale and the Questionnaire of Smoking Urges (QSU).
Results: Relative to receiving lozenge after the stressor, a smaller increase in pre-stressor to post-stressor withdrawal symptom scores occurred when lozenge was used immediately ($p = 0.03$) and 10 min prior ($p = 0.044$) to the stressor. Results were similar for factors 1 and 2 of the QSU when lozenge was used immediately prior to the stressor ($p < 0.03$) and for factor 1 of the QSU when lozenge was used 10 min prior to the stressor ($p = 0.028$). Absolute levels of post-stressor withdrawal symptom and urge to smoke severity were lower when lozenge was given prior to versus after a stressor.
Conclusions: Administering the nicotine lozenge prior to a smoking trigger can decrease trigger induced craving and withdrawal symptoms. Future studies are needed to determine if such use would increase cessation rates. Clinicaltrials.gov # NCT01522963

1. Introduction

The morbidity and mortality associated with smoking is well characterized, resulting in approximately 480,000 deaths annually in the United States (USDHHS, 2014). New treatments for tobacco dependence are rarely introduced, with only two non-nicotine pharmacological aids currently available. The low success rates and the infrequent introduction of new therapies necessitate that the efficacy of currently available therapies be maximized.

Use of a single nicotine replacement therapy (NRT) typically doubles cessation rates relative to placebo with additional benefit observed when combination NRT (i.e., combining two dosage forms) is used (Fiore et al., 2008). In combination therapy, nicotine gum or lozenge is typically used as needed in combination with scheduled use of the

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nicotine patch (Fiore et al., 2008; Puska, Vartiainen, Urjanheimo, Gustavsson, & Westin, 1995; Steinberg et al., 2009). As monotherapy, nicotine gum or lozenges are frequently used on an as needed basis following an initial period of scheduled use (Fiore et al., 2008; Kozlowski et al., 2007; McNeill, Foulds, & Bates, 2001; USPHS, 2000). Therefore, current counseling methods frequently advise smokers to use these products when they need them (i.e., when symptoms of craving or tobacco withdrawal are present); (Fant, Owen, & Henningfield, 1999; Kozlowski et al., 2007; Sweeney, Fant, Fagerstrom, McGovern, & Henningfield, 2001). Although one study found that half of smokers who lapse after an acute craving episode do so within 11 min of the onset of craving (Ferguson & Shiffman, 2009; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996), substantial concentrations of nicotine are not attained until approximately 10 to 15 min after starting use of these products (Benowitz, Porchet, Sheiner, & Jacob, 1988; Kotlyar et al., 2007). These data suggest that waiting to use nicotine lozenge or gum until craving or withdrawal symptoms are present may not result in nicotine delivery quickly enough to avert a smoking lapse.

The purpose of this study was to provide initial information assessing if using nicotine lozenge prior to exposure to a smoking trigger results in smaller trigger induced increases in withdrawal symptoms and urge to smoke than using this product after these symptoms have already occurred (i.e., after smoking trigger exposure). Exposure to a stressful task was chosen as the smoking trigger for this study since similar tasks when presented in a laboratory setting have been shown to decrease the ability to resist smoking, increase craving and withdrawal symptom severity, and increase smoking topography measures (e.g., puff volume) (Kotlyar et al., 2011; McKee et al., 2011; Pomerleau & Pomerleau, 1987). In a naturalistic setting, smokers attempting to quit frequently report that stressful events lead to smoking relapse (Cummings, Jaen, & Giovino, 1985). Therefore stress is likely to be an important trigger in smoking lapses. Our hypothesis was that exposure to a smoking trigger (i.e., a stress task) would result in larger increases in withdrawal symptoms and urge to smoke when nicotine lozenge is used immediately after the stressor than if lozenge was used prior to stress exposure.

2. Methods

2.1. Design

In this randomized, cross-over study subjects participated in two laboratory sessions at which withdrawal symptoms and urge to smoke were assessed prior to and following exposure to a common smoking trigger (i.e., a stressful situation). Each subject participated in one session at which a 4 mg nicotine lozenge (mint flavor) was given immediately after the stressor (Fig. 1: Condition A) in order to approximate current recommended use of lozenge when used on an as needed basis – i.e., after craving and withdrawal symptoms begin. This served as the control condition. Each subject participated in another session at which they were randomized to one of four experimental groups: receive a 4 mg nicotine lozenge either immediately prior (Condition B), 10 min prior (Condition C), 20 min prior (Condition D), or 30 min prior to the stressor (Condition E) (Fig. 1). The time-frames of administration span the range from when the impending trigger is presumably more predictable but nicotine concentrations during the trigger would be relatively low (i.e. Condition B) to when predicting the trigger would be more difficult but nicotine concentrations during the trigger would be highest (i.e., Condition E).

The two laboratory sessions were separated by at least 3 days and the order of laboratory sessions (i.e., control vs. experimental) was assigned randomly. In a two-step randomization process, subjects were first randomized to experimental condition (i.e., Conditions B–E) and then to the order in which they receive their assigned experimental condition or the control condition (i.e., Condition A). The nicotine lozenge was selected among the four non-patch dosage forms since it is available without a prescription (and therefore more commonly used) and is well tolerated.

2.2. Subjects

Volunteers were recruited through flyers and newspaper advertisements. Initial eligibility was assessed via a phone interview and confirmed at a screening visit at which written informed consent was obtained. This study was approved by the University of Minnesota Institutional Review Board. Study visits occurred at the University of Minnesota between December 2011 and January 2014.

Eligible participants were between the ages of 18 and 65, smoked at least 8 cigarettes daily and identified stress as a smoking trigger. Individuals were excluded who reported a current unstable medical or psychiatric condition (for example, necessitating medication changes within the past 3 months), substance abuse (other than nicotine) within six months of the study, use of medication that could interfere with study outcomes (e.g., psychoactive medications), use of smoking cessation medications in the past month, a history of severe motion sickness (due to the virtual reality (VR) technology utilized to present the stressor), and women who were pregnant or breastfeeding. Medical history was based on subject self-report. A urine pregnancy test confirmed that women were not pregnant at enrollment.

Smokers not identifying stress as a smoking trigger would be unlikely to react to the stressor thereby precluding any possible medication effect. We asked smokers to list 3 smoking triggers relevant to them and only enrolled those who listed stress (or a specific stressful situation) as a trigger.

As the stress task was presented in a VR environment, subjects were immersed in the environment at the screening visit to allow for adaptation so that responses seen at subsequent visits were due to the stressor rather than the novelty of the environment.

2.3. Laboratory sessions

Subjects abstained from smoking overnight prior to each morning laboratory session (confirmed via an exhaled carbon monoxide of ≤8 ppm). Upon arrival, subjects relaxed in a quiet room for 90 min after which questionnaires assessing nicotine withdrawal and urge to smoke were completed. Those randomly assigned to Condition E for that laboratory session then used one nicotine lozenge. All subjects again completed questionnaires at 20 min, 10 min, and immediately prior to the stressor. Those assigned to Condition D received a lozenge after completing the 20 min pre-stressor questionnaires, those assigned to Condition C after completing the 10 min pre-stressor questionnaires and those assigned to Condition B after completing the pre-stressor questionnaires. All subjects were therefore exposed to the stressor 2 h

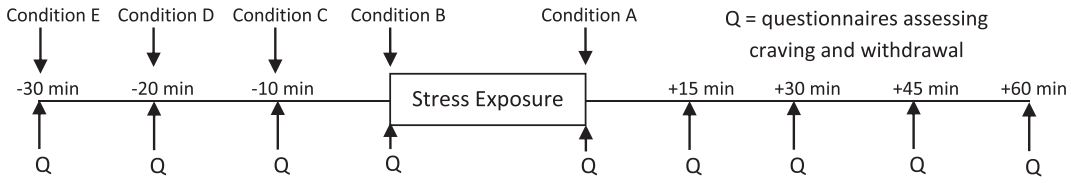

Fig. 1. Outline of each laboratory assessment with subjects assigned to Condition A at one laboratory session and one of the other conditions at the other laboratory session. The order of laboratory assessments (i.e., Condition A vs. other condition) was assigned randomly.