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Effects of Sequential Fluoxetine and Gender on Pre-quit Depressive Symptoms, Affect, Craving, and Quit Day Abstinence in Smokers with Elevated Depressive Symptoms: A Growth Curve Modeling Approach

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Abstract

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While the important roles of post-quit affect and withdrawal symptoms in the process of smoking cessation have been well established, little is known about the relations between pre-quit affective trajectories and cessation outcome on the target quit date (TQD). This study examined whether a 16-week course of fluoxetine initiated 8 weeks pre-quit ("sequential" fluoxetine) improved TQD abstinence relative to placebo through its effects on pre-quit depressive symptoms, affect (withdrawal-relevant negative affect, general negative affect, and positive affect), and craving to smoke among 206 smokers with elevated depressed symptoms. The moderating effects of gender were also examined. A total of 83 smokers (40%) failed to achieve abstinence on TQD, with no difference between treatment conditions or gender. Overall structural equation models showed that fluoxetine had significant indirect effects on TQD abstinence through changes in pre-quit withdrawal-relevant negative affect and craving, but not depressive symptoms. However, multigroup analyses revealed gender differences. Sequential fluoxetine reduced pre-quit depressive symptoms, withdrawal-relevant negative affect, and craving only among women. Reduction in pre-quit depressive symptoms and craving among women, and withdrawal-relevant negative affect among men was associated with TQD abstinence. Moreover, exploratory analysis showed negative trend-level indirect effects of fluoxetine on TQD abstinence via increased side effects, regardless of gender. This study demonstrated the importance of considering gender when examining treatment efficacy. Identifying ways to further reduce pre-quit depressive symptoms and craving for women and withdrawal-relevant negative affect for men while alleviating side effects may help smokers with elevated depressed symptoms achieve the first smoking cessation milestone.

Keywords

smoking cessation; sequential fluoxetine; withdrawal-relevant negative affect; craving; depressive symptoms

Introduction

Quitting for 24 Hours: The First Smoking Cessation "Milestone"

Quitting smoking is a notoriously difficult task, with the most intensive treatments producing long-term (i.e., ≥ 6 months) abstinence rates of 35% or less (Fiore et al., 2008). There is increasing recognition that the process of successful long-term cessation involves progressing through a series of "milestones," including achieving an initial 24-hour period of abstinence, avoiding a lapse (one instance of smoking after achieving initial abstinence), and avoiding a full relapse to daily smoking (Shiffman et al., 2006). In a typical smoking cessation clinical trial, participants choose or are assigned by the researchers a target quit date (TQD), which is the first day that they will attempt complete abstinence. The TQD typically occurs between 1 and 4 weeks from the beginning of treatment. The period before the TQD constitutes a preparation period for quitting.

Long-term outcomes conceal the significant proportion of smokers who fail to attain even the first milestone. For example, in a recent study of 1,429 smokers, all of whom received individual counseling and either pharmacotherapy or placebo, 30% who were assigned to placebo and 8–19% who received pharmacotherapy never quit for 24 hours within two

weeks of the TQD (Japuntich, Piper, Leventhal, Bolt, & Baker, 2011). Smoking on the TQD itself, regardless of whether a 24-hour period of abstinence is eventually achieved, is highly predictive of long-term outcome (Westman, Behm, Simel, & Rose, 1997; Yeh, McCarthy, & Baker, 2012). For example, in a study of 374 smokers who participated in a factorial randomized trial (bupropion vs. placebo and counseling vs. no counseling), 35.6% smoked on the TQD, and these participants were only 27.8% as likely to be abstinent at 8 weeks post-TQD as those who abstained on the TQD (Yeh, et al., 2012).

Recent studies have revealed significant differences in the individual characteristics that predict short-term (i.e., 24-hour) vs. long-term (i.e., 1-year) abstinence (Bailey, Bryson, & Killen, 2011) and in the efficacy of various pharmacotherapies for producing initial abstinence vs. preventing lapses and relapses (Japuntich, et al., 2011). Therefore, investigation of variables that have an impact on early outcomes, such as smoking on the TQD, may provide important insights to support the development of novel, more effective treatments that target preparation period for quitting (weeks prior to TQD) to increase the likelihood of achieving initial abstinence.

Depressive Symptoms and Fluoxetine for Smoking Cessation

There is a well-established relationship between smoking and negative affect states (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Kassel, Stroud, & Paronis, 2003), including depressive symptoms (Benjet, Wagner, Borges, & Medina-Mora, 2004; C. Brown, Madden, Palenchar, & Cooper-Patrick, 2000; Finney Rutten, Wanke, & Augustson, 2005; Gulec et al., 2005; Kenney, Holahan, North, & Holahan, 2006; McCaffery, Niaura, Swan, & Carmelli, 2003). Depressive symptoms prior to a quit attempt are associated with poor smoking cessation outcomes (Blondal et al., 1999; Cook, Spring, McChargue, & Doran, 2010; Kenney, et al., 2006; Kinnunen, Korhonen, & Garvey, 2008; Leventhal, Ramsey, Brown, LaChance, & Kahler, 2008; Thorndike et al., 2008). Likewise, smokers who report relatively higher levels of post-cessation negative affect (Kenford et al., 2002) and lower levels of positive affect (Strong et al., 2009), independent of depressive symptomology, are also at increased risk of relapse.

Both behavioral and pharmacological treatment approaches have been evaluated for smokers with depressive symptoms. Behavioral approaches that combine treatment for smoking cessation and mood management have produced mixed results (Brown et al., 2001; Brown et al., 2007; Haas, Munoz, Humfleet, Reus, & Hall, 2004; MacPherson et al., 2010; Spring et al., 2007). With respect to pharmacotherapy, the antidepressants bupropion and nortriptyline have established benefits for smoking cessation in the general population of smokers, with no indication of specific benefits for smokers with depressive symptoms (Hughes, Stead, & Lancaster, 2007). The antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has also been examined in a number of randomized trials, with mixed results depending on population (general population vs. smokers with elevated depressive symptoms vs. smokers with past or current major depressive disorder [MDD]). Dosage also appears to impact efficacy (Blondal, et al., 1999; Hitsman, Spring, Borrelli, Niaura, & Papandonatos, 2001; Niaura et al., 2002; Saules et al., 2004; Spring, et al., 2007), with 60-mg daily doses associated with side effects and treatment drop-out due to adverse events

(Niaura, et al., 2002) as well as poorer long-term outcome (Spring, et al., 2007). However, in one trial in which participants were assigned to placebo or fluoxetine 30 mg or 60 mg, only fluoxetine 60 mg was associated with significant increases in positive affect and decreases in negative affect. Positive affect continued to increase over time, whereas negative affect returned to baseline by the end of fluoxetine treatment (Cook et al., 2004). In all of these trials, fluoxetine treatment and smoking cessation treatment were delivered concurrently, with fluoxetine typically initiated two weeks before the TQD.

Given that it may take up to 8 weeks for fluoxetine to take effect with regard to improvement of depressive symptoms, it is possible that the temporal sequencing of fluoxetine in relation to TQD (i.e., beginning fluoxetine only 2 weeks prior to TQD) may account for these mixed results. We examined whether beginning use of fluoxetine 8 weeks prior to TQD (which we termed “sequential” fluoxetine) at a 20-mg daily dose would yield more benefit than a “standard” fluoxetine regimen of 20 mg/day begun 2 weeks prior to TQD among smokers with elevated depressive symptoms who did not meet criteria for MDD. All participants received transdermal nicotine patch (TNP) and brief counseling. We found that sequential fluoxetine resulted in significantly higher abstinence rates than standard fluoxetine (Brown et al., 2014). However, as this study could not rule out a placebo effect of sequential fluoxetine or the effect of delaying TQD, we are currently conducting a randomized, double-blind placebo-controlled trial of sequential fluoxetine among adult smokers with elevated depressive symptoms. This trial has finished enrollment and all participants have completed treatment. We are now collecting remaining follow-up data.

The current analyses focus on an early outcome of this trial for which all data have been collected: smoking on the target quit date (TQD). Specifically, we investigated whether the use of sequential fluoxetine (vs. sequential placebo) increased the likelihood of achieving abstinence on TQD through its effects on changes in depressive symptoms, affect (i.e., withdrawal-relevant negative affect, general negative affect, and general positive affect), and craving to smoke during the pre-quit period. While relationships between fluoxetine and post-cessation depressive symptoms, positive affect and negative affect have been studied (Cook, et al., 2004; Spring, et al., 2007), the effects of fluoxetine on pre-quit changes in affect and craving have not been examined. We hypothesized that 1) sequential fluoxetine (vs. placebo) would increase the likelihood of abstinence on TQD, 2) sequential fluoxetine (vs. placebo) would result in improved mood (i.e., increases in positive affect and decreases in negative affect and depressive symptoms) and decreased craving to smoke over the 8 weeks prior to quit day, and 3) sequential fluoxetine treatment would increase the odds of abstinence on TQD through its effects on pre-quit depressive symptoms, affect, and craving.

Finally, we also explored whether the relationships identified above differed across gender. Extant evidence suggests that women have more difficulty quitting compared to men (Minami et al., in press; Piper et al., 2010; Scharf & Shiffman, 2004). While our prior studies showed no gender differences in treatment outcomes, including 7-day point prevalence abstinence over 6 months (Brown, et al., 2014) and time to relapse (Minami, et al., in press), earlier findings suggested that the efficacy of fluoxetine treatment for smoking cessation might differ across gender (Spring et al., 2007).

Method

Participants

Participants were 206 adult smokers who were recruited from the local community. Eligibility criteria were: 1) between 18 and 65 years of age, 2) regular cigarette smoker for at least one year, 3) currently smoking at least 10 cigarettes per day, 4) elevated depressive symptoms, as indicated by a Center for Epidemiologic Studies Depression Scale (CES-D) score > 6, and 5) no use of other tobacco products. Exclusion criteria were: 1) current MDD or other Axis I disorder, 2) psychoactive substance abuse or dependence (excluding nicotine dependence) within the past year, 3) current use of psychotropic medication, 4) use of antidepressant medication within the past 6 months, 5) active suicidal ideation in the past month, 6) a history of significant medical illness, such as cardiovascular, neurological, gastrointestinal, or other systemic illness, pregnancy or breastfeeding, and 7) current use of any pharmacotherapy for smoking cessation. The study was approved by the Butler Hospital Institutional Review Board and all participants gave voluntary written informed consent.

Procedure

Interested individuals were initially screened by phone to assess the inclusion and exclusion criteria. Those who appeared to be eligible were invited to attend a more comprehensive baseline assessment, during which they provided consent and completed a diagnostic interview and a physical exam with the study physician to confirm eligibility. Eligible participants were then randomly assigned to fluoxetine 20 mg/day or placebo using urn randomization to balance the groups on gender, depressive symptoms (CES-D ≥16), and nicotine dependence (FTND ≥ 7). Figure 1 describes screening and enrollment. Medication assignment was double-blind, such that neither participants nor study staff (including physicians, research assistants, and counselors) were aware of whether the participant was taking fluoxetine or placebo. In both conditions, participants were instructed to take one capsule each morning, beginning 8 weeks prior to their quit date and continuing for 8 weeks after quit date for a total of 16 weeks. Participants were monitored by the study physician at the following intervals to ensure safe discontinuation of fluoxetine: prior to beginning medication, 4 weeks after initiating medication, and 8 weeks after quit date (end of medication treatment).

Brief Counseling and Transdermal Nicotine Patch (TNP)

All participants in both conditions received brief individual smoking cessation counseling that was consistent with the current Clinical Practice Guideline for Treating Tobacco Use and Dependence (Fiore, et al., 2008). Counseling consisted of five 20–30 minute sessions over a 4-week period: the day before the TQD, the day after the TQD, and 7-, 14-, and 28-days post-TQD. All sessions were in person with the exception of the second session, which was conducted by phone. All participants also received an 8-week supply of a 24-hour TNP (Nicoderm CQ®). They were instructed to begin using TNP on the TQD and to apply 1 patch daily thereafter. Participants used the 21-mg patch for 4 weeks, tapered to the 14-mg patch for the next 2 weeks, and to the 7-mg patch for the remaining 2 weeks. Smokers who lapsed during treatment were encouraged to set a new quit date and continue to attempt to

quit. No instructions or advice on behavioral change, except the medication instruction, was provided prior to the first counseling session.

Measures

All pre-quit assessments were conducted in-person, while smoking status on TQD was conducted via telephone (see below).

Smoking status on TQD—The timeline followback procedure was used to assess daily cigarette use. The timeline followback is a valid and reliable calendar-aided method of assessing daily cigarette use (Brown et al., 1998). No assessment occurred on the TQD itself, but participants reported whether they smoked on the TQD over the phone on the day after the TQD or a later visit using the timeline followback procedure. The smoking status on TQD relied on self-report without expired carbon monoxide (CO) verification given that the first in-person assessment post-TQD was 7 days after the TQD. A total of 9 participants (4.4%) who did not provide timeline followback data post-quit were coded as smoking. Of those 9 participants, 3 (vs. 6) were in the fluoxetine condition: no statistically significant difference in the rates of missingness across conditions was found ($p = .32$).

Nicotine Dependence—The Fagerström Test for Nicotine Dependence [FTND; (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991)] was administered at baseline and used as a continuous measure of nicotine dependence.

Depressive Symptoms—Depressive symptoms during the past week were assessed at baseline (8-weeks pre-quit), 4 weeks and 1 day before TQD with the 20-item CES-D (score range 0–60 with higher scores indicating higher depressive symptoms), which has demonstrated good reliability and validity (Radloff, 1977).

Affect and Craving—Affect and craving were assessed at baseline (8-weeks pre-quit) and at 6-weeks, 4-weeks, 2-weeks, and 1 day before TQD. General positive and negative affect were assessed with the 20-item *Positive and Negative Affect Scale* (PANAS), which consists of 10 positive affect adjectives and 10 negative affect adjectives that are rated on 5-point scales according to the participant's feelings at the present moment (Watson, Clark, & Tellegen, 1988). Total scores range from 10–50 with higher scores indicating greater positive and negative affect. Negative affect specifically associated with nicotine withdrawal (i.e., *withdrawal-relevant negative affect*) and *craving* were assessed using the *Minnesota Nicotine Withdrawal Scale* (Hughes & Hatsukami, 1986; Piasecki et al., 2000). Participants were asked to rate how they felt "today" on a 4-point scale. A mean score of three items, "Irritability, frustration, or anger," "Anxiety or Nervousness," and "Sadness or Depression" (1=None to 4=Severe), was used for *withdrawal-relevant negative affect*. Changes in withdrawal-relevant negative affect prior to a quit attempt are predictive of cessation success (McCarthy, Piasecki, Fiore, & Baker, 2006). *Craving* was a mean score of "wanting or craving a cigarette" (1=None to 4=Severe) and "How much of the time have you felt the urge to smoke today" (1=None of the time to 4=All of the time).

Side Effects—Common medication side effects were assessed, using a 4-point scale (0 = none to 4 = severe), at baseline (8-weeks pre-quit) and at 4-weeks, and 1 day before TQD. Participants were asked to rate each symptom according to how they felt today.

Data Analysis

Data Preparation

None of the variables included in the current analyses required modification due to violations of normality, independence or outliers. Missing data ranged from 0% (e.g., baseline depressive symptoms [CES-D]) to 26% (e.g., −1 day before TQD general negative affect [PANAS]). A total of 115 participants had complete data at all time-points and 91 participants had some missing data. No statistically significant differences were found for gender, treatment condition, nicotine dependence, baseline depressive symptoms, number of cigarettes smoked per day, or depression history with respect to amount of missing data (all *p*'s > .05). Where necessary, missing data were handled with a maximum likelihood procedure that uses all available data from each participant and assumes that data are missing at random. This method is among the best practices for handling missing data (Schafer & Graham, 2002).

Hypothesis Testing Overview

First, hypothesis 1 was tested using a logistic regression where abstinence on TQD was predicted by treatment condition (Figure 2: *path c*). Next, a series of structural equation models were run to test hypotheses 2 & 3. The model-building procedure began with estimating pre-quit trajectories of depressive symptoms, affect, and craving using a series of latent growth models (Figure 2: pre-treatment intercept, pre-quit slope). The latent pre-treatment intercept and slope variables were then added to the structural equation model to allow for tests of hypothesis 2 (Figure 2: *path* a_s) and hypothesis 3 (Figure 2: *path* ab_s indirect path from sequential fluoxetine to abstinence on TQD through pre-quit slope). Gender and baseline nicotine dependence (FTND) were added to the model as covariates, as they are known to predict initial levels of depressive symptoms, affect, and craving, as well as cessation failure. Only results from the final models are presented here due to manuscript length considerations (results of intermediate steps are available on request from the first author).

Specific Model Building Procedure

A latent variable framework (e.g., latent growth model, structural equation model) was used to examine relationships between treatment, individual changes (i.e., latent growth trajectories) in depressive symptoms, affect, and craving to smoke during the 8 weeks prior to quit day and abstinence rates on TQD. The growth models were used to construct latent parameters (i.e., intercept and slope) from repeated measures of each variable. Latent "intercept" variables were created to reflect the initial levels of the growth curve (i.e., levels at baseline, assessed at 8 weeks before TQD [pre-treatment]) and a latent "slope" variable was created to reflect the continuous growth trajectory (rate of change) in symptoms over the 8 weeks prior to the quit attempt. A latent variable framework allows us to examine treatment effects on the rate of change in variables of interests (e.g., affect or craving), and

to assess the associations between the latent variables and smoking outcome measures simultaneously, controlling for baseline variables known to predict abstinence. As a first step, latent linear growth models were estimated for each variable (i.e., depressive symptoms, affect, and craving) in order to determine the slope (rate and direction of change) during the pre-quit period. Next, a series of models that included indirect effects were estimated for each mediator variable to evaluate whether fluoxetine treatment had indirect effects on abstinence rates on TQD through its effect on changes in each mediator variable prior to quit date (hypotheses 2 & 3). Weighted least squares with mean- and variance-adjustment (WLSMV) estimation was used, as this permits a dichotomous outcome, and allows estimations of direct effects, as well as specific and total indirect effects. As a maximum likelihood procedure, the WLSMV estimator also accommodates missing data but under somewhat more restrictive missing data assumptions (see Asparouhov & Muthén, 2010 for details). Bias-corrected bootstrapped confidence intervals of the direct and indirect effects, which correct for bias in the central tendency, were estimated and reported (Mackinnon, Lockwood, & Williams, 2004; Preacher & Hayes, 2008).

As exploratory analyses, we also conducted multigroup analyses of the SEM models described above in order to examine whether the efficacy of sequential fluoxetine on pre-quit changes in depressive symptoms, affect, and craving differ by gender. Multigroup analyses allow for some paths to be freely estimated within each group while constraining other paths to be treated as equal across groups based on research hypotheses, theoretical expectations, or logical considerations (e.g., paths containing demographic variables not expected to differ by groups). This has the advantage of modeling variation across groups within a single model (Bou & Satorra, 2010). As in overall models, we also used bias-corrected bootstrapped confidence intervals to interpret the significance of effects in the multigroup models. Bias-corrected bootstrapped confidence intervals provide the most reliable estimates of model parameters when power is a concern (Hayes & Scharkow, 2013). In the multigroup models employed in these analyses, we allowed all paths to freely vary across gender, which resulted in an increase in degrees of freedom in the multigroup models. The increase in degrees of freedom has advantages for determining goodness of fit (MacCallum et al., (1996)

Model Fit

In the current study, overall model fit was evaluated with (a) the root mean square error of approximation (RMSEA values < 0.06), (b) the Comparative Fit Index (CFI values >.95), and (c) the Standardized Root Mean Residual (SRMR < .08) or weighted root mean square residual (WRMR values < 0.90), as recommended by Hu and Bentler (Hu & Bentler, 1999). For completeness, the likelihood ratio $\chi 2$ is also reported. All analyses were conducted with Mplus 6.12 software (L. K. Muthén & Muthén, 1998–2010).

Power Consideration

We used two sets of methods to estimate power to detect 1) improvement in model fit and 2) treatment effects of fluoxetine on pre-quit trajectories in growth curve modeling,

Model fit—Using MacCallum et al's (1996) criterion via the online power utility available on quantpsy.org (Schoemann, 2010), power to detect an improvement over a poor fitting model (RMSEA = 0.00 vs. 0.1) was estimated with our sample size of 206 with degrees of freedom for the depression model (*df* = 6), general negative affect model (*df* = 17), and withdrawal-relevant negative affect, general positive affect, and craving models (*dfs* = 23). These tests revealed that at an alpha level of 0.05, power for the respective models was 0.75, 0.98, and 0.99, suggesting that only the depression model has less than the recommended .80 rule of thumb for optimal power. In addition, the multigroup models, with greater degree of freedoms, substantially increased power to 0.92 (*df* = 11) for depressive symptoms model and over 0.99 (*dfs* = 40–42) for the multigroup models of the rest of the variables.

Treatment effects—Muthen and Curran (1997) demonstrated the estimation of power to detect treatment effects using growth curve modeling based on the Satorra-Saris method (Satorra & Saris, 1985) with simulated data, designed to represent a randomized controlled trial (intervention vs. control) with five assessment points including the first pre-treatment baseline assessment – similar to our current study design. The power estimates for latent growth curve modeling conducted by Muthen and Curran (1997) indicate that the minimum sample sizes of 525, 225, 130, and 80 were required to obtain a power of .80 to detect small to medium treatment effect sizes of *d* = .20, 30, 40, and 50 (Cohen's *d* – differences in the scores at the last assessment between treatments), respectively with a power of .80 (Curran & Muthen, 1999; B. O. Muthén & Curran, 1997). The sample size of 206 of the current study is sufficient to detect a medium effect size with a power of .80, even after a reduction in power due to missing data.

Effect Sizes

Based on Feingold's (2009) recommendation, we calculated effect sizes using a formula for growth curve modeling – [$d = (\beta$ *[average growth rate] *[time])*/ SD(raw)] (Eq.7 in Feingold, 2009; Raudenbush & Liu, 2001) – in order to estimate the magnitude of the treatment effects on pre-quit changes in each variable. Feingold (2009) argued that standard deviations of raw scores, not those of change scores, should be used to determine the potency of treatment effects, while effect sizes using standard deviations of change scores are appropriate to be used for power calculations. Here, the average growth rate (β) is multiplied by time to attain the model-estimated means at the last assessment (i.e., the day before TQD).

In order to estimate the strength of the indirect effects, we calculated the differences in the probability of abstinence on TQD between conditions through each indirect path when all other covariates are at their means. In Mplus, the probit link is used with WLSMV estimation, and any indirect effect that includes probit regressions should be interpreted as a probit regression coefficient (L. K. Muthén & Muthén, 1998–2010). Therefore, we used the following formula to estimate the predicted probability of TQD abstinence through each indirect path for each treatment condition: *P[treatment =1 or 0] = f (− "threshold" +* β*[covariates]*mean +* β*[indirect effects]*1 or 0)* (L. K. Muthén & Muthén, 1998–2010, p. 440) where *f* is the cumulative normal distribution function, βs are unstandardized coefficients for covariates predicting abstinence, "*mean*" represents the mean value of

covariate at baseline, and "*threshold*" can be interpreted as the intercept with an opposite sign.

Results

Participants

Of the 206 participants randomized to treatment, 99 were female (48%), 188 were white (91.3%) and the mean age was 43.54 years (*SD* = 11.16). At baseline, participants reported smoking 21.01 (*SD* = 9.70) cigarettes per day, had a mean FTND of 5.66 (*SD* = 2.08), and had a mean CES-D of 9.77 (*SD* = 8.31). A total of 49 (23.8%) participants reported prior episodes of MDD based on DSM- IV criteria, and 7.3% (n = 15) endorsed recurrent MDD episodes, leaving 157 without any MDD history. Figure 1 describes screening and recruitment, and Table 1 presents demographic, smoking and depressive symptom characteristics for each treatment group by gender. Treatment groups did not differ on demographic, smoking, nicotine dependence, depressive symptoms, history of MDD or baseline scores of any mediator variables overall (the last column in Table 1) or within each gender. At 4 weeks post-quit, a total of 112 (59%) participants answered a question that asked to what treatment condition they thought they were assigned. Among those who provided an answer, 68% of participants in the fluoxetine condition correctly identified their condition while 42% of those in the placebo condition thought they received fluoxetine. No significant difference in the rate of participants correctly identifying their assigned condition between treatment conditions was found ($\chi^2(1, n=112) = .975$, $p = .32$).

Sequential Fluoxetine and Failure to Quit on Quit day (*Path c*)—Of 206 participants, 40% (n = 83) failed to stay quit for the initial 24 hours after their TQD. Contrary to our hypothesis, there were no differences in abstinence rates on TQD between sequential fluoxetine (58.9%) and placebo (60.6%) (*AOR* = 1.02, *95%CI* = .57 – 1.81, *p* = .95), controlling for gender, nicotine dependence, and baseline depressive symptoms. There were also no differences in TQD abstinence rates by gender (*AOR* = 0.81 [female], *95% CI* = .46 – 1.44, *p* = .48). Moreover, a subsequent model that included a treatment by gender interaction term revealed that gender did not moderate the efficacy of fluoxetine on TQD abstinence rate (*AOR* = 0.72, *95% CI* = .23 – 2.29, *p* = .58). Controlling for treatment condition, logistic regression analyses suggested significantly lower odds of abstinence on TQD for participants with higher nicotine dependence (*AOR* = .83, *95%CI* = .72 – .96, *p* = .012) and a trend towards significance for participants with higher baseline depressive symptoms (*AOR* = .97, *95%CI* = .93 – 1.00, *p* = .058).

Structural Equation Models: Indirect Models (*Path a & b*)—Although no total effect (path *c*) of fluoxetine treatment on abstinence rates on TQD was found, we proceeded to examine whether fluoxetine had indirect effects on abstinence rates on TQD via its effects on pre-quit depressive symptoms, withdrawal-relevant negative affect, general negative and positive affect, or craving in five separate models (MacKinnon, Krull, & Lockwood, 2000; Rucker, Preacher, Tormala, & Petty, 2011). Model fit information and estimates of the pre-quit growth trajectories (i.e., slope) for each variable obtained from a series of latent growth models are presented in Table 2. The general path diagram of the indirect model is shown in

Figure 2. Gender and baseline FTND scores were included in the model as predictors of quit date abstinence, as well as the latent parameters in all overall models.

Overall Model Fit: All five SEM models had excellent model fit, with non-significant chi-square tests, RMSEAs less than .04, CFIs greater than .96, and WRMR values less than .60 (see Table 3). The overall pattern of results was similar across the five models.

Path a: Effects of Fluoxetine Treatment on Pre-quit Changes in Depressive Symptoms, Affect and Craving

Overall Models: Path *a* was significant for both the withdrawal-relevant negative affect and craving models, indicating that sequential fluoxetine treatment significantly predicted linear changes in both withdrawal-relevant negative affect and craving over 8 weeks prior to quit date (Table 3, top row of each variable section in bold). Specifically, those in the placebo condition reported significant increases in withdrawal-relevant negative affect (a_S) during a pre-quit period, while those who received sequential fluoxetine showed no pre-quit increase in withdrawal-relevant negative affect ($d = -0.45$). Similarly, those in the sequential fluoxetine condition reported significant decreases in craving to smoke during the pre-quit period (a_S), whereas those in the placebo condition showed no change in craving during the 8-week pre-quit period ($d = -0.34$). Unexpectedly, no significant differences in pre-quit changes in depressive symptoms or general negative or positive affect across treatment conditions were found. Neither gender nor nicotine dependence predicted significant changes in pre-quit slopes in any of the variables of interest (i.e., depressive symptoms, withdrawal-relevant negative affect, general negative affect, general positive affect or craving).

Gender Differences (Multigroup Models): Multigroup models revealed moderating gender effects on the relationships between treatment and pre-quit trajectory (a_S) in depressive symptoms, withdrawal-relevant negative affect, and craving (Table 4, top row of each gender within each variable section). That is, the sequential fluoxetine condition significantly predicted decline in pre-quit depressive symptoms ($d = -0.58$), withdrawal-relevant negative affect ($d = -0.70$), and craving ($d = -0.60$) among women, but not among men ($d = 0.04, -0.21, -0.08$) (Figure 3 A–C).

Paths b: Effects of Pre-quit Depressive Symptoms, Affect and Craving on TQD Abstinence on TQD

Overall Models: The baseline values (intercepts) of all variables, except depressive symptoms, predicted abstinence rates on TQD, such that smokers who reported lower withdrawal-relevant negative affect and general negative affect, higher positive affect, and higher craving at baseline were more likely to be abstinent on TQD (b_i) (Table 3, second or third row of each variable section). Moreover, pre-quit decline (negative slopes) in all variables except general positive affect predicted greater abstinence rates on TQD (b_S) (Table 3, third or fourth row of each variable section in bold). That is, those who showed declines in depressive symptoms, withdrawal-relevant negative affect, general negative affect or craving were more likely to be abstinent on TQD. Baseline levels of nicotine

dependence, but not gender, predicted abstinence on TQD in all models, such that higher nicotine dependence was associated with greater risks of smoking on TQD.

Gender Differences (Multigroup Models): Results of multigroup models revealed that the significant associations between baseline values and TQD abstinence found in the overall models were gender dependent. Higher baseline values of depressive symptoms were predictive of failure to quit on TQD only in women, while higher baseline craving levels and higher baseline positive affect were associated with TQD abstinence only in men. Moreover, pre-quit decline in depressive symptoms, craving and general negative affect predicted TQD abstinence only in women, but not in men (Table 4, second and third rows of each gender within each variable section). On the other hand, pre-quit decline in withdrawal-relevant negative affect predicted TQD abstinence only in men, but not in women.

Paths ab: Indirect Effects

Overall Models: Indirect effects were tested for the two variables (i.e., withdrawal-relevant negative affect and craving) that were found to be significantly associated with both fluoxetine treatment (path a_s) and abstinence on TQD (path b_s) for the overall models. There were significant indirect effects (i.e., a_s x b_s) of treatment condition on abstinence on TQD through pre-quit changes in both craving (*Indirect path coefficient estimate [*E_{indirect}*]=* 0.258, *Bias-corrected 95% CI* = 0.044, 0.613, $p < 0.05$) and withdrawal-relevant negative affect (E_{indirect} = 0.234, *Bias-corrected 95% CI* = 0.020, 1.029, $p < 0.05$). Sequential fluoxetine had a positive impact on TQD abstinence rates through the reduction of both withdrawal-relevant negative affect and craving over time prior to a quit attempt. In other words, fluoxetine increased the probability of TQD abstinence through reducing pre-quit craving and withdrawal-relevant negative affect by 8.7%, compared to placebo, when baseline covariates (i.e., FTND, baseline values of craving or withdrawal related negative affect) are at their means.

Gender Differences (Multigroup Models): A multigroup analysis of craving model revealed a significant indirect effect among women (E_{indirect} = 0.863, *Bias-corrected 95% CI* = 0.044, 0.613, $p < 0.01$), but not among men (E_{indirect} = 0.029, *Bias-corrected 95% CI* = −0.012, 0.795, $p > 0.10$). Sequential fluoxetine, relative to placebo, increased the probability of TQD abstinence through reducing pre-quit craving by 23.6% in women, but only by 1.1% in men. This was predictable, given that the significant a_s and b_s paths were only observed among women. For withdrawal-relevant negative affect, the significant indirect effects were not found in either women or men (E_{indirect} = 0.863, *Bias-corrected 95% CI* = 0.044, 0.613, $p < 0.01$, respectively). This was also expected from the results that the a_s path was significant only among women, while the b_s path was significant only among men. An indirect treatment effect through depressive symptoms was also tested using multigroup analysis, since pre-quit changes in depressive symptoms were significantly associated with both fluoxetine treatment (path *a*) and abstinence on TQD (path *b*) among women. Results showed a significant indirect effect of sequential fluoxetine on TQD abstinence through pre-quit depressive symptoms among women (E_{indirect} = 0.376, *Bias-corrected 95% CI* = 0.081, 1.215, $p < 0.01$), but not among men (E_{indirect} = −0.006, *Bias-corrected 95% CI* = −0.223, 0.256, $p > 0.10$), as expected. For women, sequential fluoxetine increased the probability of

abstinence on TQD by reducing depressive symptoms prior to quit date by 13.8 %, while virtually no indirect effect of fluoxetine treatment (0.2% reduction in the probability of abstinence) was observed among men.

Paths c′: Direct Effects of Fluoxetine on TQD Abstinence: The *c'* path was not significant in any of the five models. This indicates that the sequential fluoxetine treatment condition did not predict abstinence on TQD, even after controlling for its effects on pre-quit changes in depressive symptoms, withdrawal-relevant negative affect, general negative affect, general positive affect, or craving. Multigroup analyses showed no gender differences in the direct effects of sequential fluoxetine on TQD abstinence (*c′*) in any models.

Exploratory Analysis: Side Effects—Given the findings that fluoxetine had significant indirect effects on abstinence on TQD through its effects on pre-quit changes in affect and craving, we hypothesized that the lack of total effects of fluoxetine on initial abstinence (*c*) was due, at least partially, to increased side effects in the fluoxetine condition. That is, we hypothesized that side effects served as a "suppressor," which weakened the total effect of fluoxetine on quit date abstinence rates when they were not included in the model (MacKinnon, et al., 2000; Rucker, et al., 2011). We created a composite score of 12 common fluoxetine side effects (headache, nausea, dizziness, diarrhea, indigestion, increased flatulence, decreased appetite, changes in sexual functioning, difficulty sleeping, drowsiness, excessive sweating, tiredness). First, as in the other mediator variables, the latent intercept and slope were also estimated for side effect symptoms assessed at baseline, −4 weeks, and −1 day from quit day in a latent growth model. However, the model fitted the data poorly. Therefore, we proceeded to use an observed side effects variable. We used the side effect composite score assessed on the day before TQD as a potential pathway through which fluoxetine could have a negative impact on abstinence on TQD, controlling for gender and nicotine dependence. As in all other indirect models, WLSMV estimation was specified here as it accommodates missing data (Asparouhov & Muthén, 2010). Results indicated that those in the fluoxetine condition reported trend-level greater side effect symptoms on the day before quit date compared to those in the placebo condition (path *a*) ($E_{indirect}$ = 1.388, *Bias-corrected 95% CI* = −0.086, 2.713, *stdXY = 0. 150*, $p < 0.1$) and that levels of side effects significantly predicted failure to quit on TQD (path *b*) ($E_{indirect}$ = −0.074, *Bias-corrected 95% CI* = −0.114, −0.027, *stdXY = −0.333*, $p < 0.05$). We also found a trend-level negative indirect effect of fluoxetine on (i.e., decreases in) abstinence on TQD through inducing greater side effects (path *ab*) ($E_{indirect}$ = −0.103, *Bias-corrected 95% CI* = −0.263, 0.001, $p < 0.1$). A multigroup analysis of the side effects model did not show gender differences in the *a* or *b* path.

Discussion

The current study examined whether the use of sequential fluoxetine initiated 8 weeks before an attempt to quit smoking (vs. sequential placebo) increased the probability of abstinence on the target quit date (TQD) through its effects on changes in depressive symptoms, affect (i.e., withdrawal-relevant negative affect, general negative affect, and general positive affect) and craving to smoke during the pre-quit period. Results of the overall models indicated that while sequential fluoxetine did not increase abstinence rates on

TQD, it had positive indirect effects on abstinence rates on TQD through reduction in withdrawal-relevant negative affect and craving, but not depressive symptoms or general affect (negative or positive), over the 8 weeks prior to the TQD. However, multigroup analyses further revealed the moderating gender effects on these treatment effects. The significant indirect treatment effects on TQD abstinence through reduction in pre-quit craving were only true among women, but not among men. The significant indirect treatment effect through changes in withdrawal-relevant negative affect was no longer observed when the model was estimated with the multigroup analysis framework across gender. Moreover, the significant indirect effect of sequential fluoxetine on a decline in pre-quit depressive symptoms was also found in women, but not in men. While exploratory in nature, these findings deserve further consideration, especially since no baseline differences across gender or across treatment conditions within gender were found. In addition, exploratory analyses revealed that positive effects of fluoxetine might have been cancelled out, in part, by a negative effect of fluoxetine on TQD abstinence through increased experiencing of side effects.

As predicted, sequential fluoxetine treatment influenced changes in depressive symptoms, withdrawal-relevant negative affect, and craving to smoke during a pre-quit period, but only among women. The effect of sequential fluoxetine on a pre-quit decline in depressive symptoms in the overall model did not reach statistical significance. However, when the model was estimated within women and men, the significant treatment effect on depressive symptoms was found among women, but not among men. This suggests that the lack of significant treatment difference found in the overall depressive symptoms model was a result of the weak, but negative, treatment effects (i.e., association between fluoxetine and increases in pre-quit depressive symptoms) found in men countering the significant positive treatment effects found in women. Moreover, the significant effects of sequential fluoxetine on reduction in craving to smoke, compared to placebo, was only true for women, suggesting that the overall treatment effect on pre-quit craving was mainly driven by the effects observed among women. Similarly, the effect of sequential fluoxetine to lessen the steady increases in withdrawal-relevant negative affect prior to the TQD found in the placebo condition was significantly more pronounced in women, compared to men.

On the other hand, while participants receiving sequential fluoxetine treatment reported lower levels of general negative affect and higher levels of general positive affect during the pre-quit period compared to placebo, such treatment differences did not reach statistical significance. No gender difference in the treatment effects on pre-quit changes in general negative or positive affect was observed. Moreover, regardless of treatment, positive affect increased over the 8 weeks prior to quit, inconsistent with extant findings that positive affect tends to decline during a pre-quit period (Strong, et al., 2009). Strong et al (2009) did not, however, select for individuals with elevated depressive symptoms, which may have led to regression to the mean in the current study.

Furthermore, as expected, declines in depressive symptoms, withdrawal-relevant negative affect, general negative affect or craving during the pre-quit period predicted decreased risks of smoking on TQD in the overall models. Again, however, multigroup analyses revealed the gender differences in each of these models. The pre-quit declines in depressive

symptoms, general negative affect or craving were significantly predictive of TQD abstinence only among women, not among men. On the other hand, reduction in pre-quit withdrawal-relevant negative affect was associated with increased likelihood of abstinence on TQD only among men. Changes in positive affect during the pre-quit period were not associated with abstinence rates on TQD, regardless of gender. This suggests the importance of reducing depressive symptoms, craving, and general negative mood prior to a quit attempt in women, whereas pre-quit reduction in withdrawal-relevant negative affect may be more important for men to successfully initiate a quit attempt. In addition, this finding underscores the importance of distinguishing subgroups of negative affect, such as withdrawal-relevant negative affect and general negative affect, when examining the impact of treatment as well as its relationship to smoking outcomes.

Overall models showed that participants with lower withdrawal-relevant negative affect and higher craving and positive affect at baseline were more likely to achieve initial cessation success (abstinence on TQD). However, multigroup analyses by gender revealed that women, but not men, with lower baseline depressive symptoms, and men, but not women, with higher baseline craving and positive affect, were more likely to achieve abstinence on TQD. Again, it is evident that the overall models, by combining gender in one model, obscured the associations between baseline levels of affect and craving and abstinence on TQD by gender. Unexpectedly, higher levels of baseline craving to smoke predicted abstinence on TQD, especially for men. This seems inconsistent with past findings, which have showed that greater craving is associated with increased risks of cessation failure (Killen & Fortmann, 1997; McCarthy, et al., 2006; Shiffman et al., 1997). However, such associations were observed during a quit attempt, but not during the pre-quit period or ad lib smoking. There is evidence to suggest that craving is context-specific and more likely to occur when one is experiencing conflict between his/her own responses (e.g., smoking vs. not smoking) (Curtin, McCarthy, Piper, & Baker, 2006). Therefore, one's anticipation to quit while continuing to smoke may increase craving to smoke, and it is possible that participants who were most seriously considering quitting smoking at the beginning of the study experienced more craving.

Finally, given that fluoxetine treatment had significant indirect effects on abstinence on the TQD via withdrawal-relevant negative affect and craving without having a total effect (*path c*) on TQD abstinence, we conducted an exploratory analysis to test whether side effects acted as a "suppressor" (MacKinnon, et al., 2000; Rucker, et al., 2011) of the effects of fluoxetine treatment on TQD. While the side effect model did not reach statistical significance, the findings suggest a possible negative impact of fluoxetine-induced side effects on smoking abstinence on TQD. Unlike some of the variables of interest in this study, no gender difference was observed in the side effects indirect model. It is important to note that while the side effect measure in the current study included various commonly reported side effects of fluoxetine, it has not been tested for its validity or reliability. With a more sensitive measure, tailored specifically to the side effect profiles found in fluoxetine treatment, we might be able to capture more accurately the role of side effects in the cessation process when examining fluoxetine treatment and smoking outcome.

Limitations

There are several other limitations of this study. First, depressive symptoms were measured only at 3 pre-quit time points, while other affective and craving variables were assessed at 5 pre-quit time points. Although excellent model fit was indicated for all models, a greater number of assessment points would increase reliability and ability to detect patterns of change in variables of interest during the pre-quit period. Second, since no visit was required on TQD in this study, determination of smoking status on TQD relied on self-reports assessed using the timeline followback procedure. While this is certainly a limitation that warrants caution, the timeline followback has been shown to be reliable and have good convergent validity with biochemical markers of smoking (Brandon, Copeland, & Saper, 1995; Brown, et al., 1998). In addition, the current study used intent to treat sample and considered those who did not provide any data post-quit (n=9, 4.4%) as smoking on TQD. The rate of missing outcome data was low in this study and no statistically significant difference was found between conditions. However, it is possible that those who did not provide any assessments post-quit may have been qualitatively different (e.g., decided not to quit) from those who continued to participate in the study (e.g., actively trying to quit), and it may be an important distinction in the future studies. Finally, while the targeted population for this study was smokers with elevated depressive symptoms (CES-D > 6) regardless of history of MDD, the exclusion criteria for this study included current MDD. Therefore, the results may have limited generalizability to smokers with a current major depressive episode. Finally, it is important to note that the gender effects tested in this study were exploratory in nature, and not a priori hypotheses. Replication studies are needed before conclusions regarding the moderating gender effects on sequential fluoxetine on pre-quit depressive symptoms, affect, and craving can be reached.

Conclusion

Although no overall difference in TQD abstinence rates was observed between treatment conditions or gender, sequential fluoxetine, compared to placebo, significantly reduced depressive symptoms, withdrawal-relevant negative affect, and craving to smoke prior to a quit attempt, among which depressive symptoms and craving significantly predicted decreased risk of smoking on TQD only for women. At this point, the data do not suggest a strong effect of fluoxetine given that it only operates through a modest indirect effect for only women; however, this study demonstrated the importance of considering the moderating role of gender on treatment efficacy as well as the relationships between affect/craving and smoking outcome. Identifying ways to further reduce depressive symptoms and general negative affect for women and withdrawal-relevant negative affect for men, as well as to alleviate side effects of fluoxetine, may help smokers with elevated depressed symptoms achieve the first important smoking cessation milestone.

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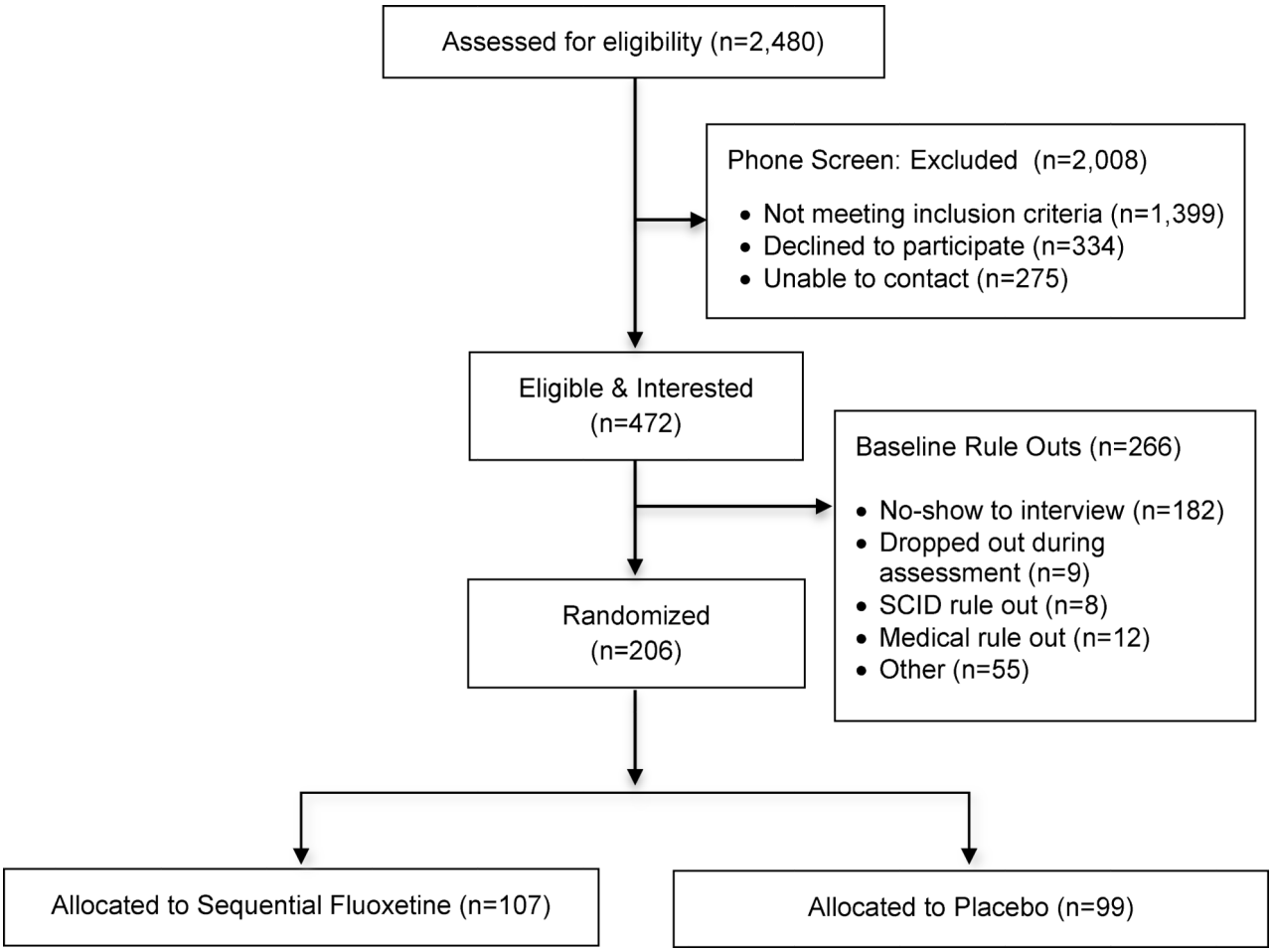

Figure 1.
CONSORT diagram for enrollment and allocation of participants for sequential fluoxetine and placebo conditions.

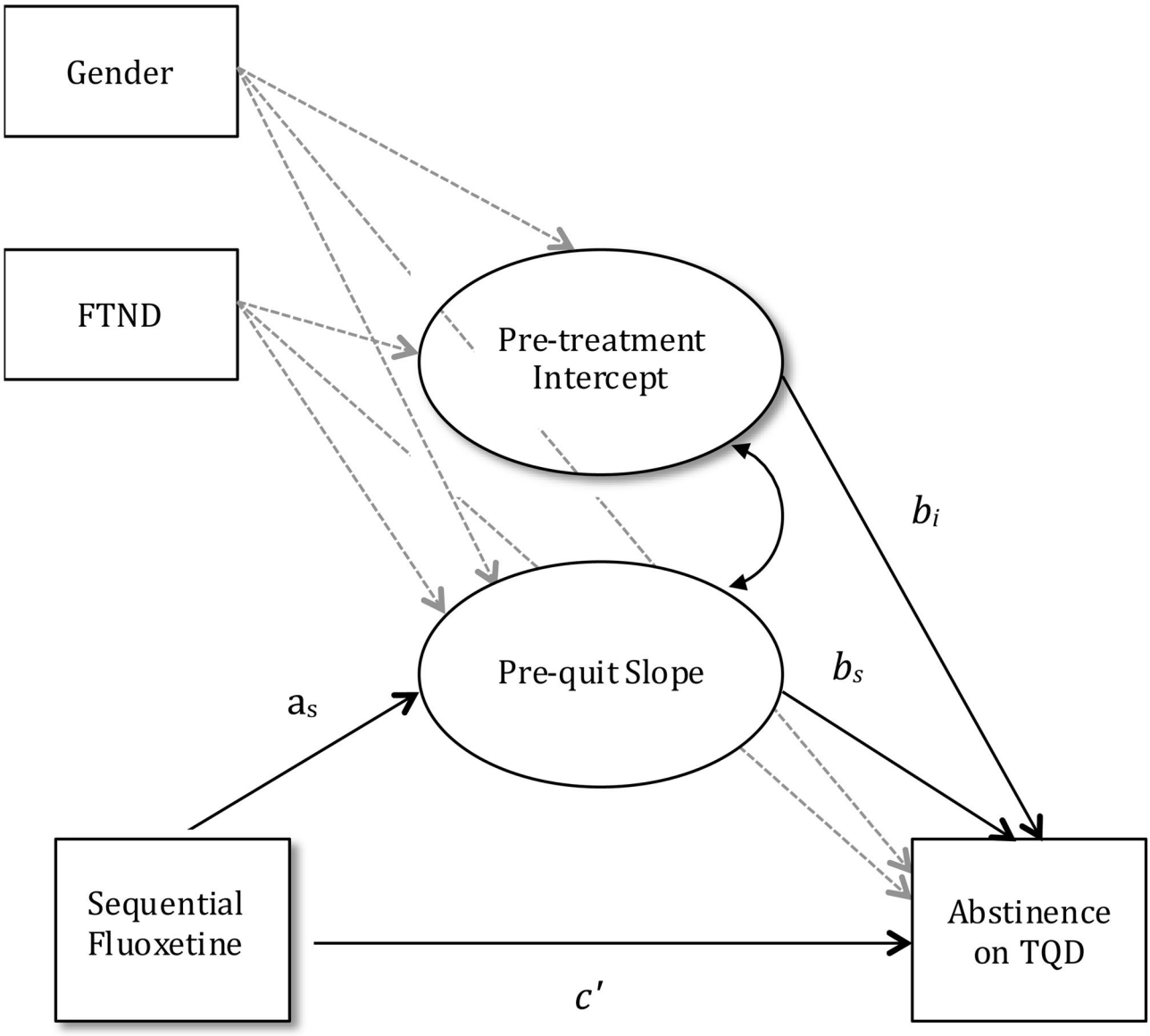

Figure 2.

General path diagram for indirect models.

The direct relationships between treatment to smoking outcome (1 = abstinent, 0 = smoking) on target quit date (TQD) are depicted in path *c'*. Path a_s represents treatment condition (1 = sequential fluoxetine, 0 = sequential placebo) predicting latent 'pre-quit slope' (changes over 8 weeks prior to quit date) variables, while paths b_i and b_s indicate the relationships between 'pre-treatment intercept' and 'pre-quit slope' and abstinence on TQD. Gender and nicotine dependence (FTND) were included as baseline covariates, predicting 'pre-treatment intercept,' 'pre-quit slope,' and abstinence on TQD (shown in dotted lines).

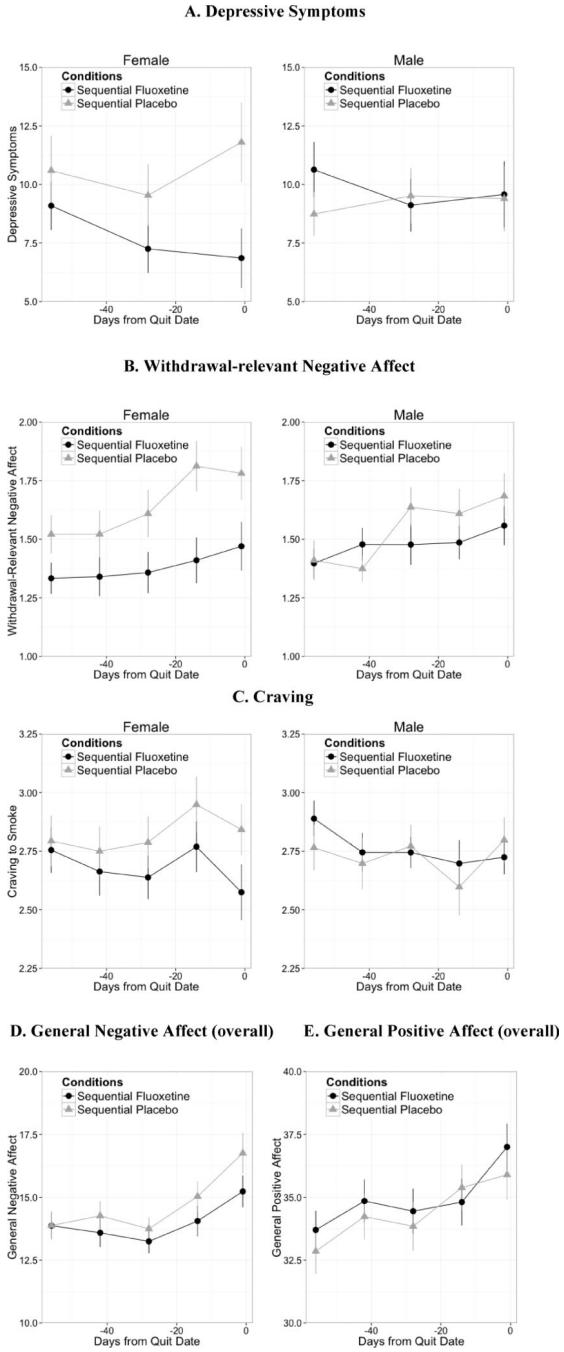

Figure 3.

Pre-quit changes by treatment condition and gender.

Plots show changes (in raw scores) in withdrawal-relevant negative affect (scores range from 1 to 4) (A), craving (scores range from 1 to 4) (B), and depressive symptoms (scores range from 0 to 60) (C) over 8 weeks prior to target quit date (TQD) by treatment condition (Sequential Fluoxetine vs. Sequential Placebo) and gender. Plots for general negative affect (scores range from 10 to 50) (D) and general positive affect (scores range from 10 to 50) (E)

show overall changes by treatment condition given that no significant differences in changes in general negative or positive affect were observed across gender.

Table 1

Baseline demographic, smoking, and depression vulnerability by treatment condition.

	Female (n=99)					Male (n=107)					*Overall Treatment Difference*
	Fluoxetine (n=51)		Placebo (n=48)			Fluoxetine (n=56)		Placebo (n=51)			
	Mean	***SD***	***Mean***	***SD***	***p***	***Mean***	***SD***	***Mean***	***SD***	***p***	***p***
Age	42.70	11.70	42.36	11.12	*0.88*	43.41	10.36	45.64	11.54	*0.30*	***0.53***
White*	0.88	--	0.88	--	*0.42*	0.96	--	0.92	--	*1.00*	***0.62***
Hispanic*	0.00	--	0.04	--	*0.23*	0.04	--	0.08	--	*0.42*	***0.16***
Cigarettes Per Day (past month)	19.74	12.18	20.08	9.37	*0.87*	22.09	8.22	22.00	8.70	*0.96*	***0.94***
FTND	5.90	1.77	5.23	2.44	*0.12*	5.90	1.73	5.56	2.31	*0.38*	***0.10***
CES-D	9.09	7.38	10.59	10.18	*0.40*	10.63	8.78	8.74	6.60	*0.21*	***0.82***
CES-D > 16*	0.14	--	0.19		*0.69*	0.25	--	0.12		*0.13*	***0.51***
General Negative Affect (PANAS)	13.48	5.18	13.53	4.36	*0.97*	14.19	4.68	14.24	5.70	*0.96*	***0.98***
General Positive Affect (PANAS)	32.21	6.82	33.69	7.98	*0.37*	34.87	7.31	32.00	8.31	*0.08*	***0.47***
Craving to smoke	2.76	0.68	2.79	0.73	*0.79*	2.89	0.56	2.77	0.67	*0.31*	***0.43***
Withdrawal-Relevant Negative Affect	1.33	0.46	1.52	0.55	*0.07*	1.40	0.47	1.41	0.60	*0.90*	***0.19***
MDD history*											
Recurrent MDD	12%	--	4%	--		3%	--	10%	--		
Single MDD episode	20%	--	21%	--	*0.44*	11%	--	16%	--	*0.31*	***0.82***

*Frequency within each group.

Note. SD: standard deviation; FTND: Fagerström Test for Nicotine Dependence; CES-D: Center for Epidemiologic Studies Depression Scale; PANAS: Positive and Negative Affect Scale; MDD: major depressive disorder.

Table 2

Latent growth models for depressive symptoms, withdrawal-relevant negative affect, general negative affect, general positive affect, and craving for the 8-week pre-quit period.

		Overall Model Fit			
Variable	***Linear Growth Slope (standardized)***	***χ2(df)***	***RMSEA***	***CFI***	***SRMR***
Depressive Symptoms	*−0.122 (−0.108)*	0.983 (1)	0.000	1.000	0.017
Withdrawal-Relevant Negative Affect	*0.057*** *(0.444)*	7.317 (10)	0.000	1.000	0.035
General Negative Affect	*−0.772*** *(−0.976)*	5.915 (7)	0.000	1.000	0.032
(qua dratic slope)	*0.321*** *(1.378)*				
General Positive Affect	*0.696*** *(0.503)*	20.757(10)	0.072	0.955	0.125
Craving	*−0.020 (−0.230)*	12.338 (10)	0.034	0.985	0.089

Note. All slopes are unstandardized. RMSEA: root mean square error of approximation; CFI: comparative fit index; SRMR: standardized root mean-square residual.

** P < 0.01.

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Table 3

Structural equation models for depressive symptoms, withdrawal-relevant negative affect, craving, general negative affect, and general positive affect.

Variable/Path	Est	Bias-Corrected 95% CI	StdXY	χ^2 (df)	p-value	RMSEA (90% CI)	Prob. ≤ .05	CFI	WRMR
Depressive Symptoms									
Pre-quit slope on fluoxetine (a_s)	−0.563	(−1.343, 0.187)	−0.260	3.64 (6)	0.725	0.000 (0.000, 0.066)	0.893	1.000	0.260
TQD abst on pre-tx intercept (b_i)	−0.039	(−0.081, 0.811)	−0.233						
TQD abst on pre-quit slope (b_s)	−0.474	(−35.64, −0.183)**	−0.498						
TQD abst on FTND	−0.157	(−1.893, −0.055)*	−0.317						
TQD abst on fluoxetine (c')	−0.266	(−18.207, 0.146)	−0.130						
Withdrawal-Relevant Negative Affect									
Pre-quit slope on fluoxetine (a_s)	−0.069	(−0.118, −0.019)**	−0.270	22.38 (23)	0.497	0.000 (0.000, 0.056)	0.916	1.000	0.539
TQD abst on pre-tx intercept (b_i)	−0.740	(−1.319, −0.058)*	−0.284						
TQD abst on pre-quit slope (b_s)	−3.717	(−7.136, −1.480)**	−0.465						
TQD abst on FTND	−0.107	(−0.208, −0.018)**	−0.217						
TQD abst on fluoxetine (c')	−0.257	(−0.690, 0.154)	−0.125						
Craving[a]									
Pre-quit slope on fluoxetine (a_s)	−0.054	(−0.109, −0.004)*	−0.233	23.01 (23)	0.520	0.000 (0.000, 0.054)	0.924	1.000	0.560
TQD abst on pre-tx intercept (b_i)	0.771	(0.019, 3.934)*	0.320						
TQD abst on pre-quit slope (b_s)	−4.345	(−12.40, −1.566)**	−0.488						
TQD abst on FTND	−0.249	(−0.618, −0.120)**	−0.503						
Pre-tx intercept on FTND	0.119	(0.082, −0.153)**	0.581						
TQD abst on fluoxetine (c')	−0.234	(−0.879, 0.235)	−0.114						
General Negative Affect[b]									
Pre-quit slope (linear) on fluoxetine (a_s)	−0.209	(−1.194, 1.135)	−0.168	18.63 (17)	0.350	0.022 (0.000, 0.068)	0.800	0.995	0.494
Pre-quit slope (curv) on fluoxetine (a_c)	−0.030	(−0.396, 0.243)	−0.058						
TQD abst on pre-tx intercept (b_i)	−0.119	(−0.715, −0.032)**	−0.525						
TQD abst on pre-quit slope (linear) (b_s)	−1.704	(−8.376, −0.499)**	−1.236						
TQD abst on pre-quit slope (curv) (b_c)	−0.165	(−2.920, 5.157)	−0.024						

Variable/Path	Est	Bias-Corrected 95% CI	StdXY	χ^2 (df)	p-value	RMSEA (90% CI)	Prob. ≤ .05	CFI	WRMR
TQD abst on FTND	−0.283	(−2.226, −0.151)**	−0.647						
TQD abst on fluoxetine (c')	−0.349	(−6.828, 0.349)	−0.209						
General Positive Affect [c]									
Pre-quit slope on fluoxetine (a_s)	0.196	(−0.518, 0.939)	0.057	29.88 (23)	0.153	0.038 (0.000, 0.073)	0.674	0.970	0.599
TQD abst on pre-tx intercept (b_i)	0.043	(0.007, 0.079)*	0.260						
TQD abst on pre-quit slope (b_s)	0.115	(−0.078, 0.292)	0.193						
TQD abst on FTND	−0.104	(−0.119, −0.021)**	−0.201						
TQD abst on fluoxetine (c')	−0.022	(−0.408, 0.335)	−0.011						

*P < 0.05,

**P < 0.00.

TQD: target quit date; pre-tx: pre-treatment; FTND: Fagerström Test for Nicotine Dependence; Est: estimate; SE: standard error; CI: confidence interval; stdXY: fully standardized; RMSEA: root mean square error of approximation; CFI: Comparative Fit Index; WRMR: weighted root mean square residual.

Note: Pre-treatment intercepts for all variables were not significantly associated with gender (not presented in the table). Gender and FTND were included as covariates, predicting pre-treatment intercepts and pre-quit slope as well as TQD abstinence in all models; however, only significant relationships are presented here (gender was not related to intercept, slope, or TQD abstinence in any models).

[a]The association between baseline nicotine dependence levels and pre-treatment intercept for each variable was estimated in each model (not presented in the table).

[b]The linear growth models for all but general negative affect had adequate-to-good model fit. A quadratic growth model for general negative affect was estimated and the model fitted the data well. Baseline nicotine dependence was significantly associated only with pre-treatment intercept of craving.

[c]The pre-treatment intercept and slope of were significantly correlated only in the positive affect model.

Table 4

Multi-group models by gender: Structural equation models of depressive symptoms, withdrawal-relevant negative affect, and craving.

Variable	Path	Est	Bias-Corrected 95% CI	χ^2 (df)	p-value	RMSEA (90% CI)	Prob. ≤ .05	CFI	WRMR
Depressive Symptoms									
Female [a]	**Pre-quit slope on fluoxetine (a_s)**	−1.321	(−2.707, −0.313)**	8.12 (11)	0.703	0.000 (0.000, 0.080)	0.847	1.000	0.457
	TQD abst on pre-tx intercept (b_i)	−0.050	(−0.097, −0.015)**						
	TQD abst on pre-quit slope (b_s)	−0.287	(−0.933, −0.116)**						
Male	**Pre-quit slope on fluoxetine (a_s)**	0.095	(−0.937, 1.035)						
	TQD abst on pre-tx intercept (b_i)	−0.056	(−0.122, 0.051)						
	TQD abst on pre-quit slope (b_s)	−0.063	(−0.695, 0.351)						
Withdrawal-Relevant Negative Affect									
Female	**Pre-quit slope on fluoxetine (a_s)**	−0.116	(−0.194, −0.039)**	47.46 (41)	0.226	0.039 (0.000, 0.081)	0.620	0.962	0.887
	TQD abst on pre-tx intercept (b_i)	−1.051	(−3.628, 0.179)						
	TQD abst on pre-quit slope (b_s)	0.104	(−0.155, 0.677)						
Male	**Pre-quit slope on fluoxetine (a_s)**	−0.030	(−0.098, 0.037)						
	TQD abst on pre-tx intercept (b_i)	−0.666	(−1.527, 0.580)						
	TQD abst on pre-quit slope (b_s)	−4.101	(−10.45, −0.273)*						
Craving [b]									
Female	**Pre-quit slope on fluoxetine (a_s)**	−0.109	(−0.181, −0.034)**	39.18 (40)	0.507	0.000 (0.000, 0.066)	0.846	1.000	0.819
	TQD abst on pre-tx intercept (b_i)	0.141	(−1.424, 3.140)						
	TQD abst on pre-quit slope (b_s)	−7.883	(−71.35, −2.396)**						
Male	**Pre-quit slope on fluoxetine (a_s)**	−0.013	(−0.077, 0.054)						
	TQD abst on pre-tx intercept (b_i)	1.619	(0.161, 6.523)**						
	TQD abst on pre-quit slope (b_s)	−2.306	(−11.97, 1.231)						

* P < 0.05,

** P < 0.00.

TQD: target quit date; pre-tx: pre-treatment; FTND: Fagerström Test for Nicotine Dependence; Est: estimate; SE: standard error; CI: confidence interval; stdXY: fully standardized; RMSEA: root mean square error of approximation; CFI: Comparative Fit Index; WRMR: weighted root mean square residual.

Note: For parsimony, *paths* c′ (i.e., TQD abstinence on fluoxetine - all non-significant) and nicotine dependence (i.e., pre-tx intercepts on FTND & TQD abstinence on FTND) are not presented in the table.

[a]The intercept and slope were significantly correlated only in the female model of depressive symptoms.

[b]The association between baseline nicotine dependence levels and pre-quit intercept was modeled in each model (not presented in the table). Baseline nicotine dependence was significantly associated only with pre-quit intercept of craving (in both the female and male models).