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Effect of Nicotine Lozenge Use Prior to Smoking Cue Presentation on Craving and Withdrawal Symptom Severity

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Abstract

Background: Smokers are often advised to use nicotine lozenge after cravings or withdrawal symptoms are present, which may be too late to prevent lapses. This study assesses if lozenge use prior to smoking cue exposure attenuates cue-induced increases in symptom severity.

Methods: In this randomized, cross-over study, participants completed three laboratory sessions at which they proceeded through 4 “rooms” in a virtual reality environment. The first and last “rooms” contained neutral cues and the others contained smoking cues. At one session, a 4 mg nicotine lozenge was not given until after cue exposure (to approximate current use: i.e., after craving and withdrawal symptoms occur). At the other two sessions either a nicotine or placebo lozenge was used 15 minutes before cue exposure procedures. Craving and withdrawal symptoms were measured throughout each laboratory session.

Results: Of 58 participants randomized; 40 completed all 3 labs. Absolute levels of craving and withdrawal symptom severity during cue exposure were lower when placebo or active lozenge was used prior to cue presentation procedures vs. no treatment until after cue presentation procedures (all p-values <0.05). There were no differences among conditions in the magnitude of symptom severity increase occurring between the first neutral room and the cue rooms.

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Contributors

This study was designed by MK and RIV. The research was performed by MK, JV, SRD and AMM. Statistical analysis was performed by RIV. The manuscript was written by MK and RIV with all authors reviewing, contributing to and approving the final version of manuscript.

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Conflicts of Interest

This work was funded by a grant from the Global Research Award for Nicotine Dependence (GRAND) program funded by Pfizer. Dr. Kotlyar has received honoraria from Western Schools for the development of a continuing education program. There are no other conflicts of interest.

Conclusions: Lozenge use prior to cue exposure may minimize cue induced symptom severity but when taken 15 minutes prior to cues the decrease is not different than placebo. Research is needed to determine if another time-frame relative to cue exposure would be more effective.

Keywords

Smoking; Craving; Withdrawal Symptoms; Cues; Sex differences

1. Introduction

Smoking cessation success rates continue to be low with fewer than 30% of smokers achieving long-term abstinence using currently available treatments (Fiore et al., 2008). With new pharmacotherapies for smoking cessation rarely introduced, it is necessary to identify methods by which to maximize the efficacy of currently available treatments.

Nicotine gum and lozenge are commonly used to assist with smoking cessation attempts and are often used when smokers feel that they most need them. Although recommended to initially be used on a scheduled basis (to ensure that a sufficient amount of nicotine is obtained), nicotine gum or lozenge is also often used on an as-needed basis either following the period of scheduled use or in combination with scheduled use of the nicotine patch (Fiore et al., 2008; Kozlowski et al., 2007; Sweeney et al., 2001).

Among the most common smoking triggers reported is the presence of people or objects associated with smoking (i.e., smoking cues) (Borland, 1990; Shiffman, 1982; Shiffman et al., 1996). Studies have shown that presentation of smoking cues leads to rapid increases in craving and withdrawal symptoms and that exposure to smoking cues often precedes relapse (Borland, 1990; Carter & Tiffany, 1999; Ferguson & Shiffman, 2009; Payne, Schare, Levis, & Colletti, 1991; Shiffman et al., 1996; Shiffman, 1982). Studies evaluating various dosage forms of medicinal nicotine (i.e., patch, gum, lozenge) have found that they are effective at reducing overall craving and withdrawal symptoms severity (Germovsek et al., 2019; Jorenby et al., 1999, 1996; Shiffman, 2008; West and Shiffman, 2001). Studies assessing the effect of nicotine patch when used during exposure to smoking triggers have similarly found it to be effective at decreasing overall craving severity but did not find it effective at attenuating smoking cue induced symptom increases (Havermans et al., 2003; Morissette et al., 2005; Rohsenow et al., 2007; Tiffany et al., 2000; Waters et al., 2004). It may be that during times of rapid increases in craving (as occurs during smoking trigger exposure), a relatively rapid infusion of additional nicotine is needed to attenuate the symptom increases. Such an increase could potentially be achieved by using products such as nicotine gum or lozenge in anticipation of smoking cue exposure, however smokers advised to use these products when needed likely often interpret these instructions as advising them to use the product after cravings or withdrawal symptoms are already present. Such use would mean that no medicinal nicotine product is taken prior to or during smoking trigger exposure. Among smokers who lapse, a study reported that 50% lapsed within 11 minutes of the onset of craving (Ferguson & Shiffman, 2009; Shiffman et al., 1996), however nicotine concentrations after starting use of gum or lozenge increase relatively gradually over an approximately 30 minute period (Kotlyar et al., 2007). Therefore, use of these products after

craving and withdrawal symptoms are already present may be too late to prevent lapses. Studies assessing the administration of faster acting dosage forms after smoking cue presentation have found that both nicotine gum and nicotine lozenge decrease craving or withdrawal symptoms faster than placebo (Nides et al., 2018; Shiffman et al., 2003) and that the speed of nicotine delivery impacts how quickly symptom relief is observed. For example, the use of a rapid-release nicotine gum or nicotine film after cue presentation results in faster symptom relief than use of standard formulations (Du et al., 2014; Niaura et al., 2005). There has been relatively little data however evaluating whether using nicotine gum or lozenge prior to (rather than after) exposure to a smoking trigger can prevent or attenuate the expected increase in symptom severity.

The purpose of the current study was to determine whether use of a nicotine lozenge prior to smoking cue exposure decreases craving and withdrawal symptoms that occur when smokers are exposed to such situations. Our hypothesis was that use of nicotine lozenge 15 minutes prior to smoking cue exposure would result in smaller cue induced increases in craving and withdrawal symptom severity than either placebo lozenge use or no product use 15 minutes prior to cue exposure. Among the four non-patch dosage forms, the nasal spray and inhaler are not well tolerated by smokers and require a prescription (Hajek et al., 1999). These two dosage forms are therefore less frequently used. Nicotine lozenge was selected over the nicotine gum largely because it can be used less conspicuously. Since many common smoking triggers involve social interactions (e.g. seeing people you smoke with, being in a stressful situation), a less conspicuous product would likely be more appropriate in these circumstances. This study expands on our previous work examining the effect of using nicotine lozenge at various time-points prior to a stress task (Kotlyar et al., 2017) by adding a placebo condition and assessing a different commonly reported smoking trigger (i.e., exposure to smoking cues).

2. Methods

2.1 Design

In this randomized cross-over study, participants were asked to complete three laboratory sessions during which craving and withdrawal symptom severity were assessed prior to and following exposure to the presentation of smoking cues within a virtual reality (VR) environment. The three conditions studied were using a placebo lozenge, a 4 mg nicotine lozenge or no lozenge 15 minutes prior to cue exposure procedures. During the session in which no lozenge was used prior to cue exposure, an active lozenge was used immediately after the conclusion of cue exposure procedure in order to determine how long craving and withdrawal symptoms are elevated during typical use (i.e., after symptoms of craving and withdrawal are present) relative to lozenge use prior to cue exposure. Placebo lozenge was acquired from Clinical Trial Services Group, Salt Lake City, UT.

The three laboratory sessions were separated by at least 3 days with the treatment order randomized. The randomization schedule for the six groups (all the combinations in which the three conditions could have been ordered) was created by the statistician using block randomization with random block sizes of 12 and 24. Participants were randomized at the first laboratory session and were blinded as to whether they were receiving active or placebo

lozenges. Investigators were aware that active lozenge was used if given after cue exposure procedures but were blinded as to whether a lozenge used prior to cue exposure procedures was active or placebo. Fifteen minutes prior to cue presentation was the time-frame chosen since nicotine concentrations after lozenge use are substantially elevated by this time-point (Kotlyar et al., 2007; Kraiczi, Hansson, & Perfekt, 2011) and it is in close enough proximity to a smoking trigger that the trigger is likely to be somewhat predictable by smokers. This timing also allowed for nicotine concentrations to continue increasing during cue exposure. Further informing this timing was a study demonstrating that when used after smoking cue presentation, craving was substantially lower 15 minutes after nicotine gum use (relative to placebo) (Shiffman et al., 2003).

2.2 Participants

This study enrolled generally healthy smokers between the ages of 18 and 64 who smoked at least 8 cigarettes on an average day. Participants were excluded if they reported current unstable medical or psychiatric conditions, use of any medication that could interfere with study measures (e.g., psychoactive medications), use of smoking cessation therapy during the month previous to screening, pregnancy, breast feeding or a history of severe motion sickness (since the VR technology used could cause nausea / vomiting in those susceptible to motion sickness). Smoking status was confirmed via exhaled carbon monoxide (CO) concentrations of ≥ 8 parts per million (ppm). A urine pregnancy test was used to confirm that women were not pregnant at the time of enrollment. All other inclusion / exclusion criteria were based on self-report. Participants who completed the study received \$320 with partial payment provided for those who dropped out prior to completing the study.

2.3 Procedures

This study was approved by the University of Minnesota Institutional Review Board. Eligibility was assessed at a screening visit at which written informed consent was obtained. Because smoking cues were presented in a VR environment (hardware and software obtained from Virtually Better Inc. in Decatur, GA), participants were immersed in the environment at the screening visit to ensure that responses seen at subsequent visits were not due to the novelty of the technology used. The software used in this study was selected based on a series of publications demonstrating its effectiveness at increasing craving during the virtual presentation of smoking (vs. neutral) cues (Bordnick et al., 2004; Bordnick, Graap, Copp, Brooks, & Ferrer, 2005; Carter, Bordnick, Traylor, Day, & Paris, 2008; Traylor, Bordnick, & Carter, 2008).

Participants were asked to abstain overnight (confirmed via an exhaled CO ≤ 7 ppm) prior to each of the three morning laboratory sessions. In order to ensure stable baseline measurements, participants sat in a quiet room for 30 minutes prior to completing baseline questionnaires assessing craving and withdrawal symptom severity. Those assigned to receive either the placebo or 4 mg nicotine lozenge fifteen minutes prior to cue exposure then used a single dose of their assigned product. The VR visor was placed immediately prior to the start of the cue presentation procedure and participants then proceeded through four virtual “rooms”. The first and last of these rooms had neutral cues (a TV displaying wildlife images) and the middle two had smoking cues. In one of the smoking cue rooms,

participants navigate around a room containing a variety of objects commonly associated with smoking such as cigarette packs, ash trays, and burning cigarettes. The other smoking cue room contains people smoking, talking about smoking, and drinking. The sensations were primarily visual with some auditory input that included a voice-over providing information regarding the wildlife images displayed in the neutral rooms, and music and / or virtual people speaking in the cue rooms. Since carry-over effects are likely to occur from the smoking cue room to the neutral room, a neutral room was always presented first in order to obtain a true baseline measurement (Sayette, Griffin, & Sayers, 2010). Participants remained in each room for approximately 3 minutes. After completing each room, craving and withdrawal symptoms were first measured by using a hand controller to answer questions displayed within the virtual environment. Participants then briefly removed the visor to rate craving and withdrawal symptoms using standard questionnaires. Upon completing the questionnaires, the visor was replaced and participants proceeded to the next virtual room. After completing the last set of questions within the VR environment, the visor was removed and participants completed the last set of standard questionnaires. Those assigned to not receive nicotine lozenge prior to cue exposure procedures now received an active lozenge. Questionnaires assessing craving and withdrawal symptoms were then assessed every 15 minutes for the next hour (Figure 1 outlines laboratory session procedures). After 10 participants completed the study, a question was added to the last visit asking at which session participants thought they had received the lozenge without nicotine (i.e., placebo).

2.4 Outcome Measures

The primary outcome for this study was the change in craving severity from the first neutral room to cue rooms as measured by the Minnesota Nicotine Withdrawal Scale (MNWS), a widely used scale assessing craving and withdrawal symptom severity (Hughes and Hatsukami, 1986). Secondary outcomes included change in withdrawal symptom severity and absolute severity of craving and withdrawal symptoms after leaving each room based on the MNWS. Craving severity from the MNWS was the response to the question (on a 0 – 4 scale) assessing “craving for cigarettes”, whereas withdrawal symptom severity was calculated by adding the scores (each on a 0 – 4 scale) of the other 7 questions. Additional secondary outcomes included absolute symptom severity after leaving each room and the change in symptom severity from the first neutral room to cue rooms as based on the total score of the Brief version of the Questionnaire of Smoking Urges (QSU) (Cox et al., 2001; Toll et al., 2006) and on answers to questions embedded within the virtual environment. Embedded questions were answered by using a hand controller to slide a bar indicating the extent to which participants craved smoking (using a 100 point scale with the anchors being “none” and “more than ever”) and the extent to which participants thought about smoking (assessed on a 0 to 10 scale with the anchors being “didn’t think about smoking at all” and “thought about smoking all the time”).

2.5 Statistical Analysis

Baseline demographics were summarized as frequency and percent for categorical variables and mean $\pm$ standard deviation (SD) for continuous variables. Each outcome was analyzed taking into account the cross-over study design using mixed model regression with fixed

effects for treatment (placebo, active lozenge before, no treatment before), order of treatment, order of VR stimulus rooms, and a random effect for participant. Model statistics and degrees of freedom (df) for the main treatment effects along with least-squares means (LS) $\pm$ standard errors and effect sizes for pairwise comparisons are reported. Comparisons of craving and withdrawal symptom severity and response in the VR system between the first neutral room and after exiting the second cue room were conducted using paired t-tests. Exploratory secondary analyses of gender or dependence (measured using the Fagerstrom Test for Nicotine Dependence [FTND]) (Heatherton et al., 1991) differences were conducted by adding main and interaction terms to the models described above. Results are only provided where differences were observed. Further, all final models were additionally adjusted for gender, age, race, and FTND scores to ensure no significant confounding. These adjusted models were similar in conclusion to the primary models listed above and therefore the data are not presented. A sensitivity analysis including only participants who completed all of the sessions was conducted and conclusions were similar and therefore all data are reported. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 58 participants were randomized, of whom 55 completed one laboratory session, 42 completed two sessions and 40 completed the entire study (Figure 2). Among the 58 participants randomized, 29 (50.0%) were female, 34 (58.6%) were Caucasian and 18 (31.0%) were African American. Participants were on average 42.6 ± 13.1 years of age and reported that on an average day they smoked 16.8 ± 6.1 cigarettes. Baseline score on the FTND was 5.3 ± 1.7 . No significant differences in demographics were observed between those who did and did not complete the study. Nine participants reported previously using nicotine replacement therapy to quit smoking of whom 6 had used nicotine gum or lozenge.

Participant self-report of treatment assignment suggests that the blind was effective. Seven (out of 30) participants correctly identified the lab at which they received the placebo lozenge, three participants stated that they received placebo at two laboratory sessions one of which included the correct one and one additional participant stated that they received placebo at all three labs.

3.1 Effectiveness of VR in eliciting a response

To assess the effectiveness of VR in eliciting a response, only data from the no treatment condition (i.e., lozenge given after cue exposure) were compared before and after cues since in the other conditions lozenge use (either active or placebo) could have affected these measures. Craving and withdrawal symptom severity (as assessed by the MNWS) in the no treatment condition was higher after the second of the smoking cue rooms relative to symptom severity measured after the first neutral cue room ($t=2.04$, $df=44$, effect size=0.30, $p=0.05$ for craving and $t=2.95$, $df=43$, effect size=0.44, $p=0.005$ for withdrawal) suggesting the VR environment was effective in eliciting a response (Figure 3) although a significant increase was not found in QSU severity (Figure 4).

Similar results were observed when evaluating measures assessed within the VR environment. In the no treatment condition, scores on craving and the extent to which

participants were thinking about smoking were higher after the second of the smoking cue rooms than after the first of the neutral cue rooms ($t=2.95$, $df=43$, effect size=0.44, $p=0.005$ for craving and $t=7.46$, $df=43$, effect size=1.13, $p<0.0001$ for thinking about smoking). These results suggest that the cue exposure procedures were effective at increasing symptom severity in these measures.

3.2 Treatment effect on overall levels of withdrawal symptom and craving intensity

Significant treatment effects after leaving each of the two smoking cue rooms were observed for craving ($F_{2,78}=8.02$, $p=0.0007$ after 1st cue room and $F_{2,78}=10.15$, $p=0.0001$ after 2nd cue room), withdrawal ($F_{2,78}=3.03$, $p=0.05$ after 1st cue room and $F_{2,78}=4.94$, $p=0.01$ after 2nd cue room) and QSU score ($F_{2,79}=12.65$, $p<0.0001$ after 1st cue room and $F_{2,79}=14.45$, $p<0.0001$ after 2nd cue room). Symptom severity after leaving the second of the smoking cue rooms was greater in the no treatment condition than when participants received either placebo lozenge ($t=2.65$, $df=78$, effect size=0.35, $p=0.01$ for craving; $t=2.69$, $df=78$, effect size=0.36, $p=0.009$ for withdrawal; $t=3.56$, $df=79$, effect size=0.48, $p=0.0006$ for QSU score) or nicotine lozenge prior to cue exposure ($t=4.48$, $df=78$, effect size=0.60, $p<0.0001$ for craving; $t=2.74$, $df=78$, effect size=0.37, $p=0.008$ for withdrawal; $t=5.26$, $df=79$, effect size=0.70, $p<0.0001$ for QSU score) (Figures 3 and 4). Effects were no longer statistically significant for craving or withdrawal symptom severity starting at 15 minutes post-cue exposure presentation procedure and for QSU score starting at 30 minutes post-cue presentation procedure (Figures 3 and 4). Although craving and QSU score during cue presentation were generally lower when participants received nicotine lozenge prior to cue exposure than when they received placebo, these differences were not statistically significant (Figure 3A and Figure 4). An exploratory analysis identified a significant treatment by gender interaction effect ($F_{2,75}=3.17$, $p=0.05$) for craving as assessed by the MNWS, with women having a greater response to placebo than men (Supplemental Figure 1).

Results were similar when evaluating scores of craving and the extent to which participants were thinking about smoking when assessed within the VR environment. Significant treatment effects were observed for both of these measures after the first ($F_{2,74}=14.87$, $p<0.0001$ for craving; $F_{2,74}=6.78$, $p=0.002$ for thinking about smoking) and the second of the smoking cue rooms ($F_{2,74}=15.36$, $p<0.0001$ and $F_{2,74}=7.45$, $p=0.001$, respectively). Overall symptom severity after the second cue room was greater when participants received no treatment than when they received either placebo lozenge ($t=3.86$, $df=74$, effect size=0.52, $p=0.0002$ for craving; $t=3.08$, $df=74$, effect size=0.41, $p=0.003$ for thinking about smoking) or nicotine lozenge ($t=5.36$, $df=74$, effect size=0.72, $p<0.0001$ for craving; $t=3.53$, $df=74$, effect size=0.47, $p=0.0007$ for thinking about smoking) prior to cue exposure (Figure 5). Although craving score was generally lower when participants received nicotine lozenge prior to smoking cue exposure than when they received placebo lozenge, these differences were not statistically significant (Figure 5A). No significant treatment by gender interaction effects were observed for measures within the VR environment.

3.3 Treatment effect on cue-induced changes in withdrawal symptom and craving intensity

No significant differences among groups were observed in the extent to which symptoms increased in response to smoking cue presentation. This was the case for measures assessed using standard questionnaires outside the VR environment and for measures assessed within the VR environment.

4. Discussion

This study demonstrated that both nicotine and placebo lozenge, when used 15 minutes prior to the presentation of smoking cues, reduce craving and withdrawal symptom severity but do not attenuate cue induced increases in these measures. Furthermore, this study did not find significant differences between active and placebo lozenge although several measures of symptom severity were lower when using active vs. placebo lozenge. These findings suggest that taking action prior to smoking cue exposure may be an effective method by which to reduce overall craving and withdrawal symptom severity although these benefits may, at least partially, be due to expectancy rather than pharmacological effects.

Few previous studies have assessed if non-patch medicinal nicotine dosage forms when taken prior to cue presentation effect cue-induced increases in subjective symptoms, although one such study found that nicotine lozenge use 30 minutes prior to cue exposure did not affect craving increases (Schlagintweit, Good, & Barrett, 2014). A study assessing cigarette smoking similarly found that smoking one cigarette prior to cue exposure reduced overall craving severity but did not prevent cue induced increases (Schlagintweit & Barrett, 2016). These data, although limited, are consistent with our findings and suggest that using nicotine containing products, regardless of the nicotine source, prior to cue exposure does not attenuate cue-induced symptom increases. Conversely, some, albeit limited, data suggest that craving increases that occur in response to stress (another commonly reported smoking trigger) can be reduced with nicotine containing products if used in close temporal proximity to stress exposure. For example, one study found that compared to no lozenge use prior to a stress task, using a 4 mg nicotine lozenge either immediately or 10 minutes prior to a stress task attenuated stress-induced increases in craving and withdrawal severity whereas using the lozenge either 20 or 30 minutes prior to the stress task did not (Kotlyar et al., 2017). Another study found that smoking a cigarette approximately 40 minutes prior to a stress task did not prevent stress induced increases in craving and withdrawal severity, yet smoking four additional puffs immediately prior to resuming a stress task did prevent further symptom increases (Perkins, Karelitz, Conklin, Sayette, & Giedgowd, 2010). Similarly, a study measuring craving severity at baseline and again after smoking one cigarette and completing a stressful task, found that craving was less severe after exposure to the combination of smoking and stress, suggesting that smoking immediately prior to a stressor negated the expected stress induced increase in craving (Kotlyar, Chau, & Thuras, 2018). These studies suggest that the timing of nicotine use prior to a smoking trigger may be of key importance in preventing trigger-induced increases in symptom severity and raise the possibility that the effects of nicotine use prior to smoking trigger exposure may differ depending on the specific trigger. Indeed, there are data suggesting that varenicline decreases cue-induced

craving but not when cues are preceded by stress (Brandon et al., 2011; Ray et al., 2013). Considering the limited data available regarding the optimal timing of nicotine use relative to smoking trigger exposure and regarding how the effects of nicotine use may differ among smoking triggers, more research is needed to address these questions.

Our finding that both placebo and active nicotine lozenge decreased symptom severity (compared to no treatment) is consistent with a study demonstrating no difference between active and placebo nicotine gum on acute cravings for cigarettes but that both were more effective than no treatment (Davies et al., 2004). Other studies have shown inconsistent effects of nicotine replacement therapy on craving and withdrawal symptom severity (West and Shiffman, 2001). These studies and those demonstrating that alternatives to smoking such as chewing gum can influence urge to smoke and nicotine withdrawal (Cohen et al., 1997; Cortez-Garland et al., 2010), suggest that the expectation of symptom relief results in substantial symptom decreases. Further contributing to expectancy effects in the current study may have been that participants were informed that the purpose of the study was to determine how lozenge use can be best timed to decrease craving and withdrawal symptoms. Our finding that when nicotine lozenge was used after smoking cues, symptom severity within 15 to 30 minutes of use was no longer higher than when taking lozenge prior to cue exposure is consistent with the nicotine pharmacokinetics of the lozenge and with a study finding that when used after smoking cue presentation, craving was substantially lower 15 minutes after nicotine gum use relative to placebo (Shiffman et al., 2003).

Our data in combination with previously published studies suggest that use of medicinal nicotine prior to smoking cue exposure decreases overall craving and / or withdrawal symptom severity (with this effect possibly due at least in part to an expectancy effect) and that depending on the timing and type of smoking trigger, it is possible that use of medicinal nicotine may attenuate smoking trigger induced increases in these symptoms. Smokers are frequently advised, as part of smoking cessation counselling, to identify high risk smoking situations and to develop strategies to either avoid or manage such situations (National Cancer Institute, 2011). This line of research leads to the possibility that pre-emptive use of nicotine lozenge can be incorporated into the counseling material provided to smokers on how to effectively manage high-risk lapse situations, thereby combining pharmacotherapy that minimizes the effects of high-risk situations with behavioral therapy targeted at the management of symptoms remaining despite medicinal nicotine use. Clinical studies assessing if such an approach would be effective are needed.

Our data showing that the craving response to placebo lozenge was stronger in women than men is consistent with data suggesting that women have reduced sensitivity to nicotine reinforcement. For example, studies show that women experience greater craving relief than men in response to very low nicotine cigarettes (Barrett, 2010), that withdrawal symptoms in women decreased to an equal extent when using very low nicotine cigarettes either with or without the nicotine patch (Vogel et al., 2014), that women are less likely to choose nicotine over placebo nasal spray and show less differential nicotine vs. placebo nasal spray self-administration (Perkins, 2009).

A limitation of studies examining the effect of interventions on craving and withdrawal severity is that it is not clear if decreasing symptoms in a laboratory setting is indicative of an effective smoking cessation intervention and if absolute levels of craving or cue-induced craving increases are more relevant to cessation success (Ferguson & Shiffman, 2009; Perkins, 2012; Sayette & Tiffany, 2013). The results of the current study found that although absolute levels of craving decreased when lozenge was used prior to smoking cue presentation, the change in craving did not. Future studies assessing cessation success are needed to determine if using medicinal nicotine prior to encountering anticipated smoking triggers results in increased cessation success. Other limitations of this study include the use of only one smoking trigger (i.e., smoking cues) and testing only one time-point for nicotine lozenge use. Since individual responses to any specific cue may vary, a limitation of this study is that several types of cues were included in the virtual rooms (e.g., cigarettes, alcohol, social interactions). Future studies are needed to determine the optimal time-frame for medicinal nicotine use and to determine the extent to which individual difference in smoking trigger response influence these results. Another limitation in the current study is that increases in measures of craving, particularly when measured outside the VR environment, were relatively modest. It is not clear if this was due to the VR technology used to present smoking cues, because participants were asked to abstain overnight and therefore ceiling effects on craving severity were found or due to other reasons. Nonetheless, significant increases occurred in almost all measures allowing for treatment effects to be observed if any were present. Finally, as the study was not designed to explore gender differences, the sample size for these analyses were small and the results should therefore be seen as preliminary.

5. Conclusion

In summary, this study found that using a lozenge 15 minutes prior to exposure to smoking cues resulted in lower overall craving and withdrawal symptom severity relative to no lozenge use but did not attenuate the cue-induced increases that occurred in these symptoms. These changes were observed during the use of both nicotine and placebo lozenges and therefore may be due, at least in part, to the non-pharmacological effects of lozenge use. Nonetheless, advising smokers who are using nicotine lozenge on an as needed basis to use them in advance of encountering anticipated smoking trigger may result in lower craving severity and perhaps increased efficacy. However, a clinical study is needed to determine if this is indeed the case and to determine the optimal timing of product use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of Funding Source

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References

- Barrett SP, 2010 The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behav. Pharmacol* 21, 144–152. 10.1097/FBP.0b013e328337be68 [PubMed: 20168213]
- Bordnick PS, Graap KM, Copp H, Brooks J, Ferrer M, Logue B, 2004 Utilizing virtual reality to standardize nicotine craving research: a pilot study. *Addict Behav* 29, 1889–1894. [PubMed: 15530734]
- Bordnick PS, Graap KM, Copp HL, Brooks J, Ferrer M, 2005 Virtual reality cue reactivity assessment in cigarette smokers. *Cyberpsychol Behav* 8, 487–492. [PubMed: 16232041]
- Borland R, 1990 Slip-ups and relapse in attempts to quit smoking. *Addict Behav* 15, 235–245. [PubMed: 2378283]
- Brandon TH, Drobos DJ, Unrod M, Heckman BW, Oliver JA, Roetzheim RC, Karver SB, Small BJ, 2011 Varenicline effects on craving, cue reactivity, and smoking reward. *Psychopharmacology (Berl)*. 218, 391–403. 10.1007/s00213-011-2327-z [PubMed: 21559801]
- Carter BL, Bordnick P, Traylor A, Day SX, Paris M, 2008 Location and longing: The nicotine craving experience in virtual reality. *Drug Alcohol Depend*. 95, 73–80. 10.1016/j.drugalcdep.2007.12.010 [PubMed: 18243586]
- Carter BL, Tiffany ST, 1999 Meta-analysis of cue-reactivity in addiction research. *Addiction* 94, 327–340. [PubMed: 10605857]
- Cohen LM, Collins FL, Britt DM, 1997 The effect of chewing gum on tobacco withdrawal. *Addict. Behav* 22, 769–773. 10.1016/S0306-4603(96)00072-X [PubMed: 9426794]
- Cortez-Garland M, Cohen LM, VanderVeen JW, Cook K, 2010 The effect of chewing gum on self-reported nicotine withdrawal: Is it the flavor, the act of chewing, or both? *Addict. Behav*. 35, 224–228. 10.1016/j.addbeh.2009.10.016
- Cox LS, Tiffany ST, Christen AG, 2001 Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 3, 7–16. 10.1080/14622200020032051 [PubMed: 11260806]
- Davies GM, Willner P, James DL, Morgan MJ, 2004 Influence of Nicotine Gum on Acute Cravings for Cigarettes. *J. Psychopharmacol* 18, 83–87. 10.1177/0269881104040240 [PubMed: 15107189]
- Du D, Nides M, Borders J, Selmani A, Wawerczak W, 2014 Comparison of nicotine oral soluble film and nicotine lozenge on efficacy in relief of smoking cue-provoked acute craving after a single dose of treatment in low dependence smokers. *Psychopharmacology (Berl)*. 231, 4383–4391. 10.1007/s00213-014-3586-2 [PubMed: 24781517]
- Ferguson SG, Shiffman S, 2009 The relevance and treatment of cue-induced cravings in tobacco dependence. *J. Subst. Abuse Treat*. 36, 235–243. 10.1016/j.jsat.2008.06.005 [PubMed: 18715743]
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, Henderson PN, Heyman RB, Koh HK, Kottke TE, Lando HA, Mecklenburg RE, Mermelstein RJ, Orleans PDMCT, Robinson L, Stitzer ML, Tommasello AC, Villejo L, Wewers ME, 2008 Treating tobacco use and dependence: 2008 Update. *Clinical Practice Guidelines*. U.S. Department of Health and Human Services Public Health Service. Rockville, MD.
- Germovsek E, Hansson A, Kjellsson MC, Perez Ruixo JJ, Westin Å, Soons PA, Vermeulen A, Karlsson MO, 2019 Relating Nicotine Plasma Concentration to Momentary Craving Across Four Nicotine Replacement Therapy Formulations. *Clin. Pharmacol. Ther* 10.1002/cpt.1595
- Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A, 1999 Randomized Comparative Trial of Nicotine Polacrilex, a Transdermal Patch, Nasal Spray, and an Inhaler. *Arch. Intern. Med* 159, 2033 10.1001/archinte.159.17.2033 [PubMed: 10510989]
- Havermans RC, Debaere S, Smulders FTY, Wiers RW, Jansen ATM, 2003 Effect of Cue Exposure, Urge to Smoke, and Nicotine Deprivation on Cognitive Performance in Smokers. *Psychol. Addict. Behav* 17, 336–339. 10.1037/0893-164X.17.4.336 [PubMed: 14640831]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO, 1991 The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br. J. Addict* 86, 1119–27. [PubMed: 1932883]

- Hughes JR, Hatsukami D, 1986 Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry* 43, 289–94. 10.1001/archpsyc.1986.01800030107013 [PubMed: 3954551]
- Jorenby DE, Hatsukami DK, Smith SS, Fiore MC, Allen S, Jensen J, Baker TB, 1996 Characterization of tobacco withdrawal symptoms: Transdermal nicotine reduces hunger and weight gain. *Psychopharmacology (Berl)*. 128, 130–138. 10.1007/s002130050118 [PubMed: 8956374]
- Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB, 1999 A Controlled Trial of Sustained-Release Bupropion, a Nicotine Patch, or Both for Smoking Cessation. *N. Engl. J. Med* 340, 685–691. 10.1056/NEJM199903043400903 [PubMed: 10053177]
- Kotlyar M, Chau HT, Thuras P, 2018 Effects of smoking and paroxetine on stress-induced craving and withdrawal symptoms. *J. Subst. Use* 23, 655–659. 10.1080/14659891.2018.1489008 [PubMed: 31768127]
- Kotlyar M, Lindgren BR, Vuchetich JP, Le C, Mills AM, Amiot E, Hatsukami DK, 2017 Timing of nicotine lozenge administration to minimize trigger induced craving and withdrawal symptoms. *Addict. Behav* 71 10.1016/j.addbeh.2017.02.018
- Kotlyar M, Mendoza-Baumgart MI, Li Z.-z, Pentel PR, Barnett BC, Feuer RM, Smith EA, Hatsukami DK, 2007 Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tob. Control* 16, 138–142. 10.1136/tc.2006.018440 [PubMed: 17400953]
- Kozlowski LT, Giovino GA, Edwards B, DiFranza J, Foulds J, Hurt R, Niaura R, Sachs DPL, Selby P, Dollar KM, Bowen D, Cummings KM, Counts M, Fox B, Sweanor D, Ahern F, 2007 Advice on using over-the-counter nicotine replacement therapy-patch, gum, or lozenge-to quit smoking. *Addict. Behav* 32, 2140–2150. 10.1016/j.addbeh.2007.01.030 [PubMed: 17360126]
- Kraiczi H, Hansson A, Perfekt R, 2011 Single-Dose Pharmacokinetics of Nicotine When Given With a Novel Mouth Spray for Nicotine Replacement Therapy. *Nicotine Tob. Res* 13, 1176–1182. 10.1093/ntr/ntr139 [PubMed: 21849415]
- Morissette SB, Palfai TP, Gulliver SB, Spiegel DA, Barlow DH, 2005 Effects of Transdermal Nicotine During Imaginal Exposure to Anxiety and Smoking Cues in College Smokers. *Psychol. Addict. Behav* 19, 192–198. 10.1037/0893-164X.19.2.192 [PubMed: 16011390]
- National Cancer Institute, 2011 Clearing the Air: Quit Smoking Today. U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health.
- Niaura R, Sayette M, Shiffman S, Glover ED, Nides M, Shelanski M, Shadel W, Koslo R, Robbins B, Sorrentino J, 2005 Comparative efficacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. *Addiction* 100, 1720–1730. [PubMed: 16277632]
- Nides M, Shanga GM, Bishop A, Becker WD, 2018 Nicotine Lozenges in the Relief of Behaviorally Provoked Craving. *Am. J. Health Behav.* 42, 69–80. 10.5993/AJHB.42.3.7
- Payne TJ, Schare ML, Levis DJ, Colletti G, 1991 Exposure to smoking-relevant cues: Effects on desire to smoke and topographical components of smoking behavior. *Addict. Behav* 16, 467–479. 10.1016/0306-4603(91)90054-L [PubMed: 1801570]
- Perkins KA, 2012 Subjective Reactivity to Smoking Cues as a Predictor of Quitting Success. *Nicotine Tob. Res* 14, 383–387. 10.1093/ntr/ntr229 [PubMed: 22140145]
- Perkins KA, 2009 Sex differences in nicotine reinforcement and reward: influences on the persistence of tobacco smoking. *Nebraska Symp. Motiv* 55, 143–69.
- Perkins KA, Karelitz JL, Conklin CA, Sayette MA, Giedgowd GE, 2010 Acute negative affect relief from smoking depends on the affect situation and measure but not on nicotine. *Biol Psychiatry* 67, 707–714. 10.1016/j.biopsych.2009.12.017 [PubMed: 20132927]
- Ray LA, Lunney K, Bujarski S, Moallem N, Krull JL, Miotto K, 2013 The effects of varenicline on stress-induced and cue-induced craving for cigarettes. *Drug Alcohol Depend* 131, 136–142. 10.1016/j.drugalcdep.2012.12.015 [PubMed: 23298651]
- Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, MacKinnon SV, Sirota AD, Kaplan GB, 2007 High-dose transdermal nicotine and naltrexone: Effects on nicotine withdrawal, urges, smoking, and effects of smoking. *Exp. Clin. Psychopharmacol* 15, 81–92. 10.1037/1064-1297.15.1.81 [PubMed: 17295587]

- Sayette MA, Griffin KM, Sayers WM, 2010 Counterbalancing in Smoking Cue Research: A Critical Analysis. *Nicotine Tob. Res* 12, 1068–1079. 10.1093/ntr/ntq159 [PubMed: 20884695]
- Sayette MA, Tiffany ST, 2013 Peak provoked craving: an alternative to smoking cue-reactivity. *Addiction* 108, 1019–1025. 10.1111/j.1360-0443.2012.04013.x [PubMed: 23075138]
- Schlagintweit HE, Barrett SP, 2016 Does acute tobacco smoking prevent cue-induced craving? *J. Psychopharmacol* 30, 468–473. 10.1177/0269881116639288 [PubMed: 27026532]
- Schlagintweit HE, Good KP, Barrett SP, 2014 The impact of nicotine lozenges and stimulus expectancies on cigarette craving. *J Psychopharmacol* 28, 773–779. 10.1177/0269881113519508 [PubMed: 24476987]
- Shiffman S, 2008 Effect of nicotine lozenges on affective smoking withdrawal symptoms: Secondary analysis of a randomized, double-blind, placebo-controlled clinical trial. *Clin. Ther* 30, 1461–1475. 10.1016/j.clinthera.2008.07.019 [PubMed: 18803988]
- Shiffman S, 1982 Relapse following smoking cessation: A situational analysis. *J. Consult. Clin. Psychol* 50, 71–86. 10.1037/0022-006X.50.1.71 [PubMed: 7056922]
- Shiffman S, Paty JA, Gnys M, Kassel JA, Hickcox M, 1996 First lapses to smoking: within-subjects analysis of real-time reports. *J. Consult. Clin. Psychol* 64, 366–79. [PubMed: 8871421]
- Shiffman S, Shadel WG, Niaura R, Khayrallah MA, Jorenby DE, Ryan CF, Ferguson CL, 2003 Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology (Berl)*. 166, 343–350. 10.1007/s00213-002-1338-1 [PubMed: 12601502]
- Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE, 2001 Combination Nicotine Replacement Therapy for Smoking Cessation. *CNS Drugs* 15, 453–467. 10.2165/00023210-200115060-00004 [PubMed: 11524024]
- Tiffany ST, Cox LS, Elash CA, 2000 Effects of transdermal nicotine patches on abstinence-induced and cue-elicited craving in cigarette smokers. *J. Consult. Clin. Psychol* 68, 233–240. 10.1037/0022-006X.68.2.233 [PubMed: 10780123]
- Toll BA, Katulak NA, McKee SA, 2006 Investigating the factor structure of the Questionnaire on Smoking Urges-Brief (QSU-Brief). *Addict Behav* 31, 1231–1239. [PubMed: 16226843]
- Traylor AC, Bordnick PS, Carter BL, 2008 Assessing Craving in Young Adult Smokers Using Virtual Reality. *Am. J. Addict* 17, 436–440. 10.1080/10550490802268876 [PubMed: 18770087]
- Vogel RI, Hertsgaard LA, Dermody SS, Luo X, Moua L, Allen S, Al'Absi M, Hatsukami DK, 2014 Sex differences in response to reduced nicotine content cigarettes. *Addict. Behav* 39, 1197–1204. 10.1016/j.addbeh.2014.03.021 [PubMed: 24746485]
- Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH, 2004 Cue-Provoked Craving and Nicotine Replacement Therapy in Smoking Cessation. *J. Consult. Clin. Psychol* 72, 1136–1143. 10.1037/0022-006X.72.6.1136 [PubMed: 15612859]
- West R, Shiffman S, 2001 Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology (Berl)*. 155, 115–122. 10.1007/s002130100712 [PubMed: 11400998]

Highlights

- Nicotine lozenges are often used after increases in craving / withdrawal symptoms
- We compared use of active vs. placebo vs. no lozenge before cue exposure
- Lozenge use prior to cue exposure decreased overall symptom severity vs. no lozenge
- Cue-induced increases in symptom severity were not different among conditions

Figure 1.

Outline of each laboratory session. At each session, participants are randomized to either active lozenge, placebo lozenge or no product taken 15 minutes prior to VR cue exposure procedures. If no product is taken then active lozenge is taken immediately after the VR cue exposure procedure. MNWS = Minnesota Nicotine and Withdrawal Scale; QSU = brief version of Questionnaire on Smoking Urges; VR ratings = ratings completed within the VR environment assessing extent of craving smoking and extent of thinking about smoking.

Figure 2.

Flow of participants through the study. Placebo = receiving placebo lozenge 15 minutes prior to cue exposure procedure; active = receiving nicotine lozenge 15 minutes prior to cue exposure procedures; no Tx = no treatment received prior to cue exposure procedures

Figure 3.

Craving (Panel A) and withdrawal symptom (Panel B) severity (LS mean $\pm$ SE) as assessed by the Minnesota Nicotine Withdrawal Scale (MNWS). Assessments prior to the cue presentation procedure are indicated as occurring during (–) time and those after as (+) time. Assessments indicated as occurring at time 0 were measured immediately prior to beginning of cue presentation procedures

Figure 4.

Smoking Urges severity (LS mean $\pm$ SE) as assessed by the Questionnaire on Smoking Urges. Assessment prior to the cue presentation procedure are indicated as occurring during (–) time and those after as (+) time. Assessments indicated as occurring at time 0 were measured immediately prior to beginning of cue presentation procedures

Figure 5. Measurements taken within the virtual reality environment assessing severity of craving (panel A) and extent to which participants were Thinking about Smoking (Panel B) (LS mean $\pm$ SE)