HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Drug Alcohol Depend. 2017 November 01; 180: 215–222. doi:10.1016/j.drugalcdep.2017.07.037.

Evaluating the Effect of Smoking Cessation Treatment on a Complex Dynamical System

Korkut Bekiroglu,
Department of Electrical Engineering and The Methodology Center, The Pennsylvania State University

Michael A. Russell,
The Methodology Center, The Pennsylvania State Univerity

Constantino M. Lagoa,
Department of Electrical Engineering and The Methodology Center, The Pennsylvania State University

Stephanie T. Lanza, and
Department of Biobehavioral Health and The Methodology Center, The Pennsylvania State University

Megan E. Piper
Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health

Abstract

Objective—To understand the dynamic relations among tobacco withdrawal symptoms to inform the development of effective smoking cessation treatments. Dynamical system models from control engineering are introduced and utilized to evaluate complex treatment effects. We demonstrate how dynamical models can be used to examine how distinct withdrawal-related processes are related over time and how treatment influences these relations.

Method—Intensive longitudinal data from a randomized placebo-controlled smoking cessation trial (N=1504) are used to estimate a dynamical model of withdrawal-related processes including momentary craving, negative affect, quitting self-efficacy, and cessation fatigue for each of six treatment conditions (nicotine patch, nicotine lozenge, bupropion, patch + lozenge, bupropion + lozenge, and placebo).

Results—Estimation and simulation results show that (1) withdrawal measurements are interrelated over time, (2) nicotine patch + nicotine lozenge showed reduced cessation fatigue and enhanced self-efficacy in the long-term while bupropion + nicotine lozenge was more effective at reducing negative affect and craving, and (3) although nicotine patch + nicotine lozenge had a better initial effect on cessation fatigue and self-efficacy, nicotine lozenge had a stronger effect on negative affect and nicotine patch had a stronger impact on craving.

Correspondence concerning this article should be addressed to Michael Russell, The Methodology Center, The Pennsylvania State Univerity, University Park, PA, 16802. mar60@psu.edu.

Conclusions—This approach can be used to provide new evidence illustrating (a) the total impact of treatment conditions (via steady state values) and (b) the total initial impact (via rate of initial change values) on smoking-related outcomes for separate treatment conditions, noting that the conditions that produce the largest change may be different than the conditions that produce the fastest change.

Keywords

dynamical modeling for smoking cessation study; dynamical systems models; smoking cessation treatment; intensive longitudinal data; withdrawal

2. Introduction

Cigarette smoking and other forms of tobacco use remain one of the leading causes of illness and preventable death (United States Department of Health and Human Services et al., 2014). Despite these negative health consequences, many continue to smoke. This is due, in large part to tobacco dependence, which produces aversive withdrawal symptoms when dependent smokers abstain. Withdrawal symptoms include increased nicotine craving and negative affect (irritability, sadness, worry) and motivate smokers to return to smoking (Hughes and Hatsukami, 2007; Welsch et al., 1999). These symptoms may also decrease a smokers' self-efficacy (belief that he or she can successfully quit) and increase cessation fatigue or tiredness of trying to quit smoking (Liu et al., 2013; Piper, 2015). Successful medical and behavioral interventions have been shown to work, in part, by reducing craving, negative affect, and cessation fatigue (Lerman et al., 2002; McCarthy et al., 2008; Piper et al., 2008), suggesting these withdrawal symptoms are promising targets for interventions aimed at helping smokers quit. However, withdrawal symptoms tend to be analyzed as a unified syndrome or in isolation, when in fact, all may be interrelated in a dynamic system that changes throughout the duration of the quit attempt (Piper, 2015; Piper et al., 2016). Further, withdrawal-related cognitive processes such as self-efficacy and cessation fatigue and their relations with withdrawal symptoms have not been well studied (Piper, 2015). A better understanding of these dynamics may provide insight into the constructs of dependence and withdrawal and inform the development of more effective smoking interventions.

The dynamics of smoking cessation, including features such as withdrawal, cessation fatigue, and self-efficacy, have been studied previously (Lagoa et al., 2014; Lanza et al., 2013; Liu et al., 2013; Piper, 2015), yet precise descriptions of the complex processes underlying withdrawal dynamics are still limited. The recent shift toward collecting intensive longitudinal data (ILD) via ecological momentary assessment (EMA) presents new opportunities to use tools from control engineering, such as dynamical systems models. These tools allow researchers to efficiently characterize dynamic phenomena pertinent to social, public health, and behavioral health problems (Ashour et al., 2016; Boker, 2012; Boker and Graham, 1998; Lagoa et al., 2014; Rivera et al., 2007; Timms et al., 2014).

Linear dynamical system models are commonly used in the engineering field, and are typical tools for characterizing the relations among two or more constructs. The dynamical model

describes not only how these constructs change over time in response to each other, but also how these constructs change in response to their previous values. In research with physical systems, this is typically done using differential equations (Ogunnaike and Ray, 1994). As has been shown in previous research (Boker, 2012; Chow et al., 2005), dynamical systems models can be applied to study change in social and psychological systems as well, such as the process by which smokers cease their use of cigarettes. Although dynamical systems models share a number of features with multilevel modeling (MLM), a popular method for studying change processes in the behavioral sciences, as well as with time-series analysis, dynamical systems models offer a unique perspective on the analysis of such data.

For example, dynamical systems models permit modeling of multiple constructs that constitute the smoking cessation process as an interrelated system; that is, interrelations among these variables can be estimated simultaneously, in real time. This is traditionally not done in a multilevel modeling framework, which is typically used to model relationships between two constructs, forcing the analyst to choose one as the outcome and one as the predictor. Therefore, instead of analyzing single outcomes, such as craving (Lanza et al., 2013) or cessation fatigue (Liu et al., 2013) as a function of other variables (e.g., negative affect, self-efficacy), dynamical models allow a more comprehensive analysis of the dynamic relations among all key constructs (e.g., negative affect, craving, self-efficacy, cessation fatigue), which may facilitate more accurate long-term predictions of cessation success. This is important because cessation fatigue, negative affect, nicotine craving, and self-efficacy are highly related to each other and together influence the success of a smoking cessation attempt (Baker et al., 2004; Lanza et al., 2013; Liu et al., 2013; Shadel and Cervone, 2006; Shiffman et al., 1997). Moreover, the model does not assume that these processes will change at the same rate. Additionally, dynamical systems approaches readily allow the analyst to characterize change processes in terms of system dynamics, facilitating an understanding of dynamic descriptors such as the *steady state*, which describes where (and when) a particular change process will come to rest, and the *rate of initial change*, which describes the onset and speed of a change process in the early moments of, for example, smoking cessation. With a better understanding of these parameters, we may be able to manipulate the dynamics of smoking cessation through a carefully designed intervention aimed at cessation success. In other words, understanding of the interrelations of these key cessation process variables over time could provide insight that could be used to tailor or adapt treatment, including the use of just-in-time interventions (Nahum-Shani, S., Smith, S. N., Tewari, A., Witkiewitz, K., Collins, L. M., Spring, B., & Murphy, 2014). Lastly, dynamical models can accommodate the effects of exogenous events or “shocks”, both measured and unmeasured, that may interrupt or alter the observed change process.

2.1. The Current Study

The current study applies a dynamical systems approach to understanding the interrelations among craving, negative affect, self-efficacy, and cessation fatigue in a sample of smokers participating in a smoking cessation trial. Ecological momentary assessment (EMA) was used to measure these process variables intensively over time. Results of the dynamic systems model are briefly divided into two sections.

1. The first section characterizes the interrelations among withdrawal symptoms and withdrawal-related cognitive factors over time during a quit attempt, showing how each dynamically influences the others from moment to moment.
2. The second section demonstrates how dynamical system models can be used to evaluate smoking cessation treatments by using the model results to
    a. Estimate the treatment effect on each outcome to analyze the total treatment effect on long term,
    b. Determine the expected speed of initial change to analyze the total treatment effect on short term.

In this study, we show that the treatment might have different impact on different measurements and these impacts differ in short term and long term. Further, linear relations among multiple aspects of smoking cessation dynamics can be explicitly described using these models. For example, researchers can interpret the expected effects of increasing negative affect on craving. Understanding the interrelations among features of smoking dynamics is important for developing new and efficient treatment methods to treat smoking behavior in time and in context (Lagoa et al., 2014; Timms et al., 2013).

3. Methods

3.1. Study and Participants

The EMA data analyzed in this study are derived from a randomized, placebo-controlled clinical trial (N=1504; 42% male; 17% Black(Piper et al., 2009). All study participants smoked more than 10 cigarettes per day for six months and were motivated to quit smoking (≥8 on a 1–10 scale where 10 is highly motivated to quit). Study participants received six smoking cessation counseling sessions and were randomly assigned to one of the six following treatment groups: [1] bupropion (n=264), [2] nicotine lozenge (n=260), [3] nicotine patch (n=262), [4] nicotine patch + nicotine lozenge (n=267), [5] bupropion + nicotine lozenge (n=262), and [6] placebo (n=189). To explore potentially complex effects of pharmacotherapy, we estimated the dynamical model separately for each treatment group.

Participants carried palmtop devices to respond to EMA prompts four times per day (wake-up, 2 random prompts, before bed) for the one week before and two weeks after the target quit day (TQD). Data from the two weeks after the TQD is used to identify the dynamical model. To ensure sufficient density of data to estimate the model, participants were included in our models if they provided data at three or more assessments per day, and none of these reports could be spaced farther than 12 hours. Thus, 1100 participants were included in the analyses: 197 in the bupropion group, 185 in the nicotine lozenge group, 191 in the nicotine patch group, 206 in the nicotine patch + nicotine lozenge group, 193 in the bupropion + nicotine lozenge group, and 128 in the placebo group. To assess the potential for differential attrition, we compared included versus excluded individuals on key characteristics including age, sex, and number of cigarettes smoked per day. In each of the groups, we found little evidence for differences in these characteristics.

3.2. Measures

The dynamical model for each treatment group included *cessation fatigue*, *negative affect*, *craving,* and *self-efficacy* as the outcomes (referred to as "states" in the engineering literature), each measured intensively over the 2 weeks post-TQD. *Negative affect* was calculated as the mean of six items from the Wisconsin Smoking Withdrawal Scale (WSWS Welsch et al., 1999; *tense or anxious*, *impatient*, *bothered by negative moods*, *irritable or easily angered, sad or depressed,* and *hopeless or discouraged*), that were assessed on an 11-point response scale. *Self-efficacy* was assessed with a single item on an 11-point response scale (*I am confident that I could go without smoking for 24 hours*). *Craving* was calculated as the mean of two items (*bothered by desire to smoke* and *urge to smoke;* Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996; Welsch et al., 1999) on an 11-point response scale. Finally, *cessation fatigue* was assessed with a single item, "*I am tired of trying to quit smoking*" with an 11-point response scale where 11 indicates the strongest level of fatigue.

3.3. Model Specification

To specify the model, we first defined how the variables and their respective associations fit within a dynamical model. To understand the complex relations at time t among cessation fatigue ($fatig(t)$), negative affect ($na(t)$), craving ($crav(t)$), and self-efficacy ($se(t)$), we estimated the dynamical models represented by Equations (1), (2), (3), and (4) for each treatment group. In the models, each of the four continuous outcomes at time t depend linearly on both the constant term (e.g., a_0) and the value of the outcome as well as all other predictors at the two prior assessments (i.e., at times $t-1$ and $t-2$). We also included a $w^p(t)$, an outcome-specific disturbance measure to model exogenous, unobserved disturbances. This $w^p(t)$ term captures sudden shifts in the outcome values for participant p that are not explained by other variables in the model and are not captured by the ε error term. These shifts might be driven by unobserved events having an effect on the outcomes, such as death of a close family member or dismissal from work (Bekiroglu et al., 2016; Lagoa et al., 2014). They may also be unobserved infrequent momentary events that may affect cessation fatigue, negative affect, craving, and self-efficacy respectively, at that moment (e.g., stressful events, health problems; see Supplemental Material for more information). Finally, we included an outcome-specific residual or error term. Therefore, four continuous dependent quantities cessation fatigue, negative affect, craving, and self-efficacy ($fat(t)$, $na(t)$, $crav(t)$, $se(t)$) were evaluated at each time t for each participant. The dynamical model is defined as:

$$\begin{aligned} fatig(t) &= a_0 + a_1 fatig(t-1) + a_2 fatig(t-2) + b_1 na(t-1) + b_2 na(t-2) \\ &+ c_1 crav(t-1) + c_2 crav(t-2) + d_1 se(t-1) + d_2 \mathrm{se}(t-2) + w^p_{fatig}(t) + \varepsilon_{fatig}(t) \end{aligned} \quad (1)$$

$$\begin{aligned} na(t) &= e_0 + e_1 fatig(t-1) + e_2 fatig(t-2) + f_1 na(t-1) + f_2 na(t-2) \\ &+ g_1 crav(t-1) + g_2 crav(t-2) + h_1 se(t-1) + h_2 se(t-2) + w^p_{na}(t) + \varepsilon_{na}(t) \end{aligned} \quad (2)$$

$$crav(t) = j_0 + j_1 fatig(t-1) + j_2 fatig(t-2) + k_1 na(t-1) + k_2 na(t-2) + l_1 crav(t-1) + l_2 crav(t-2) + m_1 se(t-1) + m_2 se(t-2) + w^p_{crav}(t) + \varepsilon_{crav}(t) \quad (3)$$

$$se(t) = r_0 + r_1 fatig(t-1) + r_2 fatig(t-2) + s_1 na(t-1) + s_2 na(t-2) + v_1 crav(t-1) + v_2 crav(t-2) + y_1 se(t-1) + y_2 se(t-2) + w^p_{se}(t) + \varepsilon_{se}(t) \quad (4)$$

where
$variance\left(\varepsilon_{fatig}(t)\right) = \sigma^2_{fatig}, variance\left(\varepsilon_{na}(t)\right) = \sigma^2_{na}, variance\left(\varepsilon_{crav}(t)\right) = \sigma^2_{crav}, variance\left(\varepsilon_{se}(t)\right) = \sigma^2_{se}$
for $t=1,2,\ldots,T$ and $\{\varepsilon_{fatig}(1), \varepsilon_{na}(1), \varepsilon_{crav}(1), \varepsilon_{se}(1), \varepsilon_{fatig}(2), \varepsilon_{na}(2), \varepsilon_{crav}(2), \varepsilon_{se}(2), \ldots, \varepsilon_{fatig}(T), \varepsilon_{na}(T), \varepsilon_{crav}(T), \varepsilon_{se}(T)\}$ with residual terms distributed with a mean of zero and variance equal to σ^2.

As part of model estimation, we identified the coefficients of the dynamical models (see Supplemental Material for identification algorithm), the variance of the residuals σ_{fatig}, σ_{na}, σ_{crav} and σ_{se}, and the structure of the exogenous disturbances w_{fatig}, w_{na}, w_{crav} and w_{se} in Equations (1), (2), (3), and (4) for each treatment group. The full set of parameters from a dynamical model contains several important pieces of information about the system. Just like in regression, we can use these dynamic model parameters to generate predicted values at current – as well as future – time points. For example, these models can generate predictions for future values – i.e., those beyond the observed data – of cessation fatigue, negative affect, craving, and self-efficacy. By estimating in this way, we can learn how well treatment conditions may be expected to perform in the long term. These estimated values can also provide information regarding how quickly participants may respond, on average, to a particular treatment in terms of cessation fatigue, negative affect, craving, and self-efficacy. That is, if model-predicted values decrease rapidly for one treatment condition but more slowly for another, we can conclude that the first treatment condition will affect our outcome more quickly. Finally, the structure of exogenous disturbances contains important information about how the system is affected by unobserved events that impact one or more outcome. The Supplemental Material describes the specific method used to simultaneously estimate the coefficients of the dynamical model in Equations (1), (2), (3), and (4) for each treatment group. Confidence intervals for dynamical model parameters were calculated using sandwich error estimation to adjust for the clustering of observations within individuals (Dziak and Li, 2006), allowing comparison of the coefficients across treatment conditions (see Supplemental Material).

3.4. Using the Dynamic Model Parameters to Estimate Treatment Outcomes

As discussed above, once we have developed the dynamic model and identified the coefficients, variance, and disturbance structure, we can use those values to predict future outcomes. First consider Equation (1) at time $t + 2$ in place of t. In this case, fatigue at time $t + 2$ is a function of fatigue at times $t + 1$ and t, negative affect at times $t + 1$ and t, craving at

times $t + 1$ and t, and self-efficacy at times $t + 1$ and t. Next consider Equations (1), (2), (3) and (4), but with time $t + 3$. If we substitute $fatig(t + 2)$, $na(t + 2)$, $crav(t + 2)$ and $se(t + 2)$ with their respective values from the previous step, it can be seen that fatigue at time $t + 3$ is actually a function of fatigue at times $t + 1$ and t, negative affect at times $t + 1$ and t, craving at times $t + 1$ and t, and self-efficacy at times $t + 1$ and t. Note that the values of each measurement is calculated based on its own equation. For instance while calculating the fatigue at time $fat(t + 3)$ in equation (1), the values $na(t + 2)$ is calculated from equation (2), $crav(t + 2)$ is calculated from equation (3), and $se(t + 2)$ is calculated from equation (4). Thus, the values at each of the time points are iteratively updated using information from the previous two time points. Finally craving at future $t + n$ time point can be calculated by using initial values that are fatigue at times $t + 1$ and t, negative affect at times $t + 1$ and t, craving at times $t + 1$ and t, and self-efficacy at times $t + 1$ and t. *In this way, we can estimate future values of cessation fatigue, negative affect, craving and self-efficacy using initial values*.

One important measure that can come from these estimates is the *steady state* or equilibrium of each of outcome. The *steady state* is achieved when the construct becomes unchanging in time; in other words, when the rate of change – expressed as the first derivative of the predicted values – becomes zero. In this context, we interpret the steady state as the total impact on an outcome (e.g., craving, negative affect) that each treatment condition can expect to achieve. For example, if the model suggested an initial value of 6 and a steady state of 3.5 for negative affect in the Patch group, this would suggest that Patch is expected to reduce negative affect by a maximum of 2.5 units over time. According to the steady state values of outcomes over time, one can clearly compare the performance of the treatment groups.

4. Results

4.1. Using the dynamical systems model to characterize the nicotine withdrawal process

The complete set of estimated model coefficients with their confidence intervals for each treatment group appears in Table 1. Note that the majority of estimated coefficients do not include 0 in their 95% confidence intervals, therefore the majority of these relationships are statistically significant. Furthermore model fit statistics for each outcome by treatment group are also given in supplemental material document for completeness. The estimated model for each treatment group describes the dynamic interrelations among cessation fatigue, negative affect, craving, and self-efficacy. Furthermore, since the current values are represented as a function of past values, the coefficients of past measurements are decreasing as the time lag increases, which is a common phenomenon in longitudinal research. For instance, in predicting fatigue at time t, the coefficients of $fatig(t - 1)$ in Table 1 is always larger than the coefficients of $fatig(t - 2)$ for all treatment groups; in the Bupropion group, the effect of fatigue at t – 1 = 0.511 and t – 2 = 0.392.

4.2. Using the model estimates to characterize short-term and estimate long-term treatment effects

Once the parameters of the dynamical system were estimated, we used this information to estimate future values of cessation fatigue, negative affect, craving, and self-efficacy. We assumed participants in each group had the same initial value of cessation fatigue (2.99), negative affect (1.886), craving (4.881), and self-efficacy (4.083). These values were calculated by taking the mean of participants' individual values across groups on the TQD (day 1). We simulated the long-term (60 days) outcomes for each group using these initial values and the model estimates. The time trajectories for each treatment group are given in Table 2; the numbers reflect how a typical participant is expected to respond to each treatment over time. For each outcome, little change occurred between days 40 and 60. Thus, estimates at day 60 were assumed to be steady state values, as change had essentially stopped by this time.

By Day 60, the Patch + Lozenge group had the lowest cessation fatigue and highest self-efficacy (2.039 and 8.283, respectively), whereas the Bupropion + Lozenge group had the lowest negative affect and craving levels (1.105 and 3.467, respectively), as indicated in bold in Table 2. According to the estimated values of each outcome at Day 60, one can conclude which treatment has the strongest impact on each outcome in the long-term.

Moreover, the model does not assume that all constructs follow the same change process. For instance, the Bupropion group shows that cessation fatigue initially increases, hits its peak value of 3.200 at day 7, and then begins a steady decrease to its predicted minimum value of 2.805.

Lastly, the trajectories (shown in Table 2) enable us to determine the *rate of initial change*, or how quickly participants respond to each treatment. We estimated the rate of initial change to show the outcome at day 7 as a proportion of the outcome at day 60. Note that a 7-day cutoff was chosen to capture change in the first week and was somewhat arbitrary; other values could also have been chosen from Table 2 to calculate the rate of initial change. Equation 5 defines this measure.

$$Rate\ of\ Initial\ Change = \frac{Outcome\ at\ day\ 60 - Outcome\ at\ day\ 7}{Outcome\ at\ day\ 60 - Outcome\ at\ day\ 1} \quad (5)$$

This information tells us how the treatments affect the outcomes at the beginning of the study (see Table 3) according to its final value. Note that if the outcome at day 7 is close to its outcome at day 60, this rate will be zero, and the majority of change will have happened during the first week. Therefore smaller rates show faster treatment responses. For instance, on Day 7, while Patch had the largest decrease in cessation fatigue (0.67) and craving (0.54), Lozenge produced in the largest decrease in negative affect (0.15), and Patch + Lozenge had in the largest increase in self-efficacy (0.37). Note that while some of the treatment groups corresponded to stronger treatment effects in the long-term, these same treatment groups did not necessarily show the largest effects at the beginning of the treatment.

5. Discussion

This study used dynamical systems modeling, a tool from engineering, to understand the dynamic relations of cessation fatigue, negative affect, nicotine craving, and self-efficacy during a smoking cessation attempt and the effect of treatment on these outcomes and their relations over time. The dynamical systems model offers a unique approach to characterizing the dynamics of smoking cessation. A major strength of these models is that they allow simultaneous modeling of multiple interconnected constructs that together, as a system, describe the smoking cessation process. From the model predictions, we can derive parameters that may be informative for clinical practice, such as the steady state and the rate of initial change, which illustrate the maximum effect we might expect from a particular treatment, as well as the speed at which therapeutic change may be seen, respectively. Additionally, our dynamical systems approach allows the modeling of unobserved momentary events (or “shocks”) and allows the impact of these events on the smoking cessation process to be determined.

The results of our dynamic systems modeling approach have important implications for our understanding of smoking cessation processes and potential treatment parameters. Model-implied steady states informed us that the largest treatment effects on cessation fatigue and self-efficacy were predicted for the nicotine patch + nicotine lozenge group since this group has minimum cessation fatigue and maximum self-efficacy with respect to other groups (see Table 2). However, it was the bupropion + nicotine lozenge treatment that produced the smallest negative affect and nicotine craving reports, although the steady state of self-efficacy of this group are close to the nicotine patch + nicotine lozenge group. These findings are consistent with other analyses of these data in that it shows that combined treatments have better results (Lanza et al., 2013), however, the current results provide additional information by showing *which* of the combined treatments may be most effective in the long term. There is also some evidence in the literature that combined treatment (bupropion+ nicotine lozenge and nicotine patch + nicotine lozenge) and nicotine patch treatment are efficacious at the end of the treatment (Piper et al., 2009), which can be seen in Table 2 since the Patch results are close to those for the combined treatment. Different than the previous results, prosed method allows to distinguish the treatment effects of each treatment on each measurement. However, there are now conflicting data showing that combined treatment may not better than the patch alone (Baker et al., 2016) suggesting that research findings in this area are inconsistent and require further study. Understanding these treatment mechanisms might help guide treatment selection. For instance, a smoker who wants to minimize negative affect may choose to use bupropion + nicotine lozenge.

The model-implied rate of initial change provided estimates of how fast participants in each group would achieve treatment impact (see Tables 2 and 3 for outcome values over time). Model predictions show that patch + lozenge treatment produces the fastest increase in self-efficacy and Patch treatment produces the fastest reduction in cessation fatigue and nicotine craving. Clinicians can integrate the results on steady state values (long-term effects) and treatment response speed (short-term effects) to select optimal treatments. For instance, by combining these two results, one can conclude that patch has a better initial effect on craving after quit day (this gives the highest decrease rate 0.54), but in the long term bupropion+

nicotine lozenge achieves a lower steady state for craving. Therefore, if a smoker is really worried about craving symptoms at the start of the quit attempt, the nicotine patch may be a better treatment choice than the combination of bupropion + lozenge. Another example is that although the nicotine lozenge treatment reduces negative affect faster than the others, the negative affect value at Day 60 for the bupropion + lozenge group is much lower. This would suggest that smokers who have trouble with sustained negative affect might be better off combining nicotine lozenge and bupropion, rather than using lozenge alone. Understanding treatment response speed is an important piece of information not only for smoking cessation but also for other behavioral or medical problems. Ultimately, dynamical models contain a large amount of information about complex systems which can be used to understand the effects of treatments on underlying dynamics that unfold a smoking quit attempt.

This study has limitations. First, we were limited to two weeks of EMA data after quit day in which to model the system dynamics. To make predictions beyond this two-week window, which allows us to estimate the maximum expected treatment effect and time to achieve it, we have to assume that the process continues similarly after the two weeks. Future validation using data with longer periods of observation is an important are for future research. With longer data sequences, the accuracy of the model in terms of dynamic relations might be increased and we might achieve a better understanding of the relationships between the measurements. Second, this research did not examine the dynamics of varenicline, one of the two FDA-approved non-nicotine pharmacotherapies for smoking cessation recommended by the 2008 Public Health Service Guideline (Fiore et al., 2008). Third, in contrast to data from physical systems (for which dynamic systems models were designed), data from human subjects often has a high level of noise and is more likely to be sampled non-uniformly across time. Algorithms for these models typically assume evenly sampled quantities and few missing measurements (Bekiroglu et al., 2015, 2014). There is no known algorithm in the literature that handles non-uniformly sampled data and missing measurements simultaneously, making it an important area of future research. To address this concern in this study, if the lag between two consecutive data points was long, we eliminated these non-uniformly sampled data. Third, the precise model structure of a specific behavior is not known. Therefore in order to use noisy EMA data efficiently, in this study, a plausible dynamical model with the unique effects of uncertainties (w, ε) in Equations (1), (2), (3), and (4) was chosen to provide good "*coverage*" of all admissible behaviors and, we believe, contains the main dynamics of smoking. Fourth, modeling these unique uncertainties, although it may capture the effects of sudden and transient "shocks" to the dynamic system (i.e. conflict, stressors, etc), it does not capture the effect of relapse, which would exert a sustained effect on the system dynamics given that it is not a "one-off" event. However, in previous analyses of this sample, similar results are achieved even after post-quit smoking was taken into account (Bolt, Piper, Theobald, & Baker, 2012; Piper et al., 2011), giving us confidence in the veracity of our results.

5.1. Potential Implementations of Dynamical Models

In this study, dynamic modeling is used to gain a better understanding of smoking cessation dynamics. With intensive longitudinal data becoming increasingly available, dynamical

modeling procedures similar to the one demonstrated here can be used to better understanding complex behavioral processes. For instance, by utilizing this type of dynamical model, we show that one can predict the change to trajectories of withdrawal during cessation for the first month, which is when most relapse occurs (Kenford et al., 1994; Timms et al., 2013).

Dynamical modeling of behavioral problems is an effective engineering tool to inform the development of personalized adaptive interventions (Bekiroglu et al., 2013; Lagoa et al., 2014). Adaptive treatments are the series of treatment which adapt and re-adapt to participant behavior changes in real time in order to improve the overall treatment effect (Bekiroglu et al., 2013; Dong et al., 2012; Lagoa et al., 2014; Rivera, D. E., Pew, M. D., Collins, L. M., & Murphy, 2005). This research illustrates that dynamical models are able to predict not only future success, but the rate at which symptoms will be reduced, making it a multifaceted index of treatment response.

Although we focus on the dynamical modeling of smoking cessation to understand the relations of cessation fatigue, negative affect, nicotine craving, and self-efficacy, and the treatment effect on these outcomes, future studies can examine other measurements such as physical conditions, socioeconomic status, gender, etc. For instance, dynamical models can be used not only for smoking cessation but also for many other health problems such as weight lost (Dong et al., 2012; Navarro-Barrientos et al., 2011), physical activity avoidance (Hekler et al., 2013), and fibromyalgia (Deshpande et al., 2014).

5.2. Conclusion

The use of this dynamical modeling method provides us with a nuanced understanding of the smoking cessation dynamics and effects of treatments. Additionally, due to the use of EMA and dynamical models, the results in this paper showed that the dynamic relations of cessation fatigue, negative affect, nicotine craving, and self-efficacy contains several pieces of crucial information for evaluating treatment effect and for analyzing how outcomes are associated with each other. Further, modeling the effect of exogenous disturbances is an important component of such models of human behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ILD	intensive longitudinal data
EMA	ecological momentary assessment

References

Ashour, M., Bekiroglu, K., Yang, CH., Lagoa, C., Conroy, D., Smyth, J., Lanza, S. On the mathematical modeling of the effect of treatment on human physical activity; 2016 IEEE Conference on Control Applications (CCA); 2016. p. 1084-1091.

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol. Rev. 2004; 111:33–51. DOI: 10.1037/0033-295X.111.1.33 [PubMed: 14756584]

Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. Jama. 2016; 315:371–9. DOI: 10.1001/jama.2015.19284 [PubMed: 26813210]

Bekiroglu K, Lagoa C, Murphy SA, Lanza ST. Control Engineering Methods for the Design of Robust Behavioral Treatments. IEEE Trans. Control Syst. Technol. 2016; :1–12. DOI: 10.1109/TCST.2016.2580661

Bekiroglu, K., Lagoa, C., Murphy, SA., Lanza, ST. 52nd IEEE Conference on Decision and Control. IEEE; 2013. A robust MPC approach to the design of behavioural treatments; p. 3505-3510.

Bekiroglu, K., Lagoa, C., Sznaier, M. 2015 54th IEEE Conference on Decision and Control (CDC). IEEE; 2015. Low-order model identification of MIMO systems from noisy and incomplete data; p. 4029-4034.

Bekiroglu, K., Yilmaz, B., Lagoa, C., Sznaier, M. 2014 European Control Conference (ECC). IEEE; 2014. Parsimonious model identification via atomic norm minimization; p. 2392-2397.

Boker, SM. Dynamical systems and differential equation models of change. In: Cooper, H.Camic, PM.Long, DL.Panter, AT.Rindskopf, D., Sher, KJ., editors. APA Handbook of Research Methods in Psychology, Vol 3: Data Analysis and Research Publication. APA; 2012. p. 323-333.

Boker SM, Graham J. A Dynamical Systems Analysis of Adolescent Substance Abuse. Multivariate Behav. Res. 1998; 33:479–507. DOI: 10.1207/s15327906mbr3304_3 [PubMed: 26753826]

Chow S-M, Ram N, Boker SM, Fujita F, Clore G. Emotion as a Thermostat: Representing Emotion Regulation Using a Damped Oscillator Model. Emotion. 2005; 5:208–225. DOI: 10.1037/1528-3542.5.2.208 [PubMed: 15982086]

Deshpande S, Rivera DE, Younger JW, Nandola NN. A control systems engineering approach for adaptive behavioral interventions: illustration with a fibromyalgia intervention. Transl. Behav. Med. 2014; 4:275–89. DOI: 10.1007/s13142-014-0282-z [PubMed: 25264467]

Dong, Y., Rivera, DE., Thomas, DM., Navarro-Barrientos, JE., Downs, DS., Savage, JS., Collins, LM. American Control Conferencemerican Control Conference (ACC). IEEE; 2012. A dynamical systems model for improving gestational weight gain behavioral interventions; p. 4059-4064.

Dziak J, Li R. Variable Selection with Penalized Generalized Estimating Equations. Methodol. Cent. Pa. State Univ. 2006

Hekler EB, Buman MP, Poothakandiyil N, Rivera DE, Dzierzewski JM, Aiken Morgan A, McCrae CS, Roberts BL, Marsiske M, Giacobbi PR, Morgan AA, McCrae CS, Roberts BL, Marsiske M, Giacobbi PR. Exploring Behavioral Markers of Long-Term Physical Activity Maintenance: A Case Study of System Identification Modeling Within a Behavioral Intervention. Heal. Educ. Behav. 2013; 40:51S–62S. DOI: 10.1177/1090198113496787

Hughes, JR., Hatsukami, DK. Instructions for use of the Minnesota Withdrawal Scale-Revised. 2007. Retrieved from www/uvm.edu/~hbpl

Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. JAMA. 1994; 271:589–94. [PubMed: 8301790]

Kozlowski LT, Pillitteri JL, Sweeney CT, Whitfield KE, Graham JW. Asking Questions About Urges or Cravings for Cigarettes. Psychol. Addict. Behav. 1996; 10:248–260. DOI: 10.1037/0893-164X.10.4.248

Lagoa CM, Bekiroglu K, Lanza ST, Murphy SA. Designing adaptive intensive interventions using methods from engineering. J. Consult. Clin. Psychol. 2014; 82:868–78. DOI: 10.1037/a0037736 [PubMed: 25244394]

Lanza ST, Vasilenko SA, Liu X, Li R, Piper ME. Advancing the Understanding of Craving During Smoking Cessation Attempts: A Demonstration of the Time-Varying Effect Model. Nicotine Tob. Res. 2013; 16:S127–S134. DOI: 10.1093/ntr/ntt128 [PubMed: 23975881]

Lerman C, Roth D, Kaufmann V, Audrain J, Hawk L, Liu A, Niaura R, Epstein L. Mediating mechanisms for the impact of bupropion in smoking cessation treatment. Drug Alcohol Depend. 2002; 67:219–223. DOI: 10.1016/S0376-8716(02)00067-4 [PubMed: 12095672]

Liu X, Li R, Lanza ST, Vasilenko SA, Piper M. Understanding the role of cessation fatigue in the smoking cessation process. Drug Alcohol Depend. 2013; 133:548–555. DOI: 10.1016/j.drugalcdep.2013.07.025 [PubMed: 23954071]

McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Baker TB. Psychological mediators of bupropion sustained-release treatment for smoking cessation. Addiction. 2008; 103:1521–33. DOI: 10.1111/j.1360-0443.2008.02275.x [PubMed: 18783504]

Nahum-Shani S, Smith SN, Tewari A, Witkiewitz K, Collins LM, Spring B, Murphy SA. Just-in-Time Adaptive Interventions (JITAIs): An Organizing Framework for Ongoing Health Behavior Support. 2014

Navarro-Barrientos J-E, Rivera DE, Collins LM. A dynamical model for describing behavioural interventions for weight loss and body composition change. Math. Comput. Model. Dyn. Syst. 2011; 17:183–203. DOI: 10.1080/13873954.2010.520409 [PubMed: 21673826]

Ogunnaike, BA., Ray, WH. Process dynamics, modeling, and control. Oxford University Press; 1994.

Piper ME. Withdrawal: Expanding a Key Addiction Construct. Nicotine Tob. Res. 2015; 17:1405–15. DOI: 10.1093/ntr/ntv048 [PubMed: 25744958]

Piper ME, Federmen EB, McCarthy DE, Bolt DM, Smith SS, Fiore MC, Baker TB. Using mediational models to explore the nature of tobacco motivation and tobacco treatment effects. J. Abnorm. Psychol. 2008; 117:94–105. DOI: 10.1037/0021-843X.117.1.94 [PubMed: 18266488]

Piper ME, Smith SS, Schlam TR, Fiore MC, Jorenby DE, Fraser D, Baker TB. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch. Gen. Psychiatry. 2009; 66:1253–62. DOI: 10.1001/archgenpsychiatry.2009.142 [PubMed: 19884613]

Piper ME, Vasilenko SA, Cook JW, Lanza ST. What a Difference a Day Makes: Differences in Initial Abstinence Response During a Smoking Cessation Attempt. Addiction. 2016; doi: 10.1111/add.13613

Rivera DE, Pew MD, Collins LM, Murphy SA. Engineering control approaches for the design and analysis of adaptive, time-varying interventions. 2005 doi:Technical Report 05–73.

Rivera DE, Pew MD, Collins LM. Using engineering control principles to inform the design of adaptive interventions: a conceptual introduction. Drug Alcohol Depend. 2007; 88(Suppl 2):S31–40. DOI: 10.1016/j.drugalcdep.2006.10.020 [PubMed: 17169503]

Shadel WG, Cervone D. Evaluating social-cognitive mechanisms that regulate self-efficacy in response to provocative smoking cues: an experimental investigation. Psychol. Addict. Behav. 2006; 20:91–6. DOI: 10.1037/0893-164X.20.1.91 [PubMed: 16536671]

Shiffman S, Engberg JB, Paty JA, Perz WG, Gnys M, Kassel JD, Hickcox M. A day at a time: predicting smoking lapse from daily urge. J. Abnorm. Psychol. 1997; 106:104–16. [PubMed: 9103722]

Timms KP, Rivera DE, Collins LM, Piper ME. A dynamical systems approach to understand self-regulation in smoking cessation behavior change. Nicotine {&} Tob. Res. 2014; 16:159–168. DOI: 10.1093/ntr/ntt149

Timms, KP., Rivera, DE., Collins, LM., Piper, ME. Control Systems Engineering for Understanding and Optimizing Smoking Cessation Interventions; Proc. Am. Control Conf; 2013. p. 1964-1969.

Warren GW, Alberg AJ, Kraft AS, Cummings KM. United States Department of Health and Human Services. The 2014 Surgeon General's report: "The Health Consequences of Smoking–50 Years of Progress": A paradigm shift in cancer care. Cancer. 2014; 120:1914–1916. DOI: 10.1002/cncr.28695 [PubMed: 24687615]

Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. Exp. Clin. Psychopharmacol. 1999; 7:354–61. [PubMed: 10609970]

Table 1

Parameter Estimates from Dynamical Systems Model for Each Treatment Group

	Bupropion			Lozenge			Patch			Patch+ Lozenge			Bupropion+ Lozenge			Placebo		
Results for Equation (1): Predictors of Cessation Fatigue																		
	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$
Constant	.353	.305	.257	.246	.230	.214	.333	.303	.272	.253	.225	.196	.323	.302	.281	.289	.258	.227
***fatig*(*t* − 1)**	.512	.511	.511	.521	.520	.519	.522	.521	.520	.491	.490	.489	.488	.487	.487	.544	.540	.536
***fatig*(*t* − 2)**	.393	.392	.391	.386	.385	.384	.382	.381	.380	.400	.399	.399	.405	.405	.404	.374	.372	.370
***na*(*t* − 1)**	.041	.040	.039	.022	.021	.019	.011	.009	.007	.046	.046	.045	.017	.016	.015	.011	.008	.006
***na*(*t* − 2)**	−.003	−.004	−.005	.005	.003	.002	.007	.006	.004	−.014	−.015	−.016	.017	.016	.015	.025	.023	.020
***crav*(*t* − 1)**	−.003	−.003	−.004	−.013	−.013	−.013	.007	.006	.006	.008	.008	.008	.001	.000	.000	.012	.011	.010
***crav*(*t* − 2)**	.011	.011	.011	.018	.018	.018	−.011	−.011	−.011	.006	.006	.006	−.002	−.003	−.003	−.009	−.010	−.010
***se*(*t* − 1)**	−.016	−.017	−.017	.003	.002	.002	−.002	−.003	−.004	.006	.006	.005	−.001	−.002	−.003	−.021	−.026	−.030
***se*(*t* − 2)**	.002	.001	.001	−.006	−.007	−.007	−.007	−.007	−.008	−.016	−.017	−.017	−.008	−.009	−.010	.017	.013	.010
Results for Equation (2)*: Predictors of Negative*																		
Constant	.371	.354	.337	.143	.125	.134	.245	.228	.211	.213	.199	.185	.418	.398	.379	.733	.228	−.277
***fatig*(*t* − 1)**	−.012	−.012	−.012	.018	.017	.018	.005	.005	.005	.028	.028	.028	−.007	−.007	−.007	.015	.008	.001
***fatig*(*t* − 2)**	.048	.048	.048	.000	−.001	.000	.016	.016	.015	.005	.005	.004	.017	.017	.017	.007	.007	.006
***na*(*t* − 1)**	.476	.475	.475	.489	.487	.488	.434	.433	.431	.387	.386	.385	.462	.461	.460	.454	.391	.327
***na*(*t* − 2)**	.255	.254	.253	.291	.289	.290	.315	.314	.313	.318	.317	.315	.326	.325	.324	.503	.296	.089
***crav*(*t* − 1)**	.021	.020	.020	.006	.006	.006	.022	.022	.022	.019	.019	.018	.007	.007	.007	.043	.021	.000
***crav*(*t* − 2)**	.001	.001	.000	.006	.006	.006	−.002	−.002	−.002	.007	.007	.007	.006	.005	.005	.132	.028	−.077
***se*(*t* − 1)**	−.022	−.022	−.022	−.024	−.024	−.024	−.014	−.014	−.014	−.001	−.001 −	.001	−.021	−.021	−.022	.155	.021	−.113
***se*(*t* − 2)**	.001	.001	.001	.027	.027	.027	.007	.006	.006	.000	.000	.000	−.006	−.006	−.006	.062	−.028	−.117
Results for Equation (3)*: Predictors of Craving*																		
Constant	1.519	1.448	1.376	1.578	1.515	1.451	1.458	1.366	1.274	1.438	1.354	1.27	1.661	1.583	1.504	1.349	1.185	1.021
***fatig*(*t* − 1)**	−.001	−.002	−.003	.017	.016	.016	.023	.022	.021	.045	.044	.042	.001	.000	.000	.036	.033	.030
***fatig*(*t* − 2)**	.034	.033	.032	.009	.009	.008	−.004	−.005	−.006	.005	.004	.003	.016	.016	.016	−.014	−.017	−.019

Drug Alcohol Depend. Author manuscript; available in PMC 2018 November 01.

	Bupropion			Lozenge			Patch			Patch+ Lozenge			Bupropion+ Lozenge			Placebo		
Results for Equation (1): Predictors of Cessation Fatigue																		
	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$	$\hat{\beta}_+$	$\hat{\beta}$	$\hat{\beta}_-$
***na*(*t* − 1)**	.076	.074	.073	.133	.130	.127	−.017	−.020	−.023	−.019	.022	−.026	.037	.034	.032	.042	.037	.031
***na*(*t* − 2)**	−.012	−.014	−.016	−.029	−.033	−.036	.056	.053	.050	.082	.080	.077	.036	.034	.031	.020	.016	.012
***crav*(*t* − 1)**	.429	.428	.427	.404	.403	.402	.433	.432	.432	.447	.446	.446	.410	.409	.408	.441	.439	.436
***crav*(*t* − 2)**	.317	.316	.316	.295	.294	.293	.304	.303	.302	.308	.307	.305	.329	.328	.327	.349	.347	.346
***se*(*t* − 1)**	−.018	−.020	−.021	−.088	−.090	−.091	−.087	−.088	−.089	−.033	−.034	−.035	−.031	−.032	−.034	−.067	−.068	−.070
***se*(*t* − 2)**	−.046	−.047	−.049	.029	.028	.027	.031	.030	.029	−.032	.033	−.035	−.061	−.062	−.063	.018	.016	.015
Results for Equation (4)*: Predictors of Self-Efficacy*																		
Constant	.969	.901	.833	.842	.799	.756	.928	.867	.805	1.036	.995	.953	1.171	1.117	1.064	1.488	.866	.244
***fatig*(*t* − 1)**	.000	−.001	−.001	.005	.004	.004	−.002	−.003	−.003	−.013	−.013	−.013	.019	.018	.018	−.006	−.016	−.026
***fatig*(*t* − 2)**	−.006	−.006	−.007	−.005	−.005	−.006	−.005	−.005	−.005	.011	.010	.010	−.020	−.021	−.021	.029	.013	−.003
***na*(*t* − 1)**	.007	.006	.006	−.013	−.014	−.015	.007	.005	.004	.007	.006	.005	.000	−.001	−.002	.002	−.042	−.085
***na*(*t* − 2)**	.003	.002	.001	.023	.022	.021	−.006	−.007	−.009	.012	.012	.011	−.003	−.004	−.005	.070	.034	−.002
***crav*(*t* − 1)**	−.017	−.018	−.018	−.006	−.006	−.006	−.019	−.019	−.019	−.005	.005	−.006	−.019	−.019	−.019	−.028	−.034	−.040
***crav*(*t* − 2)**	−.006	−.007	−.007	−.007	−.007	−.007	.008	.008	.007	−.005	.005	−.005	−.009	−.009	−.009	.014	.007	.001
***se*(*t* − 1)**	.548	.547	.546	.553	.552	.551	.519	.518	.516	.554	.553	.551	.545	.544	.543	.489	.483	.477
***se*(*t* − 2)**	.352	.351	.350	.351	.351	.350	.383	.382	.381	.331	.330	.329	.335	.334	.333	.418	.416	.414
Standard Errors of Noise from Disturbance Terms																		
σ_{fatig}		1.35			1.41			1.4			1.36			1.31			1.29	
σ_{na}		1.41			1.46			1.47			1.44			1.36			1.38	
σ_{crav}		1.41			1.49			1.47			1.41			1.38			1.34	
σ_{se}		1.34			1.4			1.4			1.35			1.31			1.3	

Note: $\hat{\beta}_+$ and $\hat{\beta}_-$ represent the upper and lower 95% confidence limits for $\hat{\beta}$, respectively

Table 2

Predicted Values Across 60 Days for Each Treatment Group

Cessation Fatigue											**Difference from Placebo at Day 60**
Beginning Of Day	**1.**	**2.**	**3.**	**5.**	**7.**	**10.**	**20.**	**30.**	**40.**	**60**	
Bupropion	2.990	3.049	3.104	3.174	3.200	3.186	3.015	2.891	2.835	2.805	0.334
Lozenge	2.990	2.986	2.974	2.932	2.880	2.804	2.634	2.569	2.546	2.537	0.066
Patch	2.990	2.963	2.923	2.834	2.745	2.626	2.380	2.287	2.255	2.243	−0.228
Patch+ Lozenge	2.990	2.965	2.927	2.830	2.723	2.569	2.223	2.093	2.053	**2.039**	**−0.432**
Bupropion+ Lozenge	2.990	2.974	2.947	2.875	2.791	2.668	2.381	2.266	2.229	2.215	−0.256
Placebo	2.990	3.000	2.996	2.968	2.924	2.850	2.644	2.538	2.494	2.471	0
Negative Affect											
Bupropion	1.886	1.854	1.814	1.753	1.703	1.638	1.501	1.445	1.425	1.415	0.053
Lozenge	1.886	1.725	1.554	1.346	1.245	1.180	1.139	1.132	1.130	1.129	−0.233
Patch	1.886	1.766	1.643	1.477	1.379	1.293	1.18	1.149	1.140	1.137	−0.225
Patch+ Lozenge	1.886	1.744	1.624	1.489	1.419	1.355	1.248	1.214	1.204	1.201	−0.161
Bupropion+ Lozenge	1.886	1.858	1.809	1.696	1.583	1.440	1.194	1.127	1.111	**1.105**	**−0.257**
Placebo	1.886	1.780	1.698	1.607	1.558	1.509	1.414	1.379	1.367	1.362	0
Craving											
Bupropion	4.881	5.012	5.099	5.106	5.013	4.842	4.483	4.361	4.321	4.304	0.005
Lozenge	4.881	4.924	4.874	4.710	4.545	4.356	4.090	4.025	4.008	4.003	−0.296
Patch	4.881	4.831	4.729	4.519	4.337	4.128	3.809	3.725	3.702	3.695	−0.604
Patch+ Lozenge	4.881	5.002	5.060	4.968	4.778	4.503	4.038	3.923	3.895	3.887	−0.412
Bupropion+ Lozenge	4.881	4.971	4.990	4.832	4.586	4.242	3.663	3.515	3.479	**3.467**	**−0.832**
Placebo	4.881	4.957	4.988	4.963	4.882	4.745	4.448	4.345	4.312	4.299	0
Self-Efficacy											
Bupropion	4.083	4.441	4.863	5.563	6.082	6.625	7.419	7.632	7.693	7.718	0.475

Cessation Fatigue												Difference from Placebo at Day 60
Lozenge	4.083	4.433	4.856	5.565	6.097	6.658	7.461	7.658	7.707	7.722	0.479	
Patch	4.083	4.457	4.896	5.649	6.222	6.831	7.719	7.945	8.003	8.023	0.78	
Patch+ Lozenge	4.083	4.574	5.153	6.077	6.724	7.353	8.114	8.251	8.277	**8.283**	**1.04**	
Bupropion+ Lozenge	4.083	4.549	5.092	5.962	6.581	7.201	8.03	8.219	8.264	8.277	1.034	
Placebo	4.083	4.382	4.721	5.300	5.742	6.217	6.947	7.156	7.218	7.243	0	

Table 3

Rate of Initial Change in Day 7, Corresponding to Speed of Initial Change, by Treatment Group[1]

	Bupropion	Lozenge	Patch	Patch+ Lozenge	Bupropion+ Lozenge	Placebo
Cessation Fatiue	2.14	0.76	**0.67**	0.72	0.74	0.87
Negative Affect	0.61	**0.15**	0.32	0.32	0.61	0.37
Craving	1.23	0.62	**0.54**	0.9	0.79	1
Self-Efficacy	0.45	0.45	0.46	**0.37**	0.4	0.48

[1]Smaller rates show faster treatment responses.