

# Psychological Intervention and Antidepressant Treatment in Smoking Cessation

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**Background:** Sustained-release bupropion hydrochloride and nortriptyline hydrochloride have been shown to be efficacious in the treatment of cigarette smoking. It is not known whether psychological intervention increases the efficacy of these antidepressants. This study compared both drugs with placebo. It also examined the efficacy of these 2 drugs and placebo with and without psychological intervention.

**Methods:** This was a 2 (medical management vs psychological intervention)  $\times$  3 (bupropion vs nortriptyline vs placebo) randomized trial. Participants were 220 cigarette smokers. Outcome measures were biologically verified abstinence from cigarettes at weeks 12, 24, 36, and 52.

**Results:** Psychological intervention produced higher 7-day point-prevalence rates of biochemically verified abstinence than did medical management alone. With the

use of point-prevalence abstinence, both nortriptyline and bupropion were more efficacious than placebo. On rates of 1-year continuous abstinence, the 2 drugs did not differ from each other or from placebo. Psychological intervention did not differ from medical management alone on rates of 1-year continuous abstinence.

**Conclusions:** Both nortriptyline and bupropion are efficacious in producing abstinence in cigarette smokers. Similarly, psychological intervention produces better abstinence rates than simple medical management. Both drugs, and psychological intervention, have limited efficacy in producing sustained abstinence. The data also suggest that combined psychological intervention and antidepressant drug treatment may not be more effective than antidepressant drug treatment alone.

*Arch Gen Psychiatry.* 2002;59:930-936

**T**HE ANTIDEPRESSANTS bupropion hydrochloride and nortriptyline hydrochloride are useful adjuncts in the treatment of tobacco dependence. A multicenter bupropion trial reported 1-year continuous abstinence rates of 24% for 300 mg/d, 18% for 150 mg/d, 14% for 100 mg/d, and 10% for placebo. The difference from placebo was significant in the 150- and 300-mg/d groups.<sup>1</sup> A trial comparing bupropion and nicotine patch reported 1-year continuous abstinence rates of 36% for bupropion and nicotine patch, 33% for bupropion alone, 16% for nicotine patch alone, and 15% for placebo. Bupropion alone or with nicotine patch resulted in significantly higher abstinence rates than did patch alone or placebo.<sup>2</sup> Our group reported 1-year continuous abstinence rates of 24% for nortriptyline and 12% for placebo.<sup>3</sup> A second study reported that 14% of patients receiving nortriptyline and 3% of patients receiving placebo were abstinent 6 months after treatment.<sup>4</sup>

Nicotine replacement treatment (NRT) is usually more effective when provided with psychosocial treatment.<sup>5,6</sup> The impact of psychosocial interventions in antidepressant treatment for cigarette smoking is unknown. Antidepressants and NRT differ in ease of use, mode of administration, adverse effects, and effects on mood and withdrawal symptoms, all of which might contribute to differences in the role of psychosocial interventions.

Antidepressant studies have involved either psychotherapy or counseling or extensive contact with project staff, including physician reinforcement for quitting smoking,<sup>1,2</sup> multiple episodes of brief counseling by "research staff,"<sup>1,2</sup> group meetings,<sup>3,4</sup> and psychotherapy.<sup>3</sup> According to the Agency for Health Care Policy and Research guidelines<sup>7,8</sup> available at the time this study was conducted, a more typical practice-based medical management (MM) protocol would entail physician advice to quit smoking and, at most, 1 to 3 brief follow-up visits, and perhaps a refer-

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ral to a smoking cessation group. Antidepressant efficacy in such a context may differ from that obtained from more extensive psychotherapy. One important question is the effect of psychological intervention (PI) when added to antidepressant therapy.

A second question is the relative efficacy of the 2 drugs. On the basis of the extant literature, we deemed differences in efficacy between bupropion and nortriptyline unlikely, and we did not predict differences between the 2. We did expect, however, that both would produce higher abstinence rates than placebo.

Thus, the following hypotheses were proposed: (1) Abstinence rates will be higher in participants receiving active antidepressant treatment, whether bupropion or nortriptyline, during a 52-week period, than for those receiving placebo. (2) Independent of drug, abstinence rates will be higher for participants receiving PI than for those receiving MM alone. (3) Active drug conditions combined with PI will be more efficacious than the other experimental conditions in producing abstinence.

## SUBJECTS AND METHODS

### SUBJECTS

Smokers of 10 or more cigarettes per day were recruited by advertising, public service announcements, and flyers. After telephone screening, potential participants were invited to an orientation meeting. Interested individuals completed an informed consent and were invited to a baseline assessment including a physical examination, electrocardiogram, and blood draws. The sections of the Structured Clinical Interview for DSM-IV<sup>9</sup> that diagnose depression, dysthymia, and bipolar disorder were administered by master's-level clinicians. Participants were assessed on demographic variables and mood by paper-and-pencil measures and interviews administered by research staff.

Exclusionary criteria included cardiovascular disease, hyperthyroidism, seizure or bulimia, use of a monoamine oxidase inhibitor within 2 weeks, severe allergies including allergies to either experimental drug, life-threatening disease, bipolar disease, current major depressive disorder (MDD), pregnancy or lactation, use of levodopa, migraines, previous treatment for cigarette smoking with nortriptyline or bupropion, treatment for alcohol or other drug use within 6 months, psychiatric hospitalization within 1 year, use of any psychiatric medication, suicidal or psychotic symptoms, and current NRT use.

### PROCEDURES

Participants were stratified by number of cigarettes smoked, sex, and history of depression vs no history, and randomly assigned to 1 of the 6 experimental cells in a 3 (bupropion vs nortriptyline vs placebo)  $\times$  2 (MM alone vs MM+PI).

Assessments were at baseline and at weeks 12 (end of treatment), 24, 36, and 52. Participants were coded as nonsmoking if they reported smoking no cigarettes, not even a puff, during the previous 7 days, had expired carbon monoxide levels of 10 ppm or less, and had urinary cotinine levels of 60 ng/mL or less.<sup>10</sup> Adverse effects were assessed by checklist at baseline and weeks 1, 2, 3, and 6. At 52 weeks, participants indicated which drug they believed they had received and its perceived helpfulness.

### MEASURES

Negative affect was assessed with the Profile of Mood States (POMS).<sup>11</sup> On the basis of the Structured Clinical Interview for

DSM-IV, participants were classified as positive or negative for MDD. We also administered the Fagerstrom Test for Nicotine Dependence<sup>12</sup> and a adverse effects scale we developed that includes the adverse effects reported for both bupropion and nortriptyline.

## COUNSELING INTERVENTIONS

### Medical Management

Medical management was developed from the 1996 Agency for Health Care Policy and Research guidelines<sup>7</sup> and from the MM condition in the Collaborative Depression Trials.<sup>13</sup> Medical management included advice to stop smoking, antidepressant medication, adverse effects monitoring, and educational materials. It did not introduce complex or time-consuming interventions that would be impractical in primary care.

Physicians were 5 licensed psychiatric and internal medicine residents. Participants were provided written information about smoking cessation (Freedom From Smoking).<sup>14</sup> During week 1, the physician reviewed the treatment rationale and prescription instructions, discussed behavioral factors important to smoking cessation, and established a quit date during week 5. This session lasted 10 to 20 minutes. Five-minute visits were scheduled during weeks 2, 6, and 11, during which participants were queried about cessation progress. The physician responded briefly to questions and provided encouragement. Advice about specific quitting strategies was not offered.

### Psychological Intervention

All participants participated in the MM sessions previously described. In addition, they participated in 5 group sessions.

Providers were 3 master's-level counselors, the most common smoking treatment provider in the health care organizations we consulted. The group intervention was an adaptation of an intervention described in detail elsewhere<sup>3,15-17</sup> and is available from the first author (S.M.H.). The first 90-minute session was during week 4. Sessions 2 and 3 were during week 5; sessions 4 and 5 were during weeks 7 and 11, respectively. Group size ranged from 3 to 11. The intervention provided health-related information for mood management and smoking cessation, and discussion of cessation. A core element was the development of a quit-smoking plan and weekly modification of it. Methods used included monitoring of cigarette use and affective states; paper-and-pencil exercises focusing on health-related information, motivation to quit, and decreasing relapse-related thoughts; informational handouts; and brief didactic presentations.

## PHARMACOLOGIC INTERVENTIONS

Medication was placebo controlled and double blind. The sustained-release properties of bupropion rest on the formulation of the tablet's coating; placebo bupropion was not available. We encapsulated both drugs to maintain the patency of the bupropion formulation and to provide a blinded drug. All participants received capsules that were identical in number and appearance.

The University of California, San Francisco Drug Product Services prepared medication capsules. For nortriptyline, lactose placebo and active drug were encapsulated in powdered form. For bupropion, Wellbutrin SR tablets (Glaxo Wellcome Inc, Research Triangle Park, NC) or similar-sized placebo tablets were inserted into lactose-filled capsules. All capsules were secured with a gelatin mixture to prevent opening.

Nortriptyline drug dose was titrated for each participant until a therapeutic serum level (50-150 ng/mL) was obtained.

**Table 1. Baseline Variables by Psychological Intervention and Drug Condition\***

Variables	Placebo		Nortriptyline		Bupropion	
	MM (n = 37)	PI (n = 36)	Hydrochloride + MM (n = 38)	Hydrochloride + PI (n = 35)	Hydrochloride + MM (n = 36)	Hydrochloride + PI (n = 37)
Age, y†	43.4 (11.8)	39.3 (10.2)	37.8 (11.8)	40.9 (12.1)	37.1 (9.7)	37.9 (11.4)
Usual No. of cigarettes/d†	23.0 (10.6)	22.2 (9.5)	20.9 (9.3)	20.2 (7.9)	19.8 (7.5)	22.5 (9.0)
Fagerstrom Scale Score†	5.4 (2.3)	4.7 (2.0)	4.6 (2.1)	4.7 (2.3)	4.1 (2.2)	5.1 (2.3)
Years regular smoker†	24.7 (11.8)	21.2 (9.9)	19.6 (11.3)	23.1 (12.6)	19.7 (10.2)	21.2 (11.6)
Carbon monoxide, ppm†	27.8 (10.9)	25.6 (12.4)	26.0 (9.2)	25.7 (12.4)	25.4 (10.2)	31.2 (15.3)
No. of previous quit attempts†	7.0 (11.9)	6.8 (9.9)	9.0 (13.8)	5.3 (7.1)	6.3 (8.0)	4.6 (4.1)
POMS Total Mood Score†	29.8 (33.2)	27.1 (33.7)	27.3 (32.2)	29.0 (34.7)	28.7 (29.9)	21.5 (34.1)
History of MDD, No. (%)	14 (37.8)	11 (30.6)	12 (31.6)	12 (34.3)	12 (33.3)	12 (32.4)
Sex, No. (%) F	15 (40.5)	17 (47.2)	17 (44.7)	16 (45.7)	15 (41.7)	17 (46.0)
Race, No. (%) white	26 (70.3)	31 (86.1)	33 (86.8)	31 (88.6)	30 (83.3)	28 (75.7)
Married/partner, No. (%) yes	10 (27.0)	14 (38.9)	15 (39.5)	11 (31.4)	8 (22.2)	16 (44.4)

\*MM indicates medical management; PI, psychological intervention; POMS, Profile of Mood States; and MDD, major depressive disorder.

†Mean (SD).

All participants assigned to active nortriptyline hydrochloride received 25 mg/d for 3 days, followed by 50 mg/d for 4 days. At the end of the week, serum levels of nortriptyline were assessed. Dosage was increased to 75 mg/d if a therapeutic serum level had not been reached. At week 4, serum levels were assessed again and, if necessary, drug dosage was increased to 100 mg/d. At week 6, serum levels were assessed to determine final dose. At the end of week 12, drug dose was decreased by 25 mg every 2 days, with the final drug administration being 25 mg over 3 days. Whenever a dose was titrated for a participant receiving active drug, the dose was titrated for a participant receiving placebo. Titration was performed by a physician who had no contact with participants or clinical staff. The mean nortriptyline blood level for participants abstinent at week 6 was 59.9 ng/mL (SD, 25.2 ng/mL). We report only blood levels for abstinent participants, since nicotine is known to result in lowered nortriptyline levels.<sup>18</sup> Daily nortriptyline hydrochloride dosages at week 7 were as follows: 50 mg/d, n=2; 75 mg/d, n=26; 100 mg/d, n=25, and 125 mg/d, n=5.

Bupropion hydrochloride dosage began at 150 mg/d for the first 3 days. The dosage was increased to 300 mg/d, where it remained until week 12, when the dose was decreased to 150 mg for 3 days, then discontinued. Dose reductions occurred if participants reported unpleasant adverse effects. Mean bupropion blood level for abstinent subjects was 36.0 ng/mL. At week 7, all participants receiving bupropion were receiving 300 mg/d.

Participants returned pill bottles at each clinic visit. Pills were counted and number of pills taken was recorded. If a patient failed to return a bottle, he or she was asked to call clinic staff with the pill count.

### STATISTICAL METHODS

The principal data analysis method was a generalized linear model (GLM), a generalization of the classic linear model that computes estimates by means of likelihood functions instead of least squares. A GLM allows use of repeated measurements when there are missing data, without dropping participants with data missing or assuming that missing data equate to smoking.<sup>19-21</sup> We used SAS PROC MIXED version 6.12 software (SAS Institute Inc, Cary, NC). When abstinence was the dependent variable, we also used the GLIMMIX Macro for SAS (SAS Institute Inc), which interacts with PROC MIXED to modify it so that it is appropriate for dichotomous data.<sup>22</sup> A single GLM was used to evaluate the 3 hypotheses. Abstinence status at weeks 12, 24, 38, and 52 were the dependent variables. The design was a 2 (active drug vs placebo) × 2 (MM vs MM/PI) × 2 (MDD

history vs no history) model with assessment entered as a repeated variable. Since no interactions of assessment with independent variables were predicted, these interactions were dropped from the final model when no significant effects emerged. Since we performed a single test for each hypothesis, the hypothesis-wise error rate was held at  $P = .05$ .

We evaluated effects of sex and its interaction with the 3 design variables on abstinence rates at weeks 12 to 52 by means of 3 GLM models computed with the GLIMMIX Macro. We used a parallel procedure to compare the 3 drug conditions (bupropion, nortriptyline, and placebo). Effect sizes are expressed as odds ratios and confidence intervals.

Analysis of variance and  $\chi^2$  tests were used to evaluate baseline differences among treatment conditions, continuous abstinence rates, and the rate of occurrence of adverse effects. Tests were 2-tailed, with  $P < .05$ , all comparisons.

## RESULTS

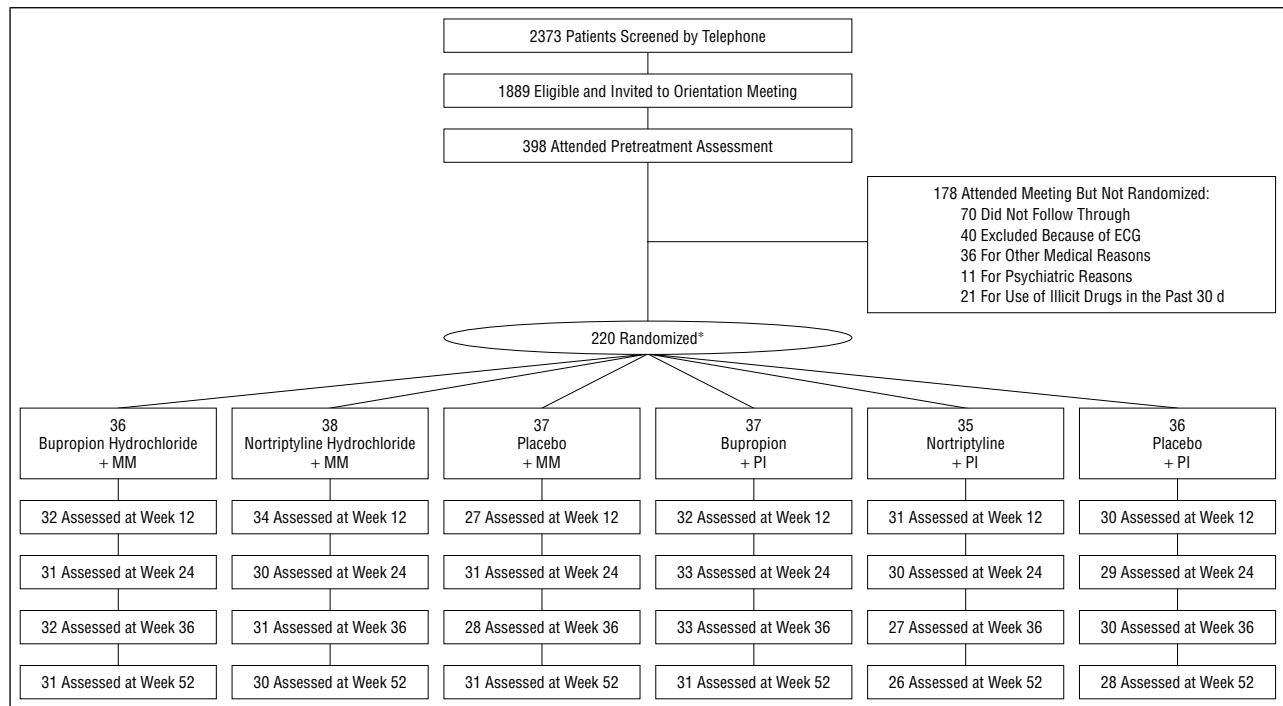
### PARTICIPANT CHARACTERISTICS

Demographic, smoking, and psychiatric characteristics of participants in each experimental condition are given in **Table 1**. There were no significant differences between conditions at baseline.

### ATTRITION

**Figure 1** shows participant flow from first telephone contact to week 52. Smokers (N=220) were randomly assigned to 1 of 3 pharmacologic treatments (nortriptyline, bupropion, or placebo) and 1 of 2 counseling treatments (MM or PI). A history of MDD was present in 33% of the participants. Because of a medical emergency, it was necessary to break the blind for 1 participant, who was receiving placebo drug. Thus, the usable sample (N=219) consisted of 122 men and 97 women.

Thirty-seven participants (17%) failed to complete treatment: 15 for personal reasons, 12 because of perceived medication adverse effects (bupropion, 6; nortriptyline, 3; placebo, 3), 1 because of an unrelated medical condition, and 9 for undisclosed reasons. There were no significant differences between psychological treatment conditions ( $\chi^2_1 [N=219] = 1.37, P = .24$ ) or diag-



**Figure 1.** Attrition flow chart. ECG indicates electrocardiogram; MM, medical management; and PI, psychological intervention. Asterisk indicates  $n=219$ , because the blind was broken for 1 female subject in the group receiving placebo and PI.

nostic categories ( $\chi^2_1 [N=219]=3.19, P=.07$ ) in treatment dropout. There were significant differences between the drug conditions ( $\chi^2_2 [N=219]=7.29, P=.03$ ; bupropion, 15.1% [ $n=11$ ]; nortriptyline, 10.0% [ $n=7$ ]; placebo, 26.0% [ $n=19$ ]). The rate for placebo was significantly greater than the rate for nortriptyline ( $\chi^2_1 [N=219]=6.74, P=.009$ ), but not for bupropion ( $\chi^2_1 [N=219]=2.69, P=.10$ ). The 2 active drugs did not differ from one another ( $\chi^2_1 [N=219]=1.01, P=.31$ ). The mean number of counseling sessions attended was 3.58 (SD, 1.61).

The percentages and numbers of participants for whom we were unable to collect smoking data were as follows: week 12, 15% ( $n=33$ ); week 26, 16% ( $n=35$ ); week 36, 17% ( $n=38$ ); and week 52, 19% ( $n=42$ ), with no significant differences between drug, psychological treatment, or diagnostic categories.

### ABSTINENCE

Main effects for drug, psychological treatment condition, and assessment time were each significant at  $P<.05$  (**Table 2**). There were no other significant effects. Neither main effects for MDD diagnosis nor the interaction of this variable with other variables was significant. Thus, both the first and second hypotheses—that active drug would be more effective than placebo (**Figure 2**) and that the PI would be more effective than MM alone (**Figure 3**)—were supported. The lack of a significant interaction between drug and PI condition indicated lack of support for the hypothesis that active medication plus PI would be the most efficacious condition.

We did not hypothesize a difference in efficacy between the 2 active drugs. None was found ( $\chi^2_1 [N=126]=1.88, P=.17$ ).

The interaction of bupropion vs nortriptyline with diagnosis fell short of traditional levels of significance ( $\chi^2_1 [N=126]=3.39, P=.07$ ). There were few differences between the 2 drugs for participants without a history of depression, but there were higher abstinence rates for bupropion than nortriptyline for participants with a history of depressive disorder. For example, with missing data omitted, the 52-week abstinence rate for participants without a history of MDD was 27% for nortriptyline and 24% for bupropion (20% with missing data coded as smoking for both drugs), whereas for participants with a history of MDD, the 52-week abstinence rate was 16% for nortriptyline (13% with missing data coded as relapsed) and 38% for bupropion (33% with missing data coded as relapsed). Continuous abstinence rates for the 1-year period were 20.7% for bupropion, 13.2% for nortriptyline, and 11.8% for placebo ( $\chi^2_2 [N=162]=1.96, P=.38$ ). For the 2 psychosocial conditions, they were 13% for MM and 18% for PI ( $\chi^2_2 [N=162]<1$ ).

Main effects for sex approached significance ( $\chi^2_1 [N=189]=2.68, P=.10$ ), favoring better abstinence rates for men when compared with women. Abstinence rates for men were as follows: week 12, 44%; week 24, 29%; week 36, 26%; and week 52, 24%. For women, these rates were as follows: week 12, 41%; week 24, 20%; week 36, 28%; and week 52, 23%.

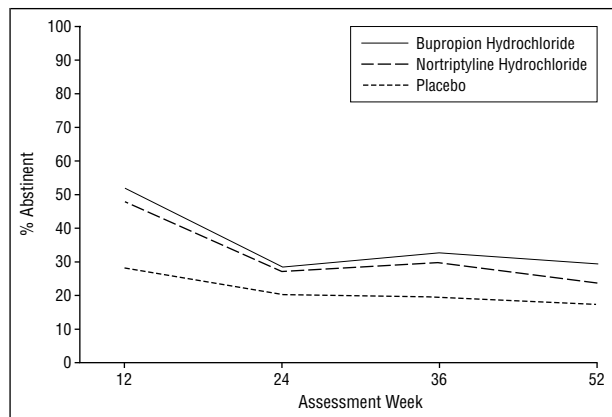
For all analyses, there were no differences in significance when the data were reanalyzed with missing data coded as smoking. With missing data coded as smoking, continuous abstinence rates were as follows: bupropion, 16.4%; nortriptyline, 9.6%; and placebo, 8.2% ( $\chi^2_2 [N=219]=2.80, P=.25$ ); and MM, 10%, and PI, 13% ( $\chi^2_2 [N=219]<1$ ).

**Table 2. Percent Abstinent, Number Assessed, and Number Abstinent by Assessment Time, Treatment Condition, and Drug\***

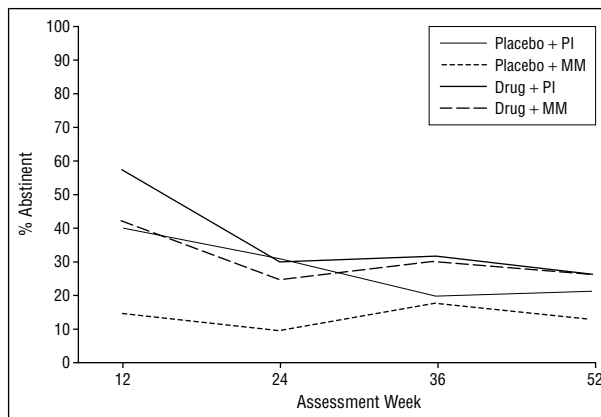
	Week 12	Week 24	Week 36	Week 52
<b>Medical Management</b>				
Bupropion (n = 36)				
% Abstinent†	47 (42)	26 (22)	34 (31)	29 (25)
No. assessed	32	31	32	31
No. abstinent	15	8	11	9
Nortriptyline (n = 38)				
% Abstinent†	38 (34)	23 (18)	26 (21)	23 (18)
No. assessed	34	30	31	30
No. abstinent	13	7	8	7
Placebo (n = 37)				
% abstinent†	15 (11)	10 (8)	18 (14)	13 (11)
No. assessed	27	31	28	31
No. abstinent	4	3	5	4
<b>Psychological Intervention</b>				
Bupropion (n = 37)				
% Abstinent†	56 (49)	30 (27)	30 (27)	29 (24)
No. assessed	32	33	33	31
No. abstinent	18	10	10	9
Nortriptyline (n = 35)				
% Abstinent†	58 (51)	30 (26)	33 (26)	23 (17)
No. assessed	31	30	27	26
No. abstinent	18	9	9	6
Placebo (n = 36)				
% Abstinent†	40 (33)	31 (25)	20 (17)	21 (17)
No. assessed	30	29	30	28
No. abstinent	12	9	6	6

\*Main effects for drug ( $\chi^2_1 [N = 189] = 10.76, P = .001$ ; odds ratio [OR], 4.3; 95% confidence interval [CI], 1.83-10.00), psychological treatment condition ( $\chi^2_1 [N = 189] = 8.53, P = .004$ ; OR, 3.32; 95% CI, 1.31-8.41), and assessment time ( $\chi^2_3 [N = 189] = 20.46, P < .001$ ; OR, 0.98; 95% CI, 0.97-0.99) were significant at  $P < .05$ .

†Numbers in parentheses represent percentages of subjects who were abstinent if those with missing data were coded as smoking.



**Figure 2.** Seven-day point-prevalence abstinence rates by pharmacologic intervention.



**Figure 3.** Seven-day point-prevalence abstinence rates by psychological intervention (PI) and drug. MM indicates medical management.

Fifty-four participants, or 25% of the sample, reported using out-of-study NRT (n = 34) or bupropion during follow-up (15 in the bupropion group, 14 in the nortriptyline group, and 25 in the placebo group). Placebo recipients were more likely than active-drug recipients to use nonstudy pharmacological therapies ( $\chi^2_1 [N = 219] = 5.42, P = .20$ ).

Of the 54 subjects who reported use of extrastudy medications, however, only 14 were abstinent at the time of the report, and they were distributed fairly equally across the treatment conditions. At week 24, 1 participant who reported out-of-study medication was absti-

nent (nortriptyline condition); at week 36, 1 abstinent participant in each of the antidepressant conditions and 2 in the placebo condition were using out-of-study medications. At week 52, the out-of-study medication count was 4 in the bupropion group, 2 in the nortriptyline group, and 3 in the placebo group.

#### MAINTENANCE OF THE BLIND

As part of the informed consent procedures, participants were informed about the adverse effects of each drug. It is not surprising that participants receiving active drug

were more likely to guess that they had received active drug (87%) than placebo participants were to believe they were receiving active drug (67%;  $\chi^2_1$  [N=160]=9.06,  $P=.003$ ; odds ratio, 3.29; 95% confidence interval, 1.48-7.30). Of the active drug participants who were able to correctly guess their assignment to active or placebo drug, 49% of the nortriptyline recipients and 58% of the bupropion recipients correctly guessed drug assignment ( $\chi^2_1$  [N=96]<1,  $P=.35$ ). Thus, bupropion recipients were no more likely than nortriptyline participants to correctly identify which drug they had received.

## ADVERSE EFFECTS

Of the potential adverse effects (dry mouth, rash, weight gain, light-headedness, shaky hands, constipation, blurry vision, sexual problems, difficulty in urinating, racing heart, swollen legs, chest pain or pressure, shortness of breath, weight loss, headaches, agitation, nausea or vomiting, dizziness, difficulty sleeping, and sweating), post-baseline endorsement rates differed between nortriptyline and placebo on the following: (1) dry mouth: nortriptyline, 72%; placebo, 33% ( $\chi^2_1$  [N=131]=19.71,  $P<.001$ ; odds ratio, 5.16; 95% confidence interval, 2.45-10.86); and (2) constipation: nortriptyline, 32%; placebo, 14% ( $\chi^2_1$  [N=131]=5.91,  $P=.02$ ; odds ratio, 2.87; 95% confidence interval, 1.20-6.85). Bupropion did not differ from placebo on any item.

## COMMENT

As predicted, bupropion and nortriptyline were more efficacious than placebo in producing abstinence when measured by point-prevalence abstinence during the course of a year. Similarly, PI was more efficacious than MM alone. The hypothesis that PI would add to antidepressant treatment was not supported. As has been the case in other recent studies (eg, Hall et al<sup>3</sup>), MDD did not predict failure to quit smoking.

The equivalent effectiveness of bupropion and nortriptyline, a generic drug, and nortriptyline's much lower cost, suggest that it might be a useful alternative to bupropion for some smokers. The drugs have different adverse effect and risk profiles, however. Nortriptyline has been shown to be related to an increased rate of serious cardiac events in patients with ischemic heart disease.<sup>23</sup>

The present study does not indicate whether it is the content of the PI or increased contact that increases abstinence. Visual inspection of data values in Figure 3 suggests potential differences between MM-placebo, and the remaining 3 conditions (MM-active drug, MM/PI-placebo, and MM/PI-active drug) at weeks 12, 24, and 52. The PI did not increase abstinence rates when added to the active drug; it may bring abstinence rates in the placebo condition to about the same level as active drug. Additional research in the role of psychological treatment with antidepressants is warranted. The interaction of drug with history of MDD did not reach statistically significant levels ( $P=.07$ ). Inspection of the data suggests potential superiority of bupropion for smokers with a history of MDD, but virtually no difference in pa-

tients without a history of MDD. The effect may warrant further examination in a study designed to address this question.

Abstinence rates in the present study were lower than those reported in earlier work with nortriptyline<sup>3</sup> and bupropion.<sup>1,2</sup> This difference may reflect the changing nature of participants entering smoking treatment trials. Smokers in the present study smoked fewer cigarettes, were less likely to have a partner or spouse, were more likely to be blue collar or service workers, and were less likely to be white. A recent study<sup>24</sup> has shown decreasing abstinence rates in smoking cessation studies during the past 25 years. The authors of that study attribute this to increasing difficulty in quitting cigarettes among individuals who continue to smoke despite current pressures.

Although nortriptyline and bupropion were significantly more efficacious than placebo when point-prevalence rates were compared, this was not the case when 1-year continuous abstinence rates were evaluated. Also, as the modest week 24 and 52 abstinence rates indicate, the field must continue to seek more efficacious treatments. Two recent clinical trials, both with acceptable rigor, one published in 1996<sup>25</sup> and the second in 1999,<sup>2</sup> failed to find differences between placebo and active NRT. Recent reviews of NRT effectiveness have suggested decreasing efficacy of nicotine patch, but not nicotine gum, since they were introduced in the 1980s.<sup>26</sup> As the population of smokers changes, interventions may experience a declining efficacy.

Given the information provided to participants as part of the informed consent procedures, it is not surprising that they were able to correctly guess which drug they had received. Indeed, in studies of drugs with detectable effects that report the maintenance of the blind, participants are often able to correctly guess which drug they received.<sup>27-29</sup> Nevertheless, given the complex blinding procedures we used because a placebo bupropion sustained-release capsule was unavailable, it was reassuring that the bupropion recipients were no more likely than the nortriptyline recipients to guess their drug.

To our knowledge, this is the first clinical trial to report the use of out-of-study medication during the follow-up period. We found a high rate of such use (54 patients [25% of the sample]), but only 14 of these 54 participants were abstinent. Recoding these abstinent participants as smoking does not change the overall findings. They represent less than 6% of the sample and were fairly equally distributed across conditions. Nevertheless, given the increasing availability of smoking cessation medications, we recommend that studies routinely report these data to better understand outcomes and the processes of abstinence and relapse.

The results of the present study are limited by the select nature of the sample resulting from the need to meet both criteria necessary to complete the research, such as availability during the course of the year, and medical exclusionary criteria.

*Submitted for publication July 20, 2001; final revision received November 12, 2001; accepted December 11, 2001.*

This study was supported by grants R01 DA02538 and 2 P50 DA09253 from the National Institute on Drug Abuse, Bethesda, Md, and grant R01 CA71378 from the National Cancer Institute, Bethesda.

We thank Kevin Delucchi, PhD, for his statistical consultation and Heather Kenna for manuscript preparation.

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