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ORIGINAL INVESTIGATION

Influence of fluoxetine on positive and negative affect in a clinic-based smoking cessation trial

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Abstract

Rationale – Fluoxetine improves affect in clinical syndromes such as depression and premenstrual dysphoric disorder. Little is known about fluoxetine's influence on mood changes after quitting smoking, which often resemble sub-clinical depression.

Objectives – The present study, a re-analysis of previously published data (Niaura et al. 2002), examined fluoxetine's effect on changes in negative and positive affect following quitting smoking.

Methods – Adult smokers (n = 175) without clinically significant depression were randomized on a double-blind basis to receive fluoxetine hydrochloride (30 or 60 mg daily) or placebo for 10 weeks in combination with cognitive-behavioral therapy (CBT) for smoking cessation. We postulated that fluoxetine would beneficially influence post-cessation changes in positive and negative affect.

Results – Mood change across treatment was analyzed using mixed linear modeling controlling for initial level of nicotine dependence, plasma fluoxetine metabolites, and change in cotinine (a nicotine metabolite) at each visit. Relative to placebo, those on 60 mg fluoxetine experienced an elevation in positive affect that increased across time [$t(526) = 2.50$, $P = 0.01$], and a reduction in negative affect that returned to baseline across time [$t(524) = 2.26$, $P = 0.02$]. There were no differences between 30 mg and placebo on changes in positive or negative affect.

Conclusions – Results indicate that 60 mg of fluoxetine improves both positive and negative mood states after quitting smoking and that diminished positive affect may be an overlooked affective response to smoking cessation.

Keywords

fluoxetine, smoking cessation, positive affect, negative affect

Introduction

Abstaining from nicotine, even during short periods of time, is accompanied by a cluster of affective responses resembling sub-clinical depression (Gilbert et al. 1998). Irritability, anxiety, and depressed mood, for example, are commonly reported mood disturbances that are experienced after quitting smoking (Hughes and Hatsukami 1986; American Psychiatric Association 1994; Gilbert et al. 1998). Reductions in positive affect, however, have largely been overlooked as a possible response to smoking cessation. That neglect is surprising, given the integral relationship between deficient positive mood states and depression (Clark and Watson 1991; Coyne 1994), and evidence that quitting smoking heightens the risk of depressive episodes (Borrelli et al. 1996; Tsoh et al. 2002). Positive affect declines after quitting smoking (Gilbert et al. 1998; Lerman et al. 2002; Cook et al. 2003) and persists across 30 days of abstinence (Gilbert et al. 1998). Further, empirical evidence that positive and negative affect are linked to different neural underpinnings (Davidson 1992) and have different psychological correlates (Watson et al. 1988) supports the independence of these constructs. Thus, low positive affect may be an important and neglected response to quitting smoking, which, in combination with elevated negative affect, constitutes a distressing affective syndrome that follows smoking cessation.

Similarities between cessation-induced mood disturbance and other affective syndromes (e.g. depression, premenstrual dysphoric disorder) suggest that antidepressant medications might also ameliorate unpleasant mood states after quitting

smoking. A variety of antidepressants with dopaminergic, noradrenergic, and/or serotonergic actions have demonstrated efficacy for promoting smoking cessation (Spring et al. 1995; Hurt et al. 1997; Hall et al. 1998; Niaura et al. 2002). Studies on the effects of the agents have, for the most part, focused on the alleviation of negative mood or depressive symptoms. Specifically, euthymic smokers treated with nortryptiline (catecholaminergic and serotonergic actions) or bupropion (dopaminergic and noradrenergic actions), report lower levels of post-cessation negative affect than smokers who did not receive these treatments (Hall et al. 1998; Shiffman et al. 2000; Lerman et al. 2002). Effects of antidepressants on positive affect are less understood (Zald and Depue 2001). Although Shiffman et al. (2000) found that bupropion attenuated a decrease in positive affect in euthymic smokers during 72-h nicotine deprivation, Lerman and colleagues (2002) did not detect an effect of bupriopion on post-cessation positive moods.

The influence of fluoxetine, a selective serotonin reuptake inhibiting antidepressant (SSRI), on mood following smoking cessation has yet to be examined. Although fluoxetine, given for 3 weeks prior to a quit attempt reduced depression among euthymic smokers (Dalack et al. 1995), fluoxetine's effect on affective distress during nicotine abstinence remains unknown. In other clinical syndromes, including major depression (Gram 1994), subsyndromal depression (Gram 1994), and premenstrual dysphoric disorder (Cohen et al. 2002), fluoxetine has been shown to alleviate negative affect. In depression, the drug's mood benefit is not confined to patients who present solely with depressed mood, but occurs also among patients with comorbid anxiety disorder (Sonawalla et al. 2002). In addition to engendering improvements in depression, fluoxetine reduces a full range of negative moods, including anxiety and anger-hostility (Sonawalla et al. 2002).

To our knowledge, there have been no prior studies examining whether fluoxetine can prevent the dysphoric mood and the decreased positive affect that typically follow nicotine abstinence. There are, however, three reasons to expect such effects. First, similar preventive benefits have been demonstrated for fluoxetine as a treatment of premenstrual dysphoric disorder, such that the drug prevents intermittent worsening of negative mood (Cohen et al. 2002). Second, although fluoxetine has yet to be established as a treatment for smoking cessation, it has been shown to yield a modest cessation advantage to smokers who are trying to quit (Niaura et al. 2002), especially among those who have higher baseline levels of depressive symptomatology (Hitsman et al. 1999). Such effects might partly arise from the drug's mood control properties. Third, administration of fluoxetine and serotonin$_{1A}$ receptor antagonist, p-MPPI, in rats prevents a rise in brain reward threshold during nicotine deprivation (i.e. reverses diminished responding to rewarding stimuli; Harrison et al. 2001). To the extent that diminished positive affect is associated with diminished reinforcing value of approach behavior to rewards (Depue and Collins 1999), fluoxetine might buffer the losses in positive affect associated with quitting smoking.

The present study examined the effect of 30 and 60 mg fluoxetine, relative to placebo, on acute change in positive and negative moods during nicotine abstinence. We postulated that fluoxetine would buffer the increase, or even diminish negative affect during smoking cessation. Moreover, we postulated that fluoxetine would buffer post-cessation losses in positive affect, or, potentially, increase positive affect during smoking cessation.

Materials and methods

Participants

Subjects were 175 euthymic male and female smokers recruited to three of 16 sites in a double-blind, placebo-controlled, multicenter trial examining the influence of fluoxetine on smoking cessation. The present study is a re-analysis of previously published data (Niaura et al. 2002), and used the three-site subset that measured positive and negative affect across visits. Subjects' mean age was 42.6 years (SD = 9.4). Most were female (57.1%), Caucasian (94.6%), and married (52.6%). Subjects averaged 30.1 cigarettes per day (SD = 12.9) for a mean of 25.1 years (SD = 9.1) prior to treatment. Enrollees were moderately dependent on cigarettes, as indicated by a mean score of 6.8 (SD = 1.8) on the Fagerstrom Tolerance Questionnaire (Fagerstrom 1978). At entry, cotinine, a nicotine metabolite, averaged 288.7 ng/ml (SD = 152.9). Subject eligibility criteria, as well as the cessation outcomes of the multi-center trial, are reported elsewhere (Niaura et al. 2002).

Measures

Positive affect

Positive affect was assessed at each visit via the Positive and Negative Affect Scale (PANAS; Watson et al. 1988). The PANAS is a self-report state mood questionnaire consisting of 20 adjectives that are rated on 5-point scales ranging from 1 (very slightly or not at all) to 5 (extremely). The positive affect subscale, manifested by feelings of activation, elation, enthusiasm, and enjoyment, consists of 10 items, with potential scores ranging from 10 to 50. The Positive Affect subscale has been shown to possess high internal consistency (Watson et al. 1988).

Negative affect

Negative affect was assessed at each visit via the negative affect subscale of the PANAS (Watson et al. 1988). The negative affect scale, encompassing feelings of distress, hostility, nervousness, scorn, and gloominess, is comprised of ten words with scores ranging from 10 to 50. The negative affect scale possesses high internal consistency (Watson et al. 1988).

Smoking characteristics

The eight-item Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom 1978) was administered to measure degree of behavioral responses suggestive of nicotine dependence (e.g. smoking many cigarettes, smokes early in the morning). Scores ranged from 0 to 11, with higher values suggesting greater nicotine dependence. Correlations between the FTQ and measures of nicotine intake support the construct validity of the scale (Fagerstrom and Schneider 1989).

Saliva cotinine concentration was measured at each visit. Saliva cotinine samples were analyzed by SciCor Laboratory (Indianapolis, Ind., USA).

Carbon monoxide, assessed via an ecolyzer (Model EC-50, Vitalograph Corporation), was also assessed at each visit.

Medication compliance

Compliance was verified by assays of plasma concentrations of fluoxetine metabolites (fluoxetine and norfluoxetine) at visits 5 (3 weeks after starting drug) and 9 (end of medication). Assays were performed after study completion using gas chromatography (Nash et al. 1992).

Axis I disorders

Axis I disorders were assessed via Structured Clinical Interview for DSM-IV, patient version (SCID; Spitzer et al. 1992). The SCID has moderate construct validity, as shown by its favorable comparison with other diagnostic assessment methods (Williams et al. 1992). Individuals with current axis I disorders other than nicotine dependence were excluded from the sample.

Procedure

All study sites were approved by appropriate ethics committees. Participants first attended a screening session where they provided informed consent and were assessed for axis I disorders via the SCID (Spitzer et al. 1992). Those who were eligible for the study began the first of nine sessions of individual cognitive behavioral treatment aimed at achieving smoking cessation by the development of coping skills and relapse prevention. Subjects were randomized on a double-blind basis to receive 10 weeks of placebo (n = 60), 30 mg (n = 57) or 60 mg (n = 58) of fluoxetine, which began during the second visit. Participants quit smoking 14 days after the beginning of the medication phase (just prior to visit 4), so that a therapeutic drug level would be achieved before quitting smoking. Assessments of positive and negative affect were collected at each visit.

Analytic plan

Mood change across seven time points (visits 3–9) was analyzed using mixed linear modeling, implemented via SAS PROC MIXED. Random effects regression models used random intercepts, linear and quadratic trend model with autoregressive errors. As recommended, this variance covariance structure for the longitudinal data was selected after comparisons with several other potential structures (Verbecke and Molenberghs 2000). Nicotine dependence, change in cotinine, and fluoxetine blood levels were utilized as covariates. Change in cotinine at each visit was analyzed as a time varying covariate, which statistically removed the influence of nicotine exposure on positive and negative affect across time. Both time and time squared terms were included in all analyses. Non-significant interaction terms were removed from the model in a backwards manner and the model was refit. Two a-priori group contrasts were specified: 30 mg versus placebo; 60 mg versus placebo.

It is important to note that mixed-effects regression modeling does not place restrictions on the number of observations per individual, so that participants with missing data at a particular assessment time were not excluded from analyses. Instead, model parameters were estimated using all available data. Essentially, the model assumes that the data that are present for a given subject reasonably reflect that subject's deviation from the usual fixed-effects regression part of the model (i.e. the regressors multiplied by their coefficients). In the present study, the following assessments of positive and negative affect were missing: 18 at visit 3, 24 at visit 4, 32 at visit 5, 39 at visit 6, 51 at visit 7, 62 at visit 8, 72 at visit 9. Broken down by group, there were 116 total data points missing from the placebo group, 83 from the 30 mg group, and 99 from the 60 mg group.

Results

Preliminary analyses

Participant characteristics

Baseline smoking history and sociodemographic variables were compared across conditions using one way analyses of variance for continuously scaled variables and chi-square tests for differences between proportions when variables were dichotomous. As shown in Table 1, smokers randomized to the different treatment conditions showed no significant differences on age, gender, baseline positive and negative affect, nicotine dependence, number of years smoked, cotinine level, and history of depression. Baseline PANAS scores are comparable to those reported in other euthymic samples (Watson et al. 1988).

Abstinence rates

Abstinence was determined via self-report, cotinine, and carbon monoxide assessments collected at each visit. At visit 5, abstinent smokers comprised 36.7% of those of placebo, 35.1% of those on 30 mg and 46.1% of those taking 60 mg. At visit 6, abstinent smokers comprised 38.3% of those on placebo, 35.1% of the 30 mg group, and 39.7% of the 60 mg group. At visit 7, abstinent smokers comprised 25% of the placebo group, 26.3% of the 30 mg group, and 25.9% of the 60 mg group. At visit 8, abstinent smokers comprised 26.7%

Table 1 Baseline demographic and smoking variable means and standard deviations by condition

	Placebo (n = 60)	**30 mg (n = 57)**	**60 mg (n = 58)**
% Female	61.7	54.4	55.2
History of depression (%)	28.4	26.3	25.8
Age	41.9 (9.3)	41.7 (9.6)	44.0 (9.5)
Baseline positive affect	33.9 (6.7)	32.1 (6.5)	31.7 (5.9)
Baseline negative affect	15.1 (3.8)	16.6 (5.8)	17.1 (4.8)
Cotinine level (ng/ml)	274.5 (135.6)	288.4 (142.6)	303.2 (178.4)
Fagerstrom	6.4 (1.8)	6.8 (1.9)	7.1 (1.8)
Number of years smoking	24.5 (10.3)	25.6 (8.8)	25.1 (8.0)

of those on placebo 19.3% of those on 30 mg, and 29.3% of those on 60 mg. At visit 9, abstinent smokers comprised 21.7% of the placebo group, 14% of the 30 mg group, and 24.9% of the 60 mg group.

Change score derivation

Simple change score analysis (visit–baseline) measured change in positive and negative affect at each visit, consistent with our interest in examining fluoxetine's influence on acute changes in affect after quitting smoking and evidence that mood change represents a clinically relevant affective disturbance during nicotine abstinence (Piasecki et al. 2000). Visits 1 and 2 were averaged together to create baseline positive and negative affect because treatment did not require smoking reduction at these measurement points and fluoxetine was not administered until after visit 2. Prior to creating baseline scores, it was established that positive and negative affect did not change across visits 1 and 2. Mean positive affect at visits 1 and 2 was 32.27 and 32.79, respectively ($P = 0.48$) and mean negative affect at visits 1 and 2 was 15.86 and 16.52, respectively ($P = 0.11$).

Correlation analyses

Pearson correlations were computed to identify appropriate covariates. The association between change in positive and negative affect and the following potential covariates were examined: history of depression, nicotine dependence (FTQ), number of cigarettes smoked daily, gender, plasma concentrations of fluoxetine metabolites (composite average of visits 5 and 9), and change in cotinine from baseline to each visit. Only nicotine dependence, fluoxetine blood levels, and change in cotinine were significantly correlated with change in positive and negative affect after cessation (all $r<0.05$), and were therefore retained as covariates. Associations between change in positive and negative affect at each visit were also examined. Correlation analysis showed that the association between change in positive and negative affect was moderate and significant at all time points [$r = –0.21$ to $–0.41$, $P<0.05$], although not to the extent that they appeared to reflect the same construct.

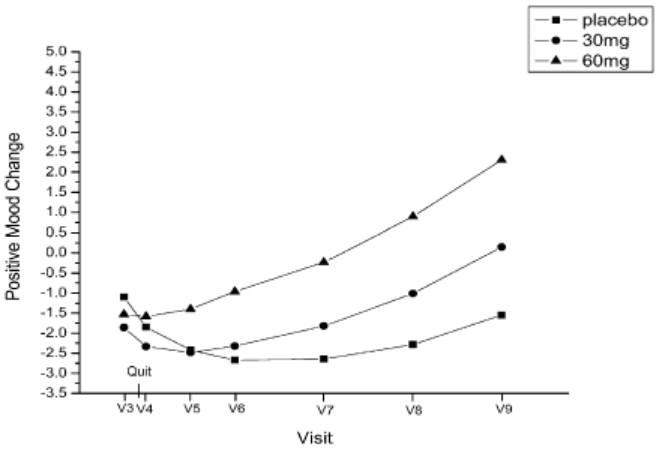

Figure 1 Regression function showing estimated positive affect change by condition across time, covariate adjusted for change in cotinine, fluoxetine blood levels and nicotine dependence. Distances represent real time. Participants quit smoking between visit 3 and 4, 14 days after beginning of medication phase

Mixed linear modeling

Positive affect model

A significant group by time interaction was present in the longitudinal analysis of change in positive affect (see Table 2). Specifically, the 60 mg versus placebo comparison showed a linear interaction with time [$t(526) = 2.50$, $P = 0.01$]. Relative to placebo, those on 60 mg fluoxetine experienced an increase in positive affect that grew across time (see Figure 1). There were no significant differences between 30 mg and placebo. Parallel analyses using residualized positive affect as an outcome variable yielded the same results.

Negative affect model

The negative affect model showed a significant linear [$t(524) = –2.21$, $P = 0.03$] and quadratic [$t(524) = 2.26$, $P = 0.02$] interaction with time (see Table 3). Relative to placebo, those on 60 mg fluoxetine experienced a decrease in negative affect. Across time, however, this advantage appeared to diminish

Table 2 Predictors of change in positive affect from visit 3 through visit 9, determined by mixed linear modeling analysis with autoregressive errors

	Variable	Regression coefficient	Standard error	*t*
Covariates	Change in cotinine	–0.18	0.11	–1.76
	Fagerstrom	–0.27	0.23	–1.20
	Fluoxetine metabolites	1.17	1.17	1.00
Main effects	Time	–0.94	0.36	–2.61**
	$(\text{Time})^2$	0.14	0.05	2.74**
	30 mg	–7.30	6.56	–1.11
	60 mg	–7.59	7.28	–1.04
Interactions	30 mg × Time	0.46	0.28	1.62
	60 mg × Time	0.73	0.29	2.50*

*$P<0.05$, **$P<0.01$

(see Figure 2). There were no significant differences between 30 mg and placebo. Parallel analyses using residualized negative affect as an outcome variable yielded the same results.

Subanalyses

We ran parallel analyses among continuous abstainers versus non-continuous abstainers to examine whether fluoxetine's beneficial mood effects were secondary to feelings of success associated with quitting smoking. Those identified as continuous abstainers were abstinent at visit 6 and maintained continuous abstinence through visit 9. Fluoxetine produced similar trends in positive and negative affect in both groups. That is, 60 mg fluoxetine increased positive affect and decreased negative affect after quitting, regardless of smoking status. To examine the impact of smoking cessation on changes in affect further, continuous abstinence was statistically controlled in both regression models. Even after controlling for abstinence, those taking 60 mg fluoxetine experienced a linear increase in positive affect ($P = 0.01$) and decrease in negative affect (linear, $P = 0.04$; quadratic, $P = 0.04$). Results suggest that positive and negative affect changes are influenced by fluoxetine rather than feelings of success after quitting smoking.

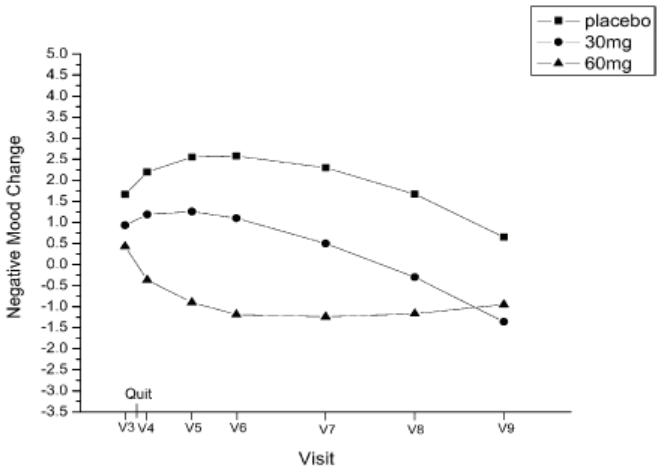

Figure 2 Regression function showing estimated negative affect change by condition across time, covariate adjusted for change in cotinine, fluoxetine blood levels and nicotine dependence. Distances represent real time. Participants quit smoking between visit 3 and 4, 14 days after beginning of medication phase

Discussion

The current results are the first to show that fluoxetine improves post-quit positive and negative mood states. The findings accord with growing evidence that antidepressants may be used to reduce affective distress following quitting smoking (Hall et al. 1998; Shiffman et al. 2000; Lerman et al. 2002). Notably, fluoxetine produced a reduction in negative affect and a rise in positive affect. That observation is particularly noteworthy when considering that other antidepressants have simply attenuated increases in negative affect (nortriptyline, bupropion) and decreases in positive affect (bupropion) while abstaining from nicotine. The current results showing that fluoxetine increased post-cessation positive affect suggest that the drug may be unique in not only buffering against an aversive mood response to nicotine abstinence, but actually producing improvement in positive affect following quitting smoking.

Fluoxetine's enhancement of positive affect is interesting to consider given that human pharmacology studies have focused primarily on SSRI modulation of negative affect (Zald and Depue 2001). The dearth of research examining SSRI influences on positive affect may partially result from the view that positive mood states reflect little more than the opposite of negative moods along a single affective dimension (Russell and Carroll 1999). Our data, however, showed that changes in post-quit positive and negative affect were only moderately intercorrelated. That fluoxetine exerted a more sustained influence on positive affect than on negative affect also suggests that these two parameters of affective responses are at least partially independent. Although those on 60 mg fluoxetine experienced reductions in negative affect during the first few weeks after quitting smoking, improvements in negative affect dissipated by end of treatment (see Figure 2). In contrast, fluoxetine's influence on positive affect grew stronger across time (see Figure 1), resulting in assessments of positive mood that exceeded pre-quit levels. The positive affect pattern

Table 3 Predictors of change in negative affect from visit 3 through visit 9, determined by mixed linear modeling analysis with autoregressive errors

	Variable	Regression coefficient	Standard error	*t*
Covariates	Change in cotinine	0.22	0.12	1.98*
	Fagerstrom	0.30	0.21	1.41
	Fluoxetine metabolites	–1.4	1.11	–1.3
Main effects	Time	0.88	0.55	1.11
	$(\text{Time})^2$	–0.17	0.09	–1.93
	30 mg	0.19	6.19	0.03
	60 mg	–0.57	6.87	–0.08
Interactions	30 mg × Time	–0.65	0.76	–0.85
	60 mg × Time	–1.73	0.78	–2.21*
	30 mg × $(\text{Time})^2$	0.06	0.12	0.52
	60 mg × $(\text{Time})^2$	0.29	0.13	2.26*

*$P<0.05$

that emerged for the 60 mg group is strikingly different than reported losses in positive affect in the placebo group and in others abstaining from nicotine (Gilbert et al 1998; Lerman et al. 2002; Cook et al. 2003). Fluoxetine appears to have not only reversed typical reported losses in positive affect following smoking, but stimulated a positive mood improvement that continued to grow 8 weeks after quitting smoking.

Animal models of brain reward function are relevant to understanding positive mood effects in humans to the extent that positive emotions can be viewed as subjective cues that motivate approach behavior toward rewards (Depue and Collins 1999). Findings from animal studies indicate that fluoxetine heightens responsivity to rewards, and suggest dopaminergic (DA) and serotonergic (5-HT) mechanisms of action. In animal studies, nicotine abstinence leads to a decrement in reward functioning that is reversed or prevented by fluoxetine (Harrison et al. 2001), a finding analogous to fluoxetine's enhancement of positive affect in the present study. Fluoxetine's positive mood enhancing effects might plausibly come about via 5-HT/DA interaction. Fluoxetine administration directly enhances 5-HT activity, which has been shown to facilitate dopamine release in the nucleus accumbens (Benloucif and Galloway 1991; De Deuwaerdere et al. 1996), and increase sensitivity to reward (Sasaki-Adams and Kelley 2001). Conversely, decreased 5-HT release inhibits DA activity (Ichikawa et al. 1995), a mechanism that has been linked with acquisition of anhedonia (Harrison et al. 2001; Zagen et al. 2001). Plausibly, therefore, reduction in positive affect during nicotine deprivation may be engendered by decreased 5-HT activity with consequent inhibition of DA release. We posit that a relatively high dose of fluoxetine (60 mg) may be needed to induce sufficient 5-HT activation to normalize DA release in the nucleus accumbens, thereby increasing positive affect.

Study limitations include the selective nature of the sample in the respect that participants were motivated to quit smoking and generally in good physical and mental health. Generalizability to populations with greater physical and psychological comorbidities cannot be assumed. Nor is it known to what degree study results would generalize to populations of smokers who were attempting to quit without behavioral assistance. Another limitation is that other mood measures were not examined, potentially limiting the generalizability with regard to other assessments of affect. A final limitation is that missing data increased over time and differed between groups. We therefore utilized mixed linear modeling, an analytic strategy designed for handling time and group differences in missing data. Random effects regression creates model parameters using all available data, therefore estimating rate of change for missing participants.

More generally, this study suggests the utility of SSRIs for treating not only elevated negative affect, but also deficient positive affect, a common feature of depression (Clark and Watson 1991; Coyne 1994). In the context of smoking cessation, our data show that 60 mg fluoxetine, relative to placebo, improved positive and negative affect during nicotine abstinence. In view of prior findings that link mood problems during smoking cessation with relapse, it is plausible that beneficial effects of antidepressants on smoking cessation (Spring et al. 1995; Hurt et al. 1997; Hall et al. 1998; Niaura et al. 2002) may be modulated via effects on positive and negative affect. Clinically, the current findings indicate that fluoxetine is helpful in alleviating affective distress triggered by quitting smoking, and might therefore prove helpful in preventing post-cessation decline into depression (Borrelli et al. 1996; Tsoh et al. 2002). An important question that remains to be examined in future research is whether fluoxetine's effects on post-cessation affect mediate cessation outcome.

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