ORIGINAL ARTICLE

Nortriptyline and Cognitive-Behavioral Therapy in the Treatment of Cigarette Smoking

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Background: A history of major depressive disorder (MDD) predicts failure to quit smoking. We determined the effect of nortriptyline hydrochloride and cognitive-behavioral therapy on smoking treatment outcome in smokers with a history of MDD. The study also addressed the effects of diagnosis and treatment condition on dysphoria after quitting smoking and the effects of dysphoria on abstinence.

Methods: This was a 2 (nortriptyline vs placebo) × 2 (cognitive-behavioral therapy vs control) × 2 (history of MDD vs no history) randomized trial. The participants were 199 cigarette smokers. The outcome measures were biologically verified abstinence from cigarettes at weeks 12, 24, 38, and 64. Mood, withdrawal, and depression were measured at 3, 5, and 8 days after the smoking quit date.

Results: Nortriptyline produced higher abstinence rates than placebo, independent of depression history. Cognitive-behavioral therapy was more effective for participants with a history of depression. Nortriptyline alleviated a negative affect occurring after smoking cessation. Increases in the level of negative affect from baseline to 3 days after the smoking quit date predicted abstinence at later assessments for MDD history–negative smokers. There was also a sex-by-depression history interaction; MDD history–positive women were less likely to be abstinent than MDD history–negative women, but depression history did not predict abstinence for men.

Conclusions: Nortriptyline is a promising adjunct for smoking cessation. Smokers with a history of depression are aided by more intensive psychosocial treatments. Mood and diagnosis interact to predict relapse. Increases in negative affect after quitting smoking are attenuated by nortriptyline.

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THE LINK between cigarette smoking and depressed mood is well established in population studies.[1-4] There is also evidence that diagnosable depression, particularly major depressive disorder (MDD), and a diagnosis of nicotine dependence are correlated in the general population.[5] Individuals with current or historical depressive disorders seem to be overrepresented among those seeking smoking treatment.[6,7] Smokers with a history of MDD may experience more severe mood-related symptoms when they quit smoking.[8,9]

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This study investigated the efficacy of antidepressant therapy as smoking treatment for MDD history–positive smokers. Antidepressants that have been studied in smoking cessation include imipramine hydrochloride,[10] doxepin hydrochloride,[11] bupropion hydrochloride,[12,13] and fluoxetine hydrochloride.[14] The results of imipramine[10] and doxepin[11] studies are mixed and difficult to interpret because of methodological problems. Bupropion has shown short-term efficacy in small trials.[12,13] Recently, a large-scale pharmaceutical industry–sponsored study was sufficiently convincing that the drug received a Federal Drug Administration indication for the treatment of cigarette smoking.[15] Results from multisite pharmaceutical industry–sponsored studies of fluoxetine have not been published, but a secondary analysis of part of that data set suggested that participants reporting depressive symptoms at study enrollment showed significantly improved cessation rates with the administration of active drug.[14]

Nortriptyline hydrochloride has adrenergic activity; therefore, it might be useful in smoking cessation. Nortriptyline is an inexpensive generic drug. Also, therapeutic serum levels, at least for the treatment of depression, are known (190-532 nmol/L),[16] thus providing initial treatment parameters.

One study by Hall and colleagues[7] found that smokers with a history of de-

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PARTICIPANTS AND METHODS

PARTICIPANTS

This study was approved by the Institutional Review Board of the University of California, San Francisco. Participants were recruited by public service and newspaper announcements. After giving written, informed consent, 248 individuals completed the Diagnostic Interview Schedule,[19] and their conditions were evaluated for study enrollment. Three withdrew for personal reasons before random assignment. We excluded 46 patients: 27 because of electrocardiographic abnormalities, 11 because of a current MDD, and 8 for other reasons. Thus, 199 participants were randomly assigned to 1 of 2 psychological treatments, CB vs HE therapy, and to 1 of 2 drug treatments, active nortriptyline vs placebo. They were men (n = 89) and women (n = 110), aged 21 to 65 years, who smoked 10 or more cigarettes per day, and who wanted to quit smoking.

Individuals who met the criteria for MDD within 3 months of the baseline were excluded and referred for depression treatment. Individuals who were taking prescribed psychotropic drugs or who showed evidence of alcohol or other nonnicotine drug use were excluded. Individuals who had taken a monoamine oxidase inhibitor within the last 2 weeks were excluded even if they were not currently taking that drug. A history of MDD was diagnosed in 65 (32.7%) of the participants. Fifty participants reported recurrent episodes.

PROCEDURES

Nortriptyline was dispensed from week 1 through week 12. Psychological treatment occurred from week 4 through week 12. The smoking quit date was during week 5 so that therapeutic nortriptyline levels could be reached.

Participants were assessed at baseline on demographic variables, mood, depressive and withdrawal symptoms, and current and historical MDD. Additional assessments were held at weeks 12, 24, 38, and 64. Psychological measures were completed and smoking status was determined at each assessment. Participants were asked if they had smoked at all, even a puff, during the last week. If they had not, and their expired air carbon monoxide level was 10 ppm or less, their urine sample was analyzed for cotinine. If cotinine levels were 341 nmol/L or less, participants were coded as abstinent. In addition to serum samples for nortriptyline levels, compliance was assessed by capsule counts (capsules allotted – capsules returned). We determined side effects by a checklist administered at baseline and at weeks 1 through 4 and 6.

Participants completed the Profile of Mood States (POMS)[20] and a withdrawal scale[21] at 3, 5, and 8 days after their smoking quit date. The Beck Depression Inventory[22] was completed 8 days after the smoking quit date.

Participants were stratified on MDD history vs no MDD history and on number of cigarettes smoked and randomly assigned from within stratification blocks to the 4 experimental conditions using a computerized randomization program.

MEASURES

Bachelor's and master's level survey workers, trained by one of us (R.F.M.), administered the computerized Diagnostic Interview Schedule.[23] Based on the Diagnostic Interview Schedule, participants were classified as MDD history positive or MDD history negative. Negative affect was assessed using the POMS total mood disturbance (TMD) score. We assessed depressive symptoms during the past week by the Beck Depression Inventory and trait anxiety by the State-Trait Anxiety Inventory Trait scale.[24]

We administered 2 smoking scales, the Shiffman Tobacco Withdrawal Scale,[21] a widely used scale that shows changes in scores as a function of time since last cigarette smoked and differentiates between partial and total abstinence, and the Fagerstrom Tolerance Questionnaire,[25,26] a measure of tobacco dependence. High scores predict smoking treatment failure and correlate with physiological smoking-induced changes.

TREATMENT INTERVENTIONS

Drug Treatment

Medication was placebo controlled and double blind. Placebo and active drug were identical in appearance. Participants met with study physicians at week 1 to begin the administration of medication and at weeks 2 and 3 for the administration of medication and a review of the side effects. The drug dose was titrated to therapeutic levels for depression. Participants received nortriptyline hydrochloride, 25 mg/d, for 3 days; the dose was then increased to 50 mg/d for 4 days. Serum levels were assessed at week 2; the dose was increased to 75 mg/d if a therapeutic level had not been reached. Serum levels were reassessed at week 4, and the dose increased to 100 mg/d, if necessary, and at week 6, when the dosage was titrated downward, if necessary. The modal dose was 100 mg/d. Whenever titration occurred for a participant receiving active drug, the dose was titrated for a participant receiving placebo in the same cohort. Participants continued to receive the maintenance dose of medication until week 12, and the medication was tapered during week 13.

pression were more likely to be abstinent if treated with 10 sessions of cognitive-behavioral (CB) therapy than if treated with 5 sessions of health education therapy. Zelman and colleagues[17] found that dysphoric smokers were helped by a supportive treatment to a greater extent than nondysphoric smokers. Hall and colleagues,[18] using a control that was equivalent in contact time to cognitive-behavioral therapy, failed to replicate their original findings; one purpose of the proposed study was an attempt to recapture the findings of the original study. Thus, we compared the 10-session CB intervention for smoking cessation with the 5-session health education (HE) control intervention used in the original study.

The present study was a $2 \times 2 \times 2$ factorial design in which medication (nortriptyline vs placebo) was crossed with CB vs HE intervention and with presence vs absence of a history of MDD. We hypothesized the following: (1) Participants with a history of MDD would show higher abstinence rates with the administration of nortriptyline than with the administration of placebo. No differences were hypothesized for MDD history–negative participants. (2) Participants with a history of MDD would show higher absti-

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Psychological Treatment

CB Treatment. The central premise of the CB treatment, described in detail elsewhere,[7] was that thoughts, activities, and mood interact to influence smoking. Sessions focused on mood management skills to manage dysphoria and maintain nonsmoking, including methods to increase the frequency of pleasant activities and decrease relapse-related thoughts, by thought stopping, increasing pleasant thoughts, and rational-emotive techniques. Techniques for increasing positive social contacts, decreasing negative contacts, and improving relationships were developed.

Participants met for ten 2-hour group sessions (with 5-11 members) for 8 weeks. The therapist manual is available (S.M.H., R.F.M., and K. Organista, PhD, unpublished data, 1992).

HE Intervention. The HE intervention, also described in detail elsewhere,[7] provided health-related information and facilitated discussion. A core element was the development of a plan to quit smoking and weekly modification of that plan. Methods used included paper-and-pencil exercises, informational handouts, brief didactic presentations, homework assignments, and smoking monitoring. Participants met for five 90-minute sessions (with 5-11 members) for 8 weeks.

PROVIDERS

The therapists were 3 doctoral-level clinical psychologists. All had experience in CB and psychoeducational interventions. All therapists treated participants in each of the 4 experimental conditions. Therapists were supervised weekly by two of us (R.F.M. and G.H.). Adherence to the protocol was monitored; if situations arose that were not in the protocol, audiotapes were reviewed and a standard response was developed. Medication was prescribed by 1 of 2 psychiatric residents, who were supervised by two of us (V.I.R. and K.L.S.).

STATISTICAL METHODS

The principal data analysis method was a generalized linear model (GLM), a generalization of the classic linear model estimated using likelihood functions instead of least squares.[27] Generalized linear models allow use of repeated measurements when there is missing data, without excluding participants with data missing or imputing values.[28,29] We used a computer program (PROC Mixed, SAS Institute Inc, Cary, NC) to estimate and test the GLM. When abstinence was the dependent variable, we also used another computer program (GLMMIX Macro, SAS Institute Inc)[30] that interacts with the first program mentioned (PROC Mixed) to modify it so that it is appropriate for dichotomous data. To evaluate the 3 hypotheses (hypotheses 1, 2, and 5) that predicted abstinence, abstinence status at weeks 12, 24, 38, and 64 were the dependent variables. Hypotheses 1 and 2 were tested by a 2 (active vs placebo drug) by 2 (CB vs HE intervention) × 2 (MDD vs no MDD history) model. Hypothesis 5 was tested by a model that included the baseline POMS-TMD score, the day 3 POMS-TMD score, and the 3 design variables (drug, psychological treatment condition, and diagnostic status) and their interaction as independent variables.

For hypotheses 3 and 4, which predicted changes in dysphoria after the quit date, we completed 3 parallel analyses. In the first analysis, the dependent variables were the POMS-TMD scores at baseline and at days 3, 5, and 8 after the smoking quit date. In the second analysis, withdrawal scores replaced POMS scores. In the third analysis, dependent variables were Beck Depression Inventory scores at baseline and at day 8. The 3 design variables and their interaction were the independent variables.

To provide a comparison with recent antidepressant studies,[15] we present continuous abstinence rates (abstinent at each assessment) and use a χ^2 test to evaluate this univariate variable.

We evaluated the effects of sex and its interaction with the 3 design variables on abstinence rates at weeks 12 through 64 using 3 GLM models computed using a macro (GLMMIX). A parallel model was used to determine therapist effects. The effects of nortriptyline levels and capsules ingested on abstinence rates at the 4 assessments were evaluated by 2 GLM analyses. For nortriptyline, the independent variables were serum level, diagnostic category, and their interaction; for capsules, the independent variables were active drug vs placebo, capsule count, and their interaction. For GLM analyses, if the overall effect was significant, post hoc contrasts were completed using a computer program (PROC Mixed) and, if appropriate, a macro (GLMMIX). Effect sizes are expressed as odds ratios (ORs) and confidence intervals (CIs).

We used Student t tests and χ^2 tests to determine whether there were differences between participants with and participants without missing data at assessments on baseline demographic, smoking, mood, and psychiatric variables ($P>.05$, all comparisons).

Analysis of variance and χ^2 tests were used to evaluate baseline differences among treatment conditions. A χ^2 test was used to evaluate the rate of occurrence of side effects. The tests were 2 tailed, with $P<.05$ for all comparisons.

nence rates with the CB intervention than with the HE intervention. No differences were hypothesized for MDD history–negative smokers. (3) Major depressive disorder history–positive participants would show greater increases in dysphoria while quitting smoking than MDD history–negative participants. (4) Nortriptyline would be more effective than placebo in reducing the dysphoria occurring after quitting smoking in MDD history–positive participants only, with no difference predicted for MDD history–negative participants. (5) Independent of MDD history, participants with smaller increases in dysphoria immediately after quitting smoking would be more likely to be abstinent at later assessments than participants with greater increases in dysphoria after quitting smoking.

RESULTS

PARTICIPANT CHARACTERISTICS

The demographic, smoking, and psychiatric characteristics of the participants in each experimental group are given in **Table 1**.

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Table 1. Data for Variables by Psychological Treatment and Drug Condition*

Variables	Drug Condition/Psychological Treatment			
	Active Drug/CB Intervention (n = 51)	Active Drug/HE Intervention (n = 48)	Placebo Drug/CB Intervention (n = 52)	Placebo Drug/HE Intervention (n = 48)
Demographic				
Age†	41.7 (9.4)	40.7 (9.6)	40.0 (9.9)	39.4 (9.7)
Sex (female)‡	22 (43)	28 (58)	30 (58)	30 (63)
Race (white)‡	45 (88)	41 (87)	45 (87)	42 (89)
Married or with a partner (yes)‡	22 (43)	16 (34)	19 (37)	25 (53)
Smoking†				
No. of cigarettes smoked per day	22.1 (11.9)	24.9 (12.1)	21.1 (7.6)	22.5 (8.5)
Fagerstrom Tolerance Scale score	5.6 (2.1)	5.6 (2.2)	5.4 (2.2)	5.5 (2.1)
Years a regular smoker	23.0 (10.7)	22.2 (10.3)	21.7 (10.0)	21.7 (10.4)
Carbon monoxide level, ppm	24.0 (10.2)	25.3 (11.9)	25.8 (12.6)	24.1 (12.4)
Prior quit attempts	3.0 (1.2)	2.6 (1.4)	2.8 (1.2)	2.5 (1.5)
Psychiatric				
Beck Depression Inventory score†	8.6 (7.2)	9.5 (7.5)	7.7 (6.5)	9.7 (6.8)
POMS-TMD*	30.7 (38.1)	31.4 (33.5)	22.6 (30.5)	33.4 (32.2)
Shiffman Withdrawal Scale score†	50.4 (11.1)	55.5 (10.0)	55.5 (11.8)	56.9 (12.3)
Speilberger State Anxiety Score†	40.7 (11.6)	39.3 (11.3)	39.0 (10.2)	41.9 (10.6)
Confidence Scale total score†	47.1 (14.8)	48.8 (15.5)	43.8 (14.9)	46.9 (16.0)
History of MDD‡	17 (33.3)	15 (31.3)	17 (32.7)	16 (33.3)

*There were no significant differences among treatment conditions, except that psychological treatment conditions differed in the presence or absence of previous quit attempts (χ^2_1 [N = 196] = 6.9, P<.009) and drug condition on baseline withdrawal scores (t_{195} = 1.9, P = .53). Neither potential confounding variable correlated significantly with abstinence rates at any assessment. CB indicates cognitive-behavioral; HE, health education; POMS, Profile of Mood States; TMD, total mood disturbance; and MDD, major depressive disorder.

†Data are given as the mean (SD).

‡Data are given as the number (percentage) of subjects.

Table 2. Baseline Mood- and Withdrawal-Related Variables for Participants With and Without a History of Major Depressive Disorder (MDD)

Variables	MDD History–Negative Participants (n = 134)	MDD History–Positive Participants (n = 65)
Demographic		
Age*	40.5 (9.5)	41.1 (9.9)
Sex (female)†	68 (49)	42 (64)
Race (white)†	114 (87)	59 (89)
Married or with a partner (yes)†‡	66 (50)	16 (24)
Smoking		
No. of cigarettes smoked per day*	23.0 (10.2)	21.8 (10.4)
Fagerstrom Tolerance Scale score*	5.5 (2.1)	5.5 (2.2)
Years a regular smoker*	22.0 (9.7)	22.2 (11.4)
Carbon monoxide level, ppm*	24.2 (10.6)	26.0 (13.7)
Prior quit attempts†	121 (92)	60 (92)
Psychiatric*		
Beck Depression Inventory score‡	7.2 (5.6)	12.1 (8.3)
Profile of Mood States total mood disturbance	21.4 (29.0)	45.9 (36.8)
Shiffman Withdrawal Scale score	54.0 (11.6)	56.1 (11.7)
Speilberger State Anxiety score	38.7 (10.4)	39.3 (8.4)
Confidence Scale total score	46.6 (15.2)	46.4 (15.5)

*Data are given as the mean (SD).

†Data are given as the number (percentage) of subjects.

‡There were no significant differences, except that MDD history–positive participants were less likely to be married or have a partner than MDD history–negative participants (χ^2_1 [N = 197] = 11.6, P<.001) and to have higher Profile of Mood States total mood disturbance (t_{195} = 4.90, P<.001) and Beck Depression Inventory (t_{190} = 5.03, P<.001) scores.

The demographic, smoking, and psychiatric characteristics of MDD history–positive and MDD history–negative participants are given in **Table 2**.

ATTRITION

Forty-seven (24%) of the participants reported that they did not want to complete treatment. Of these participants, 23 dropped out because of personal reasons, 5 dropped out because of medication side effects (4 in the active drug group and 1 in the placebo group), and 11 dropped out because of program issues (eg, dislike of the group format); 1 participant moved, 1 had an unrelated medical problem, and 6 gave no reason for dropping out. There were no differences between psychological interventions (χ^2_1 [N = 199] = 1.51, P = .22) or between diagnostic categories (χ^2_1 [N = 199] = .63) in dropout rates, but participants in the placebo group had a higher overall dropout rate (30%) than did participants in the active drug group (17%) (χ^2_1 [N = 199) = 4.54, P = .04; OR, 2.07; 95% CI, 1.05-4.06).

The no-show rates at each assessment were as follow: week 12, 19%; week 24, 17%; week 38, 20%; and week 64, 17%. There were no significant differences in the number of assessments missed for any of the design variables (for the psychological treatment condition, t_{197}<.42; for the drug treatment condition, t_{197} = 1.63, P = .25; and for the diagnosis, t_{197} = .72).

ABSTINENCE RATES

The main effect for the drug was significant (χ^2_1 [N = 199] = 4.34, P = .04; OR, 2.42; 95% CI, 1.75-3.35), as

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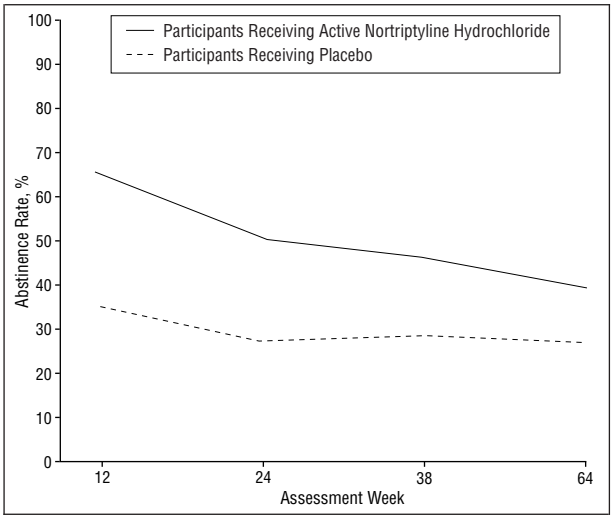

Figure 1. *Abstinence rates across time for participants receiving active nortriptyline hydrochloride (n = 99) and placebo (n = 100). The effect of drug is significant across weeks 12 through 64 whether the dependent variable is abstinence at each assessment (P = .04) or continuous abstinence for the year (P = .02). There were no significant main or interaction effects for diagnosis (P>.05, all comparisons).*

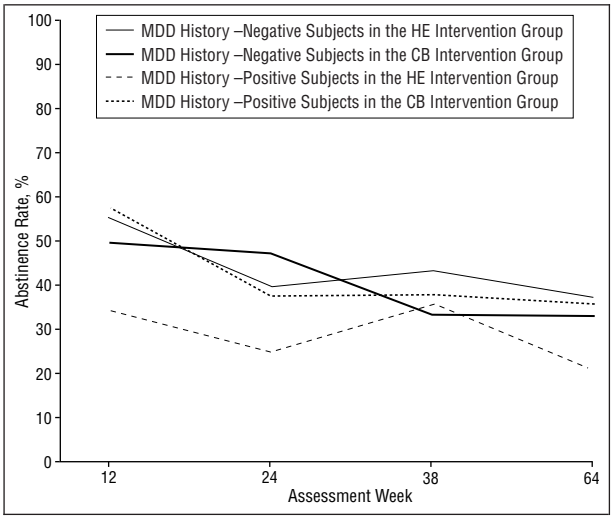

Figure 2. *Abstinence rates across time for those in the cognitive-behavioral (CB) (n = 100) vs health education (HE) (n = 99) intervention by major depressive disorder (MDD) history–negative (n = 134) vs MDD history–positive (n = 65) diagnosis. The significant interaction effect (P = .05) reflects a significantly poorer abstinence rate for MDD history–positive subjects (n = 31) than for MDD history–negative subjects (n = 68) in the HE intervention group ($\chi^2_{1,68}$ = 6.44, P = .01; OR, 1.70; 95% CI, 1.00-2.98) and no significant difference (P = .91) between MDD history–positive (n = 34) and MDD history–negative (n = 66) participants in the CB intervention group.*

was the treatment condition × diagnosis interaction (χ^2_1 [N = 199] = 3.84, P = .05). The main effect of assessment (at weeks 12, 24, 38, and 64) was also significant (χ^2_3 [N = 199] = 10.33, P = .02; OR, 0.78; 95% CI, 0.68-0.90), indicating a decline in abstinence rates for both conditions from week 12 to week 64. There were no other significant effects (P<.05), including the hypothesized diagnosis × drug interaction (χ^2_1 [N = 199]<.92), the psychological treatment condition × drug interaction (χ^2_1 [N = 199]<.98), or the diagnosis × psychological treatment condition × drug interaction (χ^2_1 [N = 199]<.59). The abstinence rates at each assessment are shown in **Figure 1**.

Table 3. Abstinence Rates at All Assessments by Baseline Diagnosis, Psychological Treatment, and Drug Dose*

Characteristics	Week 12	Week 24	Week 38	Week 64
MDD history–negative participants				
Health education intervention group				
Receiving placebo	**36** (31)	**30** (25)	**33** (25)	**27** (22)
(n = 32)	28	27	24	26
Receiving active drug	**74** (61)	**46** (39)	**48** (42)	**44** (36)
(n = 33)	27	28	29	27
Cognitive behavioral intervention group				
Receiving placebo	**30** (20)	**31** (23)	**25** (20)	**24** (20)
(n = 35)	23	26	28	29
Receiving active drug	**66** (56)	**61** (50)	**39** (32)	**41** (35)
(n = 34)	29	28	28	29
MDD history–positive participants				
Health education intervention group				
Receiving placebo	**21** (19)	**15** (13)	**20** (13)	**15** (13)
(n = 16)	14	13	10	13
Receiving active drug	**47** (47)	**33** (33)	**46** (40)	**23** (20)
(n = 15)	15	15	13	13
Cognitive behavioral intervention group				
Receiving placebo	**54** (41)	**21** (18)	**27** (24)	**36** (29)
(n = 17)	13	14	15	14
Receiving active drug	**62** (47)	**50** (41)	**46** (35)	**29** (24)
(n = 17)	13	14	13	14

**Abstinence rates computed with missing data omitted are in boldface. Abstinence rates with missing data coded or indicative of smoking are in parentheses. The sample size in the first column indicates the number of participants originally assigned to the condition; the columns for weeks 12, 24, 38, and 64 are the number of subjects assessed for the reference cells at that point. MDD indicates major depressive disorder.*

In the active drug condition, 24% of the participants achieved continuous abstinence; in the placebo drug condition, 12% achieved continuous abstinence (χ^2_1 [N = 199] = 5.03, P = .02; OR, 2.3; 95% CI, 1.1-5.0). We concluded that there was evidence of superiority of nortriptyline vs placebo for cigarette smokers, for MDD history–negative and MDD history–positive smokers.

The abstinence rates by psychological treatment condition and diagnostic grouping are shown in **Figure 2**. As Figure 2 indicates, MDD history–positive participants assigned to the CB intervention achieved abstinence rates comparable with the MDD history–negative participants, but MDD history–positive subjects assigned to the HE intervention were less likely to be abstinent than those assigned to the CB intervention.

We concluded that we achieved support for the second hypothesis, that participants with a history of MDD would be more likely to benefit from CB therapy than would participants without a history of MDD. Abstinence rates by diagnosis, psychological treatment condition, and active vs placebo drug are given in **Table 3**.

Abstinence rates did not differ because of therapist, the interaction of therapist with drug, psychological treatment, or drug × psychological treatment condition (P>.05, all comparisons).

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Table 4. Maintenance Nortriptyline Serum Levels by Abstinence Status at Each Assessment for 86 Participants Receiving Active Nortriptyline Who Provided Blood Samples at Week 6*

Participant Status	Week 12	Week 24	Week 38	Week 64
Relapsed	132.2 (101.5)	151.6 (120.8)	162.3 (107.5)	166.1 (116.7)
Abstinent	209.8 (116.3)	218.9 (108.3)	216.6 (112.1)	219.6 (117.8)

*Data are given as the mean (SD) level of nortriptyline (given as nanomoles per liter). The maintenance nortriptyline serum level predicts abstinence at later assessments (P<.001). Nortriptyline was given as nortriptyline hydrochloride.

PREDICTION OF ABSTINENCE BY NORTRIPTYLINE SERUM LEVELS AND NET CAPSULE COUNT

Nortriptyline serum levels for participants who were assigned to receive active nortriptyline and who were abstinent the week before the blood draw predicted abstinence at weeks 12, 24, 38, and 64 (χ^2_1 [N = 86] = 14.28, $P<.001$; OR, 1.02; 95% CI, 1.01-1.03). Abstinent participants were selected because smoking is known to result in lowered nortriptyline levels.[31] Of the participants who received nortriptyline for whom we were able to obtain serum samples at week 6, 44 (51%) achieved serum levels considered therapeutic for the treatment of MDD. Mean week 6 nortriptyline serum levels for abstinent and smoking subjects by week are given in **Table 4**.

Capsules ingested did not differ between conditions (χ^2_1 [N = 199] = 1.43, $P = .23$) nor did capsules interact with drug (χ^2_1 [N = 199]<.68). Controlling for these 2 variables, drug (abstinent vs placebo) remained significant (χ^2_1 [N = 199] = 4.32, $P = .04$; OR, 3.03; 95% CI, 1.07-8.57).

SIDE EFFECTS

Of the 14 potential side effects (dry mouth, rash, weight gain, lightheadedness, shaky hands, constipation, blurry vision, sexual problems, difficulty in urinating, racing heart, swollen legs, chest pain or pressure, shortness of breath, and "other"), postbaseline endorsement rates differed between drug condition for 4: (1) dry mouth (active = 78%; placebo = 33%; χ^2_1 [N = 198] = 39.6, $P<.001$; OR, 7.00; 95% CI, 3.73-13.17); (2) lightheadedness (active, 49%; placebo, 22%; χ^2_1 [N = 198] = 16.01, $P<.001$; OR, 2.42; 95% CI, 1.85-6.35); (3) shaky hands (active = 23%; placebo = 11%; χ^2_1 [N = 198] = 5.11, $P = .02$; OR, 2.42; 95% CI, 1.11-5.29); and (4) blurry vision (active = 16%; placebo = 6%; χ^2_1 [N = 198] = 5.11, $P = .02$; OR, 3.00; 95% CI, 1.12-7.99).

SEX EFFECTS

Sex interacted with diagnostic category (χ^2_1 [N = 199] = 9.08, $P = .002$), not with drug (χ^2_1 [N = 199] = 3.33, $P = .07$) or psychological treatment condition (χ^2_1 [N = 199]<1, $P = .93$). Post hoc analyses indicated poorer abstinence rates for MDD history–positive women than for MDD history–negative women ($\chi^2_{1,110}$ = 9.82, $P = .002$; OR, 2.05; 95% CI, 1.32-3.23) but not for MDD history–positive men ($\chi^2_{1,89}$ = 1.66, $P = .20$). For women, the abstinence rates were as follow: week 12, MDD history positive = 38%, MDD history negative = 53%; week 24, MDD history positive = 22%, MDD history negative = 47%; week 38, MDD history positive = 29%, MDD history negative = 39%; and week 64, MDD history positive = 20%, MDD history negative = 37%. For men, the abstinence rates were as follow: week 12, MDD history positive = 61%, MDD history negative = 52%; week 24, MDD history positive = 45%, MDD history negative = 37%; week 38, MDD history positive = 47%, MDD history negative = 36%; and week 64, MDD history positive = 37%, MDD history negative = 31%.

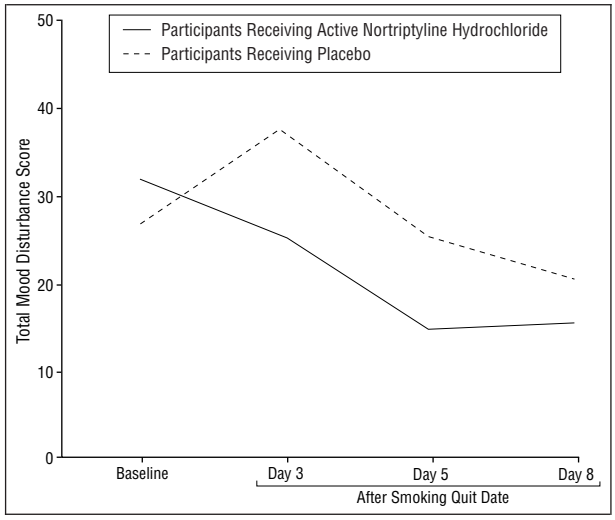

Figure 3. *Profile of Mood States Total Mood Disturbance scores for participants receiving active nortriptyline hydrochloride and placebo at baseline (n = 192) and at days 3 (n = 139), 5 (n = 119), and 8 (n = 130) after the smoking quit date. The significant drug × assessment interaction (P = .02) reflects a downward slope for participants receiving active drug ($F_{3,181}$ = 8.38, P = .001) and an upward slope for participants receiving placebo ($F_{3,178}$ = 2.55, P = .06).*

CHANGES IN NEGATIVE AFFECTIVE STATES AS A FUNCTION OF DIAGNOSTIC AND DRUG CONDITION

For POMS-TMD score, there was a significant drug (active vs placebo) by assessment (baseline and days 3, 5, and 8) interaction effect ($F_{3,359}$ = 3.30, $P = .02$). As **Figure 3** shows, POMS-TMD scores for participants given placebo increased from baseline to day 3, while the scores for those given active drug decreased. There was also a significant main effect for assessment ($F_{3,359}$ = 6.77, $P = .001$.) The hypothesized diagnostic status by assessment interaction failed to meet traditional levels of significance ($F_{3,359}$ = 2.47, $P = .06$). The POMS-TMD scores tended to decrease over time for MDD history–positive participants from baseline to day 8 (baseline mean = 45.93, SD = 36.83; day 3 mean = 38.36, SD = 36.08; day 5 mean = 24.71, SD = 26.85; and day 8 mean = 22.72, SD = 33.52). For MDD history–negative participants, the POMS-TMD scores tended to increase from baseline to day 3 (baseline mean = 21.37, SD = 29.03; day 3

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mean = 28.11, SD = 33.37) and decrease thereafter (day 5 mean = 17.67, SD = 28.03; day 8 mean = 15.53, SD = 27.39). There were no significant effects for Beck Depression Inventory ($P>.05$ for all) or total withdrawal symptoms ($P>.05$ for all).

PREDICTIONS OF ABSTINENCE BY POSTQUIT MOOD CHANGES

We hypothesized that increases in the POMS-TMD score occurring from baseline to the smoking quit date would predict lower rates of abstinence. The day 3 score was used because it showed the greatest change from baseline. Controlling for the baseline POMS-TMD score, the day 3 score interacted with diagnostic history (χ^2_1 [N = 199] = 5.26, $P = .02$). The POMS-TMD scores at baseline and at day 3 by diagnostic condition for subjects smoking and abstinent at weeks 12 and 64 are given in **Table 5**. Only 2 weeks were selected for clarity of presentation. Data at weeks 24 and 38 show similar patterns and magnitude of change.

As Table 5 indicates, the postquit increase in poor mood predicted abstinence for MDD history–negative participants only.

Table 5. POMS-TMD Scores for Participants With and Without a History of Major Depressive Disorder, Smoking vs Abstinent, Weeks 12 and 64*

Major Depressive Disorder History	Abstinent Participants	Smoking Participants
Negative (n = 134)		
Week 12	(n = 47)	(n = 38)
Baseline	21.4 (30.2)	19.5 (26.3)
Day 3	26.3 (31.4)	28.4 (32.3)
Week 64	(n = 31)	(n = 53)
Baseline	19.2 (29.4)	20.9 (28.0)
Day 3	24.1 (26.4)	30.6 (37.4)
Positive (n = 65)		
Week 12	(n = 19)	(n = 23)
Baseline	42.4 (33.8)	50.8 (38.2)
Day 3	32.3 (40.2)	45.8 (32.5)
Week 64	(n = 10)	(n = 31)
Baseline	58.6 (46.0)	42.3 (34.4)
Day 3	20.0 (34.3)	43.5 (32.3)

*Data are given as the mean (SD) at baseline and day 3. POMS indicates Profile of Mood States; TMD, total mood disturbance. Major depressive disorder history-negative participants showed increased POMS-TMD scores from baseline to day 3, and the magnitude of this increase predicted smoking at weeks 12 through 64 ($\chi^2_{1,134} = 5.48$, P = .02; OR, 1.01; 95% confidence interval, 1.00-1.01). Major depressive disorder history-positive participants showed decreased POMS-TMD scores for baseline to day 3, but the magnitude of the decrease was not a significant predictor of smoking status ($\chi^2_{1,65} = 2.26$, P = .13).

COMMENT

The outcome data suggest that nortriptyline is a useful adjunct to smoking cessation efforts. This is supported by the correlation between serum levels and abstinence status. That it reflects more than compliance is indicated by the sustained significance of nortriptyline dose when net capsules ingested for active and placebo treatment were entered into the statistical model. Although there were differences in side effects between the active and placebo groups, they were not perceived as sufficiently troublesome to cause a high dropout rate. In fact, the dropout rate for participants in the active drug group was less than that for participants in the the placebo group.

Industry-sponsored studies have garnered a Federal Drug Administration indication for bupropion. Yet nortriptyline, a generic drug, is less expensive. Contrary to hypotheses, there was not a differential abstinence effect for smokers with a history of MDD using nortriptyline. These findings parallel those reported by others using bupropion.[13,14] These 2 antidepressant drugs have similar effects on smoking cessation; both have effects on noradrenergic transmission, although effects on other neurotransmitter systems may differ between the 2 drugs. Independent of diagnosis, nortriptyline seems to have alleviated the increases in poor mood that occurred the first few days after smoking cessation. This finding has implications for the use of antidepressants to ameliorate the negative mood that follows smoking cessation in non–clinically depressed patients, as well as for use of the drug for instances of poor mood that are not part of a diagnosable disorder. It could be argued that differences in rates of smoking cessation among the 4 experimental cells could have confounded the observed differences in mood between the active and placebo drug conditions. We did not collect smoking data on days 3, 5, and 98, so we cannot definitely refute this argument. However, the effects observed are not easily explainable by possible differences in cessation rates. Dysphoria decreased from baseline to day 3 in participants in the nortriptyline treatment group and increased in participants in the placebo group. Increases in dysphoria are frequently noted after quitting smoking[8,9]; therefore, the observed differences between the drug conditions are not likely to be due to confounding by smoking quit rates.

We replicated the original findings that MDD history–positive participants are differentially helped by a 10-session CB intervention when it is compared with a 5-session HE intervention.[7] These results contrast with a lack of significant enhancement of outcome for MDD history–positive participants when therapeutic contact time was held equivalent in the control condition.[17] Thus, increased psychotherapeutic contact may differentially benefit smokers with a depressive history. This interpretation of the data is further supported by the failure of the psychotherapeutic condition to differentially alter cessation-induced changes in mood.

A history of MDD has predicted poor treatment outcome in some studies[6] but not others.[7,17] Only a few reported sex differences, and lack of analysis for such differences may explain the inconsistencies in the literature.[6,32]

The results do not support the hypothesis that MDD history–positive participants would have a greater increase in negative affect after quitting smoking than MDD history–negative smokers. Indeed, while MDD history–negative smokers did show an increase in poor mood after quitting smoking, MDD history–positive smokers showed a nonsignificant decrease. These data are not consistent with earlier investigations. These earlier investigations are difficult to compare with the current study, because of lack of baseline data,[8] failure to include sub-

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jects who successfully quit,[33] or small sample size.[9] However, the failure of current data to agree with the existing literature, even though the literature is imperfect, is troubling, and the current findings should be considered tentative until replicated.

Similarly, increase in the POMS-TMD scores from baseline to 3 days after the quit date predicted failure to maintain abstinence for MDD history–negative participants but not for MDD history–positive participants. For the latter participants, a greater decrease in poor mood from baseline to day 3 was related to abstinence but not significantly so.

There are limitations to the study. First, the outcomes reported do not represent those that could be expected were nortriptyline to be used in a typical medical setting. Psychological intervention in this study provided more contact time and intensity than could be provided by most physicians. Second, this is a volunteer sample of participants who sought treatment and who were more motivated to change than the smokers encountered in physicians' practices. Third, most participants, independent of condition, were smoking at the 64-week follow-up.

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