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Effects of smoking and paroxetine on stress-induced craving and withdrawal symptoms

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Abstract

Background: When smokers relapse, many cite stressful circumstances as the cause. Most smoking cessation medications do not prevent stress induced increases in craving and withdrawal symptom severity; however the effect of smoking prior to stress exposure on symptom severity is unclear.

Methods: We examined how smoking a cigarette immediately prior to a stressful task affects craving and withdrawal symptom severity by analyzing data from a double-blind, crossover study assessing paroxetine's effects on the physiological response to the combination of stress and smoking. Measures were obtained prior to and following smoking / stress exposure and following a subsequent 30 minute period at two laboratory sessions (i.e., after one month each of paroxetine and placebo).

Results: Among study completers (n=63), severity of craving decreased from the beginning of the session to immediately following the smoking / stress exposure ($p<0.01$) and severity of smoking urges decreased from the beginning to the end of the laboratory session ($p<0.001$). Withdrawal symptoms were less severe while taking paroxetine vs. placebo ($p<0.05$) but no treatment x time effects were observed.

Conclusions: Additional research is needed to identify interventions that could similarly decrease stress induced craving in order to determine if smoking cessation rates can be increased.

Keywords

Smoking; Craving; Withdrawal Symptoms; Paroxetine; Stress

Introduction

Laboratory studies have found that stressful tasks decrease the ability to resist smoking (McKee et al., 2011), increase craving and withdrawal symptom severity, and increase

smoking topography measures (e.g. puff volume) (Kotlyar et al., 2011; Pomerleau & Pomerleau, 1987). In retrospective studies, up to 50% of smokers report that lapses during cessation attempts occur while experiencing stress or tension (Cummings et al., 1985; Shiffman et al., 1996). Prospective studies using ecological momentary assessment have found that in smokers attempting to quit, stress often precedes a smoking lapse (Businelle et al., 2016; Shiffman, et al., 1996). In order to minimize stress-induced smoking lapses, it is necessary to better understand how stress affects smoking and to identify interventions that can alter how smokers respond to stress.

Pharmacological interventions have not consistently been found to be effective at reducing smoking trigger induced increases in craving and withdrawal symptom severity. The nicotine patch and bupropion, although effective at decreasing overall craving and withdrawal symptom severity, have limited effects on reducing the extent to which these symptoms increase in response to smoking trigger exposure (Ferguson & Shiffman, 2009; Kotlyar, et al., 2011). Varenicline has been found to somewhat decrease smoking cue induced craving although a study evaluating stress induced symptoms did not find an effect (Brandon et al., 2011; Ray et al., 2013). Data with the nicotine lozenge suggests no effect on smoking cue or stress induced symptoms if used 20 to 30 minutes prior to smoking trigger exposure but a reduction in stress induced symptom increases if used either immediately prior to or 10 minutes prior to a stressor (Kotlyar et al., 2017; Schlagintweit et al., 2014). There is additionally conflicting data regarding the extent to which smoking a cigarette prevents smoking trigger induced increases in craving and withdrawal symptom severity. For example, one 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 increases in symptoms (Perkins et al., 2010). Another study found that smoking prior to presentation of smoking cues did not prevent cue induced increases in craving (Schlagintweit & Barrett, 2016). Characterizing the effect of cigarette smoking on smoking trigger induced changes in craving and withdrawal symptoms can help determine reasons that smoking can occur not only in response to an anticipated stressful event but also in the period prior to the event (Steptoe et al., 1996; West & Lennox, 1992). Additionally, a better understanding of the effects of smoking on smoking trigger induced symptoms can help identify interventions that could decrease the extent to which smoking triggers lead to smoking.

In this secondary analysis of a previously published study, we examined how smoking a cigarette immediately prior to completing a stressful task affects craving and withdrawal symptom severity. Additionally, as this data was collected in a study assessing the effects of a serotonin reuptake inhibitor (SSRI) on the physiological response to the combination of stress and smoking (Kotlyar et al., 2013), the effects of paroxetine on craving and withdrawal symptom severity following the combination of stress and smoking are also described. Since SSRIs have been shown to reduce physiological response to stressors (Golding et al., 2005; Golding et al., 2002; Kotlyar, et al., 2013; Ljung et al., 2001; Tucker et al., 2000), it is not known if they would also reduce craving and withdrawal symptom severity measured after stress exposure.

Methods

Study design details of this double-blind, randomized, cross-over study have been described previously (Kotlyar, et al., 2013). In brief, generally healthy individuals who smoked on average 10 cigarettes daily completed a screening visit and five study visits. One visit was a baseline visit before any medication was taken, two were visits occurring approximately 1 week after starting medication (i.e., paroxetine or placebo) and two were laboratory visits which occurred after approximately 4 weeks of medication (i.e. paroxetine 10 mg daily for 1 week followed by 20 mg daily or matching placebo). Written informed consent was obtained from all subjects and this study was approved by the University of Minnesota Institutional Review Board.

Subjects were asked to abstain from smoking on the day of morning laboratory sessions. At each laboratory session, subjects relaxed in a quiet room for thirty minutes, then smoked one cigarette over five minutes, and then completed two stressful tasks (i.e. giving a short speech and mental arithmetic) based on the Trier Social Stress Test (Kirschbaum et al., 1993). A thirty minute relaxation period followed the stress tasks.

Questionnaires were completed at each visit as indicated in Figure 1. The Minnesota Nicotine Withdrawal Scale (MNWS) assessed severity of craving and withdrawal symptoms (Hughes & Hatsukami, 1986). Craving severity was scored by the “craving for cigarettes” item and withdrawal symptom severity by the sum of the other 7 items. The brief version of the Questionnaire of Smoking Urges (QSU) was used to further assess urge to smoke with a score calculated for each of two factors (i.e. intention and desire to smoke, anticipation of relief from negative affect) (Cox et al., 2001).

The overall baseline measures were those observed at the visit occurring prior to medication use (i.e., the baseline visit). Paroxetine and placebo measures were determined at the subsequent four visits (i.e., the visits after 1 week of medication use and the laboratory sessions). Mixed effects models were used to examine differences between groups (i.e., paroxetine, placebo), change over time and interactions between groups and time. SPSS v.19 was used for these analyses.

Results

Sixty-three subjects completed the study and were included in the analysis. At baseline, average ($\pm$) age of subjects was 40.2 ± 12.6 years, 49.2% were female, subjects smoked an average ($\pm$) of 18.6 ± 7.1 cigarettes daily and average ($\pm$) score on the Fagerstrom Test for Nicotine Dependence was 5.0 ± 1.9 .

Among study completers, significant time ($F(4,558)=4.01, p<0.01$) and treatment ($F(1,558)=4.84, p<0.05$) effects were observed for withdrawal symptoms (measured by the MNWS) with no treatment x time effect observed (figure 2, Panel A). While taking placebo, no changes in withdrawal symptoms occurred between the pre-treatment and the one week post-placebo visits. Withdrawal symptoms significantly increased at the first measure during the laboratory session (i.e., prior to smoking and stress exposure) ($F(1,201.6)=8.36, p<0.01$) then decreased (relative to pre-stress measures) at both subsequent time-points but these

decreases did not reach statistical significance ($F(1,197.2)=1.08, p>0.05$; $F(1,200)=1.40, p>0.05$). While taking paroxetine, withdrawal symptoms followed a similar pattern but were lower overall.

A significant time effect ($F(4,558)=4.39, p<0.01$) was observed in craving (measured by the MNWS) (figure 2, Panel B); however no significant treatment or treatment x time effects were observed. Craving decreased significantly between the pre-treatment visit and the one week post-treatment visit ($F(1,196.4)=10.7, p<0.01$). During the laboratory session, craving decreased significantly between the beginning of the session and the post-stressor measures (2.5 vs 2.2; $F(1,186)=9.95, p<0.01$), with this difference no longer present 30 minutes post-stressor. A significant time effect was found for QSU factor 1 ($F(1,185.2)=18.8, p<0.001$) and factor 2 scores ($F(1,185)=12.8, p<0.001$) with each score significantly higher at the beginning of the laboratory session than at the visits prior to the laboratory sessions [$F(1,198.1)=111.0, p<0.001$ and $F(1,195.3)=99.1, p<0.001$]. Within the laboratory session, both factor 1 and factor 2 scores decreased significantly from the pre-stressor to the 30 minutes post-stressor time-points (factor 1: 83.9 vs. 77.2; $F(1,185.2)=18.8, p<0.001$; factor 2: 42.7 vs. 39.3; $F(1,185)=12.8, p<0.001$). No significant treatment or treatment x time effects were found.

Discussion

This study found that the severity of craving decreased after smoking one cigarette immediately prior to performing a stress task. This study further found that paroxetine decreased the overall severity of withdrawal symptoms relative to placebo but did not affect overall levels of craving or urge to smoke and did not result in larger decreases in craving and withdrawal symptom severity than did placebo.

Stress exposure in laboratory settings results in increases in craving, withdrawal symptoms and negative affect as well as increased difficulty in abstaining from smoking (Childs & de Wit, 2010; Kotlyar, et al., 2011; McKee, et al., 2011). Whereas smoking a cigarette after stress exposure results in decreases in craving, withdrawal symptoms, negative mood and anxiety (Ashare et al., 2012; Evatt & Kassel, 2010; Juliano & Brandon, 2002; McKee, et al., 2011), the effect of smoking a cigarette prior to stress exposure on these symptoms is less clear. One 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 although additional smoking immediately prior to resuming a stress task did prevent further increases in symptoms (Perkins, et al., 2010). Another study found that smoking a cigarette approximately 40 minutes prior to listening to a script describing a stressful situation did not prevent increases in craving but neither did smoking a cigarette prior to again being exposed to the stress script (Beckham et al., 2007). Studies assessing smoking at time-points ranging from immediately prior to 30 minutes prior to cue exposure have all found significant cue-induced increases in craving (Bailey et al., 2010; Drobles & Tiffany, 1997; McBride et al., 2006; Powell et al., 2002; Schlagintweit & Barrett, 2016). The current study extends previous findings by demonstrating that craving and withdrawal symptom severity decreases when a stress task is preceded by smoking a single cigarette and is consistent with a study demonstrating a lack of stress-induced increases in craving and withdrawal symptom

severity when nicotine lozenge is used immediately prior to stress exposure (Kotlyar, et al., 2017). These results suggest that the largest effects of nicotine on stress induced increases in craving and withdrawal symptom severity occur when nicotine containing products (e.g., cigarettes or nicotine lozenge) are used immediately prior to stress exposure. Although the data are somewhat inconsistent, these studies also raise the possibility that nicotine exposure immediately prior to a stressor may have greater effects on stress induced increases in craving and withdrawal than nicotine exposure immediately prior to cue exposure has on cue induced increases in symptoms. Further research is needed to confirm if this is the case. If so, this would suggest that different strategies may need to be developed for minimizing the effects of different smoking triggers. Indeed, some data suggest that varenicline decreases cue induced craving but not when cues are preceded by stress (Brandon, et al., 2011; Ray, et al., 2013).

Our finding of lower withdrawal symptom scores when taking paroxetine is consistent with studies finding lower withdrawal symptom scores (relative to placebo) in those taking either fluoxetine (Saules et al., 2004) or sertraline (Covey et al., 2002) and lower craving scores in those taking paroxetine (Killen et al., 2000). These previous findings were in studies that did not find SSRI's to consistently increase smoking cessation rates suggesting that decreasing withdrawal symptom severity is likely insufficient evidence to conclude that a medication would be an effective smoking cessation intervention. More research is needed on identifying markers of an effective smoking cessation medication and on the relationship between withdrawal symptoms and cessation.

A limitation of the current study is the lack of a control group in which a cigarette was not smoked prior to the stress task in order to confirm that craving and withdrawal symptom severity would have increased in response to the stress task. Increases in physiological responses suggest however that the intervention was effective at eliciting a stress response (Kotlyar, et al., 2013) and many studies have demonstrated that craving and withdrawal symptoms increase after stress exposure (Businelle, et al., 2016; Childs & de Wit, 2010; Kotlyar, et al., 2011; Kotlyar, et al., 2017; McKee, et al., 2011). It is therefore likely that in the absence of smoking a cigarette, craving and withdrawal symptoms severity would have increased in this study as well. An additional limitation is that craving and withdrawal symptom severity was not measured in between smoking a cigarette and exposure to a stress task. As the primary purpose of the study was to assess physiological response to the combination of stress and smoking, including a questionnaire between stress and smoking would have resulted in an increased amount of time between them thereby decreasing the ability to interpret the primary results. This limitation precludes the determination of whether an initial decrease in symptom severity in response to smoking was then followed by an increase in response to stress. The results only allow for the conclusion that the effect of the cigarette in reducing symptom severity was greater than the increase that would have likely resulted in the absence of smoking. An additional limitation is that there was no denicotinized cigarette control group to determine if craving and withdrawal symptom reduction was due to the pharmacological effects of nicotine or expectancy effects. Previous studies have demonstrated that cigarettes with no nicotine can be effective at decreasing urge to smoke (Barrett, 2010; Juliano & Brandon, 2002). Regardless of whether the effects observed in our study are due to pharmacological or expectancy effects, smokers'

experiences demonstrating altered response to stress after smoking a cigarettes likely impacts their smoking behavior.

In summary, these results demonstrated that the severity of craving decreases after smoking one cigarette immediately prior to performing a stress task and that paroxetine decreases withdrawal symptoms. These data suggest that future research is needed to identify interventions that could similarly affect stress induced craving in order to assess if such interventions would result in increased smoking cessation rates.

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Figure 1:
Study Outline. MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges

Figure 2:
Craving and Withdrawal symptom severity scores during paroxetine and placebo use as measured by the MNWS.