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Understanding the role of cessation fatigue in the smoking cessation process☆

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ABSTRACT

Background: To understand the dynamic process of cessation fatigue (i.e., the tiredness of trying to quit smoking) with respect to its average trend, effect on relapse, time-varying relations with craving and negative affect, and differences among genders and treatment groups.
Method: Randomized placebo-controlled clinical trial. Participants received either placebo, monotherapy (bupropion SR, nicotine patch, nicotine lozenge), or combined pharmacotherapy (bupropion SR + nicotine lozenge, nicotine patch + nicotine lozenge). Data were collected from 1504 daily smokers who were motivated to quit smoking. The participants completed baseline assessments and ecological momentary assessments for 2 weeks post-quit.
Results: Cessation fatigue reduced the likelihood of 6-month post-quit abstinence (OR = 0.97, 95% CI (0.95, 0.99)), and was positively associated with craving and negative affect. After controlling for these two factors, average cessation fatigue increased over time. Compared to men, women experienced greater fatigue ($t = -10.69$, $p < 0.0001$) and a stronger relation between fatigue and craving ($t = -8.80$, $p < 0.0001$). The relationship between fatigue and negative affect was significantly stronger in men ($t = 5.73$, $p < 0.0001$). Cessation fatigue was significantly reduced by combined pharmacotherapy ($t = -13.4$, $p < 0.0001$), as well as monotherapy ($t = -6.2$, $p < 0.0001$).
Conclusions: Cessation fatigue was closely related to craving, negative affect, and cessation outcomes. Women reported greater cessation fatigue than men. Current treatments appeared to reduce fatigue and weaken its relations with craving and negative affect.

1. Introduction

Many smokers trying to quit ultimately relapse within a few weeks. Even with various medications and behavioral interventions, less than 30% of smokers achieve long-term abstinence (Fiore et al., 2008). Effective treatments have been shown to work by reducing cravings or negative affect, but these mechanisms only account for a small proportion of treatments' effects on relapse (Lerman et al., 2002; McCarthy et al., 2008; Piper et al., 2008; Piasecki, 2006). Thus, it is important for researchers to identify other potential factors that not only convey relapse risk but also can be modified by effective treatment.

One possible relapse risk factor that has been posited but rarely studied is cessation fatigue. Cessation fatigue, defined as tiredness of trying to quit smoking, may be an important construct in understanding the relapse process (Piasecki et al., 2002). At the beginning of a quit attempt, individuals may be enthusiastic about quitting; however, motivation may diminish over time in the presence of stressors, strong urges to smoke, and the extra effort required to cope with negative affect by means other than smoking. Cessation fatigue, manifested by decreases in self-efficacy and exhaustion of self-control resources, mounts accordingly. This is consistent with the strength model of self-regulation (Muraven et al., 1998; Hagger et al., 2010; Vohs and Heatherton, 2000; Inzlicht and Schmeichel, 2012) which holds that individuals have a limited capacity for self-regulation (i.e., a limited amount of strength or energy) and that exertion of self-control diminishes capacity for subsequent self-control efforts.

Simmons et al. (2010) developed a measure to assess motivation to maintain abstinence, which taps related constructs. To the best of our knowledge, however, there are little empirical studies

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

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directly measuring cessation fatigue. Because fatigue is posited to be something that develops over time, it is important to understand the dynamic process of fatigue. Further, it is important to understand how withdrawal symptoms – specifically, craving and negative affect, which motivate smoking and require self-control resources to prevent cigarette use, are related to fatigue during the course of a quit attempt. Understanding these dynamics is critical to understanding the relapse process and developing new interventions to address specific relapse risk factors. For instance, it could be that smokers can cope with craving for only a few days, but then their self-control resources are exhausted and their fatigue reaches a level that prevents them from inhibiting their desire to smoke. If this were true, then interventions could be developed to help increase self-control capacity, similar to training for a marathon (Muraven et al., 1998).

Previous research has shown that relapse rates differ by treatment (e.g., combined pharmacotherapy; Fiore et al., 2008; Smith et al., 2009; Stead et al., 2008). If cessation treatments work by suppressing craving and negative affect (Bolt et al., 2012), thereby reducing fatigue, then we would expect that participants who received the most effective treatments would show less overall cessation fatigue. Further, the relation between craving/negative affect and fatigue should be attenuated among smokers receiving treatment relative to these relations in a placebo treatment group.

Gender also influences relapse risk. Research has shown that women are less likely to be successful quitters in the long term and are particularly responsive to specific medications (Piper et al., 2010; Shiffman et al., 2005; Smith et al., 2003). However, the underlying mechanisms of women's increased relapse risk and treatment response are unclear. Therefore, it is important to understand whether there are gender differences in fatigue that might account for the gender differences in relapse.

In the current study, we explore the dynamic process of cessation fatigue using ecological momentary assessment (EMA) data (Shiffman et al., 2008; Shiffman, 2009). We first examine its general dynamics during a quit attempt and its relation to cessation, hypothesizing that fatigue will increase over time and be positively associated with relapse (H1); second, we analyze its time-varying relations to other relapse risk factors – craving and negative affect, testing the hypothesis that craving and negative affect will be positively associated with fatigue, with the strength of association increasing during the quit attempt (H2). This research will also examine the effects of treatment and gender on the dynamic process of cessation fatigue, addressing the hypotheses that participants who received active pharmacotherapy will report less overall fatigue relative to those who received placebo (H3); and women will report more fatigue relative to men and combined pharmacotherapy will be especially helpful in attenuating fatigue among women (H4).

We addressed these questions using multilevel modeling (MLM; Raudenbush and Bryk, 2002; Schwartz and Stone, 1998; Walls and Schafer, 2006) and a relatively new analytical approach, the time-varying effect model (TVEM; Hastie and Tibshirani, 1993). MLM is a well-established parametric approach that is used to model longitudinal data. TVEM, by contrast, is a nonparametric modeling technique that may provide new insight in the same data context. In previous work (Shiyko et al., 2012; Selya et al., 2012), TVEM was employed to examine the dynamic associations between smoking urges and negative affect during a quit attempt. This study extends the application of TVEM to more complex models to incorporate interactions between time-varying effects of key predictors, and to the important but less studied outcome of cessation fatigue.

2. Methods

2.1. Participants

We used data from a randomized, placebo-controlled clinical trial ($N = 1504$) of five active smoking-cessation pharmacotherapies, in which daily smokers who were highly motivated to quit were recruited (Piper et al., 2009). The study was registered in http://clinicaltrials.gov/with the identification number NCT00332644.

In our analysis, we removed the subjects with zero observations for the outcome or the key covariates ($n = 373$) and those who failed to establish initial abstinence (i.e., quit for at least 24 h in the first 7 days after the target quit date, $n = 127$). We used only the observations before full relapse (i.e., 7 consecutive days of smoking). Ultimately, data from 1004 subjects were analyzed; 102 received placebo, 522 received monotherapy (nicotine patch, nicotine lozenge or bupropion) and 380 received combined pharmacotherapy (nicotine patch + nicotine lozenge or nicotine bupropion + nicotine lozenge). On average, participants provided 27.1 observations ($SD = 11.8$), contributing to 27,173 EMA occasions in all. The resulting sample was 59% female and 87% White with the average age of 45.5 years ($SD = 10.8$), reporting a baseline mean of 21.1 cigarettes per day ($SD = 8.8$) and a mean of 26.9 years smoked ($SD = 11.2$). No baseline characteristic differences were found across the three treatment groups due to randomization of the experiment.

2.2. Measures

Prior to quitting, participants answered questions about gender, ethnicity, age, marital status, education level, employment and smoking history features. Tobacco dependence was assessed with one item from the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991): "How soon after you wake up do you smoke?" This item has strong predictive validity (Baker et al., 2007).

Participants also provided intensive longitudinal data; they responded to four EMA prompts per day (morning, night, and 2 random times) for two weeks post-quit. These EMAs assessed the number of cigarettes smoked since last prompt and how participants felt within the last 15 min in terms of withdrawal symptoms (e.g., negative affect, Watson et al., 1998, craving) and cessation fatigue. The withdrawal symptoms were assessed using 11 items from the Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999), such as feeling tense or anxious, feeling sad or depressed, being bothered by the desire to smoke a cigarette, and having difficulty thinking clearly, but with an eleven-point response scale to increase response variability (see McCarthy et al., 2008). Negative affect is a combination of six items from the Positive and Negative Affect Scale (PANAS; Watson et al., 1998): tense or anxious, impatient, bothered by negative moods, irritable or easily angered, sad or depressed, and hopeless or discouraged. Cessation fatigue was also measured by an eleven-point response scale to the single item recording the feeling that "I am tired of trying to quit smoking", with scale 0 as disagree most and scale 10 as agree most.

2.3. Statistical analysis

For Hypothesis 1, we used both the parametric approach, MLM, and the nonparametric approach, TVEM, to delineate the temporal trajectory of cessation fatigue. A generalized MLM was used to examine the relation between fatigue and cessation outcome. Both MLM and TVEM can be used to depict time-varying trends and relations. MLM typically exerts functional forms (i.e., linear, quadratic) on the outcome over time and does not allow for effects of covariates, even time-varying ones, to change with time. In contrast, TVEM is able to capture temporal changes over time because the only restriction it imposes is that change over time in the coefficient curves (intercept and effects of covariates) is smooth (Hoover et al., 1998; Li et al., 2006).

For Hypothesis 2, we explored the dynamic association between fatigue, craving, and negative affect using TVEMs, where the model coefficients were estimated non-parametrically and model selection procedures were used to determine model complexity (Shiyko et al., 2012; Tan et al., 2012). We first fit a TVEM with cessation fatigue as the outcome and craving and negative affect as the predictors (see Model 1). We also controlled for baseline dependence (i.e., FTND) and episodes of smoking at each time (LAPSE; 0 = no lapse, 1 = lapse).

$$\text{Model 1}: \text{FATIG}_{ij} = \beta_0(t_{ij}) + \beta_1(t_{ij})\,\text{CRAV}_{ij} + \beta_2(t_{ij})\text{NA}_{ij} + \beta_3\text{FTND}_i + \beta_4\,\text{LASPE}_{ij} + \varepsilon_{ij}.$$

In Model 1, FATIG_{ij}, CRAV_{ij} and NA_{ij} are intensively measured longitudinal variables for subject i measured at time t_{ij}. All continuous predictors were standardized. Thus, the intercept $\beta_0(t_{ij})$ represents the mean value of FATIG_{ij} at time t_{ij} for a typical person with the average level on all continuous predictors and no lapse. Similarly, the slopes $\beta_1(t_{ij})$ and $\beta_2(t_{ij})$ represent the strength and direction of the relation between craving and fatigue, and between negative affect and fatigue, respectively, at time t_{ij} after adjusting for other covariates in the model. The fact that β_0, β_1 and β_2 are time-specific makes the model fundamentally distinct from MLM. Interpretation of the intercept and the slope coefficients requires plotting the estimated values against time, along with the corresponding confidence intervals to determine whether the lines differ from 0 or from other curves. The random errors ε_{ij} are assumed to be continuous with mean zero.