Development of Major Depressive Disorder During Smoking-Cessation Treatment

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Background: Several studies have shown an association between smoking and major depressive disorder (MDD), but few have prospectively examined subjects who develop MDD after quitting smoking. This descriptive study evaluated the development of MDD after smoking cessation, as assessed by a structured clinical interview at both baseline and the end of treatment.

Method: Nondepressed participants (N = 114) in a trial investigating the effect of fluoxetine on smoking cessation were administered the Structured Clinical Interview for DSM-III-R at baseline and posttreatment to evaluate the impact of quitting smoking on the development of MDD. Depressive symptoms were additionally assessed with the Beck Depression Inventory and the Hamilton Rating Scale for Depression.

Results: At baseline, 32% of the subjects reported a history of MDD. Sixty-nine subjects completed the SCID at baseline and posttreatment. At posttreatment, 5 subjects (7%) met threshold criteria for MDD; none were taking the highest dose of fluoxetine (60 mg), 4 were taking 30 mg, and 1 was taking placebo. All 5 had a history of MDD; 3 were women. Four had a history of substance abuse and attained at least 3 consecutive biochemically verified weeks of smoking abstinence. Those who developed MDD after treatment scored significantly higher on measures of depressed mood at baseline than those who did not develop MDD after smoking-cessation treatment.

Conclusion: The results from this descriptive study suggest that a subset of smokers may be at risk for developing MDD after smoking cessation.

(J Clin Psychiatry 1996;57:534–538)

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The authors gratefully acknowledge Eli Lilly and Company for sponsoring this study. The opinions presented in this paper are those of the authors and may not reflect the opinions of Eli Lilly and Company.

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Research continues to provide evidence for the link between depression and smoking. Cross-sectional studies have found that smoking rates increase and quit rates decrease as symptoms of depression increase.[1] Other epidemiologic studies have shown that those without a history of depression quit at more than twice the rate of those with a history of depression.[2] Similarly, prospective studies have found that either historical or current depression predicts failure to quit smoking.[1,3,4] In clinic-based studies, history of depression has been found to be associated with higher levels of depressive symptoms at pretreatment[5–7] which, in turn, have been associated with a lower likelihood of cessation[3,8,9] and a greater likelihood of relapse.[10,11] While a few studies have also found increases in depressive symptoms after subjects quit smoking,[12] few have evaluated the development of a major depressive syndrome. While depression appears to hinder smoking cessation and maintenance of abstinence, the reciprocal relationship (i.e., the effect of smoking cessation on the development of major depression) is less clear and has not been systematically evaluated. A bidirectional relationship is tenable given the orthogonal effects of smoking behavior and depression on similar neurochemical systems.[13,14]

Clinical lore has noted the relationship between smoking cessation and the subsequent development of major depression, but few prospective studies have actually tested this assumption. In a letter to the editor, Flanagan and Maany[15] anecdotally reported on two cases of depression following smoking cessation. In his study investigating the effect of clonidine on smoking cessation, Glassman[16] noted that 2% of smokers with no psychiatric history developed depression upon smoking cessation versus 18% of those with a history of depression. While Glassman states that 8 of 113 subjects developed "depressive symptoms," it is unknown how depression was assessed at follow-up or if these symptoms constituted an episode of major depression.

The goal of the present descriptive study was to evaluate the impact of smoking cessation on the development of major depression, as assessed by a structured clinical interview at both baseline and the end of treatment. A sec-

ond exploratory aim was to identify the baseline risk factors that differentiate those who develop major depression after smoking cessation from those who do not. It was hypothesized that a history of depression and greater dysphoria at baseline would be associated with development of major depression after smoking cessation.

METHOD

Subjects

Subjects were participants in a double-blind, placebo-controlled multicenter trial investigating the effect of fluoxetine on smoking cessation (Eli Lilly and Co., Indianapolis, Ind. Unpublished data). Analyses were conducted with subjects (N = 114) who were enrolled at two sites at which the Structured Clinical Interview for DSM-III-R[17] (SCID) (nonpatient edition) was administered. Subjects gave their informed consent after the procedure and side effects of the medication were fully explained. Entry criteria required that subjects had to be 18 to 65 years old, have smoked daily for at least 1 year and have a baseline expired carbon monoxide level ≥ 8 ppm, and agree to declare a quit date within 2 weeks after the second visit. Exclusionary criteria were a Hamilton Rating Scale for Depression[18,19] (HAM-D) score > 14; pregnancy; hypertension; use of psychotropic medication or current psychiatric illness; alcohol or drug abuse in the last year; current use of nicotine replacement; unstable medical condition or major health event in the last 6 months; use of smokeless tobacco, pipes, or cigars; recent experience of a major life event (e.g., divorce, major job change); suicidal ideation; and history of bipolar disorder.

The sample was composed of 63.2% women. The mean age was 50 years, and most subjects were well educated (98.8% high school graduates). Subjects had a mean ± SD 3.8 ± 3.8 prior quit attempts and 29.7 ± 12.2 cigarettes per day. Subjects were moderately dependent on nicotine, as indicated by their mean ± SD scores on the Fagerstrom Tolerance Questionnaire[20] (FTQ) of 6.8 ± 1.9.

Procedure

Subjects were randomly assigned to one of three treatment conditions: 30 mg or 60 mg of fluoxetine per day or placebo. Subjects were administered one pill per day for 10 weeks (through Visit 9) and were required to set a quit date within 14 days of randomization. All patients participated in a smoking-cessation behavioral modification program consisting of nine 30- to 60-minute sessions with a doctoral- or masters-level counselor (R.N., J.D.D., N.J.K.).

Measures

Measures of major depressive disorder (MDD) and depressive symptoms were administered at screening (Visit 1) and at the end of drug treatment (Visit 9). Historical depression and current depression were assessed by using the SCID (nonpatient edition),[17] which was administered by a trained interviewer. The HAM-D interview consists of 25 items tapping current depressive symptoms[18,19] and was administered by trained psychiatrists. The Beck Depression Inventory[21] (BDI) was administered to assess additionally the presence and severity of depressive symptoms. The Beck Anxiety Inventory[22] (BAI) was administered to assess symptoms of anxiety.

The Shiffman Withdrawal Scale,[23] a 15-item measure of withdrawal after smoking cessation, was given at each visit. Abstinence was biochemically verified at each visit through expired-air carbon monoxide (< 8 ppm) and saliva cotinine (< 20 ng/mL). The FTQ[20] was given at Visit 1 to assess level of nicotine dependence.

Analytic Plan

Where sample sizes were sufficient, t tests for independent groups were used. The nonparametric Mann-Whitney U test was used in all other analyses comparing the MDD and non-MDD groups since the normality of the distribution could not be assumed given the small sample size of the MDD group.

RESULTS

Development of Major Depression

Subjects who missed Visits 5 through 9 were considered dropouts. Dropouts (N = 9) did not significantly differ from those who completed treatment on baseline smoking variables (smoking rate, FTQ scores, cotinine levels), baseline mood variables (BDI, HAM-D, BAI), demographics, or Shiffman Withdrawal Scale scores. However, 66.7% of the dropouts reported a history of major depression at baseline versus 28.6% of the treatment completers. None of the dropouts were assigned to the 30-mg condition, while 44.4% were assigned to 60 mg of fluoxetine and 55.6% to placebo.

While 114 smokers completed the SCID at baseline, 69 repeated the SCID at Visit 9. The condition assignments for those who did not repeat the SCID at Visit 9 were placebo, 27.7%; fluoxetine 30 mg, 29.8%; and fluoxetine 60 mg, 42.6%. The condition assignments for those who repeated the SCID at Visit 9 were placebo, 38.8%; fluoxetine 30 mg, 35.8%; and fluoxetine 60 mg, 25.4%. Those who repeated the SCID had significantly lower baseline Shiffman Withdrawal Scale scores ($t = -2.42$, $df = 112$, $p \leq .02$), lower baseline scores on the BDI ($t = -2.70$, $df = 76.91$, $p \leq .01$), and lower baseline cotinine levels ($t = -2.04$, $df = 66.62$, $p \leq .05$) than those who did not repeat the SCID. No significant differences were found between SCID repeaters and SCID nonrepeaters on baseline smoking rate, history of depression, condition assignment, or scores on the FTQ, HAM-D, or BAI.

No subjects met the criteria for current MDD at baseline. The prevalence of lifetime history of depression reported at baseline was 31.6% (N = 36) of the total sample, 31.3% (21 of 67) of those who completed the SCID at Visit 9, and 31.9% (15 of 47) of those who did not complete the SCID at Visit 9. Seven percent (5 of 69) met threshold criteria for development of MDD over the last 3 months (i.e., during smoking treatment). While none of these subjects were taking the highest dose of fluoxetine (60 mg), four of the five had received 30 mg of fluoxetine, and the remaining subject received placebo. All five subjects in the MDD group had a history of depression as assessed by the SCID at baseline, and three were women. Four of the five subjects had a history of substance abuse. None of the five subjects had a history of any other mood disorders (bipolar, anxiety) except for one subject who had a history of dysthymia. The MDD group did not significantly differ from the non-MDD group on baseline smoking rate, FTQ scores, number of prior quit attempts, confidence to quit, age, or education.

Smoking Status and Withdrawal Symptoms

Of those in the MDD group, one subject continually smoked since Visit 1 (but reduced his smoking rate by half), and one subject was continuously abstinent since Visit 4. One subject had been continuously abstinent since Visit 3 but relapsed by the end of treatment. The remaining two subjects cycled between abstinence and smoking, but each had three consecutive visits at which they were abstinent prior to the assessment of depression at Visit 9. One of these subjects met threshold criteria for major depression within the last 3 months, but did not meet criteria within 1 month of Visit 9. Interestingly, this subject subsequently relapsed by Visit 8, after four consecutive visits of abstinence. Since we were primarily interested in differences between those who were depressed at the end of treatment versus those who were not, we excluded this subject from further analyses because his depression was resolved by the time of the readministration of the SCID at Visit 9.

Subjects in the MDD group (N = 4) reported significantly greater withdrawal symptoms at Visit 6 (mean ± SD = 3.76 ± 0.56, M rank = 54.1, U = 49.5, $p < .04$) and at Visit 8 (mean = 3.95 ± 0.82, M rank = 56.6, U = 35.5, $p < .02$) than subjects in the non-MDD group (N = 64) at Visit 6 (mean = 2.93 ± 0.96, M rank = 33.3) and at Visit 8 (mean = 2.68 ± 0.88, M rank = 32.6). No significant differences in withdrawal ratings were found at any other visit.

Depressive Symptoms

The MDD and the non-MDD groups were compared on the HAM-D, BDI, and BAI scales at both baseline and end of treatment (Visit 9). While the groups did not significantly differ in their baseline HAM-D scores, the MDD group had significantly higher HAM-D scores at Visit 9, (mean ± SD = 8.5 ± 5.1, M rank = 54.25, U = 45, $p < .03$) than the non-MDD group (mean ± SD = 3.17 ± 3.01, M rank = 32.7). The MDD group also had significantly higher BDI scores at Visit 1 (mean ± SD = 7.25 ± 5.3, M rank = 55.4, U = 44.5, $p < .03$) than the non-MDD group (mean ± SD = 2.83 ± 3.06, M rank = 33.2), but no significant differences between the groups were found at Visit 9. Similarly, the MDD group had significantly higher baseline scores on the BAI (mean ± SD = 8.25 ± 3.6, M rank = 57.6, U = 35.5, $p < .02$) than the non-MDD group (mean ± SD = 3.31 ± 3.4, M rank = 33.0), but no significant differences between groups were obtained at Visit 9. Therefore, the development of depression at Visit 9 was unconfounded by difficulties with concomitant anxiety. While these scores did not meet the cutoffs for depression or anxiety at baseline, they suggest that patients with even small amounts of negative affect at baseline may be at risk for developing depression over the course of smoking-cessation treatment.

DISCUSSION

While other researchers have noted the association between smoking cessation and the development of MDD, to our knowledge, this is the first study to (1) use the SCID to diagnose depression in ex-smokers and (2) assess depression at both baseline and end of smoking-cessation treatment. While none of the sample met diagnostic criteria for depression at baseline, 7% had developed depression over the course of smoking-cessation treatment. Although the patients were self-selected volunteers who were screened to exclude depression, the rate of depression was higher than the prevalence of current depression in a national community sample (4.9%).[24] Furthermore, approximately 32% of the sample reported a lifetime history of depression, as assessed by the SCID at baseline. This is higher than the lifetime prevalence of depression in national community samples (17.1%)[24] and is consistent with data found in other clinic-based smoking-cessation programs.[2,6,7]

Despite a lack of psychiatric and medical comorbidity and neither a history of bipolar disorder nor current substance abuse (all of which correlate highly with depression), not an insignificant number of patients developed diagnosable major depression. Interestingly, though, none of the subjects who developed MDD posttreatment were assigned to the 60-mg fluoxetine treatment condition. While it is difficult to proffer conclusions given the small sample size, one interpretation of these data is that higher doses of fluoxetine may be prophylactic to the development of depression in depression-prone ex-smokers. Alternatively, it could also be reasoned that fluoxetine 30 mg iatrogenically increases the risk of depression as compared with placebo.

It is notable that four of the five subjects who developed major depression were not smoking for at least 3 consecutive weeks prior to the assessment of depression. The one subject who continually smoked and developed depression had significantly reduced his smoking rate by 50% for several weeks. Several hypotheses have been posited to explain the higher risk of major depression after smoking cessation, but none have been systematically tested: (1) Smokers who are predisposed to depression have protected themselves from depression by smoking and suffer from depression upon cessation because of the loss of the affect regulation properties of nicotine (i.e., the "self-medication" hypothesis).[13,25] (2) Genetic factors may predispose individuals to both smoking and depression.[26]

The second aim of the present study was to identify baseline risk factors for the development of major depression after smoking cessation. As hypothesized, those who developed major depression scored significantly higher on the BDI and the BAI at baseline than those who did not develop depression. While each of the individual scores were not within the clinical range for depression or anxiety, these relatively higher scores suggest that subjects with subsyndromal mood disturbances at baseline may be at higher risk for the development of depression after smoking cessation. Other research has shown that nonclinical depression scores predict smoking relapse.[10] It is important to note that no significant differences in anxiety or withdrawal symptoms were found at the end of treatment, when major depression was diagnosed. Thus, it is difficult to conclude that the major depression was due to some general state of negative affect or withdrawal syndrome. One final difference between the MDD group and the non-MDD group was the greater HAM-D scores obtained by the MDD group at the end of treatment, but not at baseline. This may reflect the sensitivity of the HAM-D to diagnose depression.

Unlike previous studies, we used the SCID to assess MDD. Other measures of depression, such as the Center for Epidemiological Studies—Depression (CES-D) scale, measure depressive symptoms, not major depression, and may be sensitive to other Axis I diagnoses, such as anxiety and substance abuse disorders.[16] We concur with Glassman,[16] who argues that the development of depression after smoking cessation is not simply the random onset of depression in those who are at risk for depression, given that the depression appears to remit upon resumption of smoking. The sensitivity of the SCID to diagnose depression and the relatively similar withdrawal scores between the MDD group and the non-MDD group suggest that the depression goes beyond withdrawal-related dysphoria.

Several caveats need to be addressed that preclude further interpretation of these data. First, the nonparametric tests may not have been as sensitive to group differences, but normality of the data could not be assumed with our small number of subjects. Second, the number of dropouts who developed major depression could not be obtained; therefore, the incidence of major depression may be underestimated in our sample. Third, this was a highly selected sample of treatment-motivated smokers. It is unknown whether similar results would be obtained in self-quitters in the general population. Fourth, this study would be best conducted by examining the development of depression after smoking cessation in a placebo group. Finally, other comparison groups, such as smokers who were not trying to quit, were not included. Instead, this paper represents the first descriptive, prospective study to investigate the development of MDD after smoking cessation using the SCID, and future studies should include relevant comparison groups.

Despite these cautions, health practitioners should be aware that some of their patients may be at risk for the development of MDD after smoking cessation. Conversely, patients presenting with MDD should be queried about their smoking status and recent quit attempts. Furthermore, large scale epidemiologic studies may be underestimating the rate of depression in the general population, since self-medication by cigarette smoking may mask depression.[27] Future studies with larger samples would better estimate the risk and prevalence of developing MDD after smoking cessation, as well as the efficacy of antidepressant therapy in the treatment of smoking cessation.

Drug names: clonidine (Catapres), fluoxetine (Prozac).

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