

# A Double-blind, Placebo-Controlled, Randomized Trial of Bupropion for Smoking Cessation in Primary Care

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**Background:** Studies undertaken in academic settings have shown that bupropion hydrochloride can double the odds of smoking cessation compared with placebo. To assess whether these results are applicable in primary care, we launched a double-blind, placebo-controlled, randomized trial to be conducted by general practitioners.

**Methods:** We assigned 593 healthy smokers to receive bupropion hydrochloride, 150 mg twice a day, or placebo daily for 7 weeks (hereinafter, bupropion group [n=400] and placebo group [n=193], respectively). After the baseline visit, 4 clinical visits and 3 telephone calls were scheduled over the 1-year period. The primary end points were biochemically confirmed continuous abstinence at week 7 and at week 52.

**Results:** Seventy-one Italian general practitioners enrolled participants from April 2004 to May 2005. Of the bupropion group, 41.0% were continuously abstinent from

week 4 to week 7 compared with 22.3% of the placebo group (multivariate odds ratio, 2.37; 95% confidence interval, 1.60-3.53). The continuous abstinence rates from week 4 to week 52 were 25% in the bupropion group and 14% in the placebo group (odds ratio, 2.11; 95% confidence interval, 1.32-3.39). The mean weight gain was similar in both groups and among long-term abstainers was 3 kg in women and 4 kg in men. More participants in the bupropion group experienced an adverse event than those in the placebo group, but the percentage who discontinued use of the study medication was similar.

**Conclusions:** Bupropion more than doubled the odds of continuous abstinence from smoking. The adherence of general practitioners and participants to the protocol was excellent, making our findings robust and easy to generalize to the context of primary care.

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**A**CCORDING TO RIGOTTI,<sup>1(p511)</sup> “Physicians should routinely identify patients’ smoking status and readiness to quit, advise and assist smokers to quit, and offer pharmacotherapy to help them quit.” Although general practitioners (GPs) are the best candidates for this important role, the efficacy of pharmacotherapies is often assessed in clinical settings that are very different from those in primary care. Pharmacotherapies for stopping smoking can double the rates of quitting compared with placebo,<sup>2</sup> but the real question is whether these results are applicable in primary care, where smokers have routine access to their physicians and patients have personal contact and treatment for any medical problem. Smokers entering most randomized clinical trials are recruited in specialized clinics or academic medical centers experienced in helping people to stop smoking, and treatment often involves follow-up according to very strict and frequent programs.

We decided therefore to test the efficacy of bupropion hydrochloride, a non-nicotine replacement therapy as first-line smoking cessation agent, with minimal levels of psychosocial support. We conducted this trial in the primary care setting to verify the general applicability of the results to the intended end users.

## METHODS

### STUDY DESIGN AND TREATMENT

This was a double-blind, placebo-controlled randomized clinical trial conducted in 6 administrative areas in northern Italy in compliance with the Declaration of Helsinki. A central national review board and the ethics committees in each area approved the protocol, and all participants provided written informed consent prior to any procedures. At the baseline visit (visit 1) participants completed the Fagerstrom Test for Nicotine Dependence,<sup>3</sup> and their GP assigned them a randomization code. They then received, in a 2:1 ratio, either a sustained-release form of bupropion hydrochloride at a dosage of

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150 mg/d for 6 days followed by 150 mg twice a day for 7 weeks, or placebo (hereinafter, bupropion group and placebo group, respectively). The 2:1 ratio was chosen to encourage participants' acceptance of the random assignment to treatments. The drug and the placebo were made and packaged by GlaxoSmithKline (Research Triangle Park, North Carolina), and all the tablets were identical in appearance. Participants set a target quit date, usually during the second week after the start of medication, and were scheduled to attend the GP's practice on 4 other occasions at week 4 (visit 2), week 7 (visit 3), week 26 (visit 4), and week 52 (visit 5). Patients received additional courtesy and counseling telephone calls 1 day before and 3 days after the quit date and 10 weeks after study enrollment. As a service, the coordinating center sent all GPs a short message to remind them to make the telephone calls and also sent all participants a postcard appointment reminder before visits 4 and 5. At each visit, GPs recorded concomitant medications, adverse effects, blood pressure, body weight, and the carbon monoxide content of expired air. Self-reported abstinence was biochemically validated if the carbon monoxide content of expired air was 10 ppm or less (measured with a Smokerlyzer monitor [Bedfont Scientific Ltd, Rochester, England]).<sup>4</sup> Carbon monoxide concentration is a reliable method for detecting recent smoking because carbon monoxide remains in the bloodstream for up to 24 hours. Its half-life is about 5 hours. Self-reported continuous abstinence was confirmed by a simple diary, which each participant was invited to keep and which would show that he or she had "not even had a puff" since the previous contact. Data were collected by GPs and sent to the coordinating center on an ad hoc developed electronic clinical data registration form.<sup>5</sup> This general data entry engine was developed to centralize the data collection and handling while satisfying the requirements of both Italian and European directives about protection of confidentiality and privacy. Each GP entered the data in a local computer and then transferred them via the Internet to the master database stored on the coordinating center server.

### ELIGIBLE POPULATION

Participants were recruited by their GPs through personal or telephone contact. To be eligible for this trial, subjects had to be 18 years or older; had to have smoked 10 cigarettes or more per day for the previous year, with no interruption longer than 3 months; had to be motivated to quit smoking; and had to be in good health and bupropion naive. Subjects with a medical history of seizure or a predisposition toward seizure were not included. Patients taking drugs that lower the seizure threshold (eg, systemic corticosteroids, antidepressants, theophylline, antipsychotics) were not eligible. Subjects were also excluded if they had a medical history of eating disorders or severe renal, hepatic, neurologic, or chronic pulmonary disease.

### PRIMARY AND SECONDARY END POINTS

Primary end points were (1) biochemically confirmed continuous abstinence from smoking for 4 weeks from the start of week 4 to the end of week 7 and (2) biochemically confirmed continuous abstinence from smoking from week 4 to week 52. Secondary end points of efficacy were (1) biochemically confirmed point prevalence of abstinence (ie, smoking abstinence during the previous 7 days) during treatment (visits 2 and 3) and follow-up (visits 4 and 5); (2) the number of cigarettes smoked daily in nonabstinent subjects; and (3) body weight changes in continuously abstinent subjects in both groups. Blood pressure was measured at each visit, and bupropion safety was assessed by carefully recording the type and degree of any adverse events occurring during treatment and in the 2 weeks following treatment.

## STATISTICAL ANALYSIS

The trial was planned to recruit 585 subjects (195 in the placebo group and 390 in the bupropion group in a randomization bupropion-control ratio of 2:1) to detect a 13% absolute difference in continuous abstinence at week 7 and at week 52 (differences ranged from 20% for the placebo group to 33% for the bupropion group, with at least 90% power, using a 2-sided test and  $\alpha$  of 5% and assuming that those lost to follow-up would be considered smokers). We used the  $\chi^2$  and analysis of variance to test differences in categorical or continuous variables. All statistical tests were 2-sided and had an  $\alpha$  level of .05. Participants who withdrew from the study were assumed to be smokers as of the date of the skipped scheduled visit.

Continuous abstinence at week 7 and at week 52 was analyzed as a binary variable using logistic regression to establish whether treatment was independently associated with smoking cessation after adjustment for other characteristics. Variables in the model included the patient's age (ages were stratified at 18-64 years and >64 years), sex, and score for the Fagerstrom Test for Nicotine Dependence. The estimates from the logistic regression model are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The time to first lapse after the quit date was estimated by the Kaplan-Meier method and compared using the log-rank test.

## RESULTS

### STUDY POPULATION

The trial started on April 15, 2004, and the last subject was randomized on May 15, 2005. A total of 593 subjects were enrolled in the study (193 assigned to placebo and 400 to active drug) from 71 GPs. Each GP enrolled a median number of 9 subjects (range, 3-18 subjects). Baseline characteristics and the smoking history of the participants are detailed in **Table 1**. All variables were well balanced between groups.

### COMPLIANCE WITH TREATMENTS

The median number of telephone contacts and counseling calls per subject was 3 (25th and 75th percentiles). The percentages of subjects presenting at visits 2, 3, 4, and 5 were 89%, 87%, 84%, and 85%, respectively, in the placebo group and 92%, 91%, 84%, and 83%, respectively, in the bupropion group ( $P = .14$ ).

Twenty-eight percent of the patients discontinued treatment in the placebo group vs 30% in the bupropion group ( $P = .63$ ). These similar percentages were the result of adverse events in 26% of the placebo group and in 46% of the bupropion group ( $P = .02$ ).

Adherence to the medication regime was further assessed by counting the pills given back to the GP at the end of the treatment period (at visit 3). Subjects were to take about 92 pills; the percentages who took less than 50, 50-79, and 80 or more pills were 4%, 26%, and 70%, respectively, for those who did not discontinue treatment and 66%, 29%, and 4%, respectively, for those who discontinued treatment ( $P < .001$ ). Sixty-four percent (255 of 400) of subjects correctly guessed that they had received bupropion, and 44% (85 of 193) of subjects correctly guessed they had received placebo.

**Table 1. Baseline Characteristics of the Subjects**

Characteristic <sup>a</sup>	Bupropion Hydrochloride Group (n=400)	Placebo Group (n=193)
Age, y		
Median	49.4	48.5
25th Percentile	40.5	41.8
75th Percentile	57.3	56.3
BMI		
Median	25.0	24.2
25th Percentile	22.4	21.6
75th Percentile	27.5	26.9
Sex, %		
Male	62.0	55.4
Female	38.0	44.6
Level of education, %		
Not a high school graduate	52.3	44.6
High school graduate	37.4	42.5
Some education after high school	10.3	13.0
Age when subject began smoking regularly, y	17.6±4.3	17.8±3.9
Cigarettes smoked daily over last week, No.	21.1±8.7	21.6±9.4
Cigarettes smoked daily over last year, No.	22.8±9.2	22.5±8.8
Carbon monoxide, ppm (baseline)	22.3±11.0	22.8±11.8
Another smoker in household, %	51.5	51.8
Patients with at least 1 previous serious attempt to quit, %	68.5	71.0
Fagerstrom score <sup>b</sup>	5.0±2.1	5.2±2.0

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

<sup>a</sup>Data are presented as mean±SD unless otherwise indicated.

<sup>b</sup>The Fagerstrom Test for Nicotine Dependence includes 6 questions, and the score ranges from 0 (least-dependent smokers) to 10 (most dependent).<sup>3</sup>

### PRIMARY END POINT

Rates of verified continuous abstinence from week 4 to week 7 and from week 4 to week 52 were considerably higher for the bupropion group (41.0% and 25.3%, respectively) compared with the placebo group (22.3% and 13.6%, respectively) (see **Table 2** for the *P* values). **Figure 1** depicts the Kaplan-Meier curves for the continuous abstinence function (time to first lapse) for the treatment group.

**Table 3** shows the multivariate logistic analyses of the continuous abstinence rates for week 4 to week 7 and for week 4 to week 52. The model accounted for the effects of sex, age, and Fagerstrom score. The ORs comparing bupropion with placebo were significant for both primary end points (OR, 2.37 [95% CI, 1.60-3.53], *P*<.001; and OR, 2.11 [95% CI, 1.32-3.39], *P*=.002). The Fagerstrom score was positively associated with the chance of continuous abstinence from week 4 to week 7 (*P*=.009) but lost its predictive power for the lasting abstinence end point (*P*=.08). When we analyzed the potential interaction of baseline characteristics of participants by treatment we found a significant interaction between body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and treatment (*P*=.005). The OR for the difference between the bupropion and placebo groups was 4.38 (95% CI, 1.99-9.62) for subjects with BMIs higher than the

**Table 2. Efficacy and Safety Rates at End Points**

End Point	Bupropion Hydrochloride Group (n=400)	Placebo Group (n=193)	<i>P</i> Value
<b>Efficacy</b>			
Primary end points			
Continuous abstinence rate between weeks 4 and 7, % (95% CI)	41.0 (36.1-46.0)	22.3 (16.6-28.8)	<.001
Continuous abstinence rate, weeks 4 to 52, % (95% CI)	25.3 (21.1-29.8)	13.6 (9.1-19.3)	.001
Secondary end points			
Point-prevalence abstinence rate at each visit, % <sup>a</sup>			
Visit 2	50	31	<.001
Visit 3	47	27	<.001
Visit 4	38	24	.001
Visit 5	35	20	<.001
Mean change in the No. of cigarettes at each visit			
Visit 2	-15.0	-15.0	.86
Visit 3	-15.0	-14.0	.06
Visit 4	-9.0	-9.0	.68
Visit 5	-7.0	-8.0	.81
Mean change in body weight in continuously abstinent patients at 52 wk, kg	4	3	.67
<b>Safety</b>			
Participants reporting at least 1 adverse event during treatment, No. (%)	179 (44.8)	51 (26.4)	NA
Severity of adverse event, %			
Low	37	46	NA
Medium	46	43	NA
High	16	11	NA
Participants with adverse events that required treatment, %	21	22	NA
Participants reporting serious adverse events at any time point, No. (%)	8 (2)	2 (1)	NA

Abbreviations: CI, confidence interval; NA, not applicable.

<sup>a</sup>Smoking abstinence during the previous 7 days.

median, compared with an OR of only 1.09 (95% CI, 0.58-2.07) for subjects with BMIs lower than the median.

### SECONDARY END POINTS

Table 2 shows the carbon monoxide-confirmed point-prevalence abstinence rates by treatment groups. The point abstinence rates at visits 2, 3, 4, and 5 for the bupropion group were significantly higher than those of the placebo group (*P*<.01 for all comparisons).

**Figure 2** depicts the mean number of cigarettes smoked daily by participants who were not continuously abstinent at week 52. The decrease was similar in the 2 treatment groups, but the reduction changed over time: at visit 2 it was about 12 cigarettes less than baseline, but this ben-

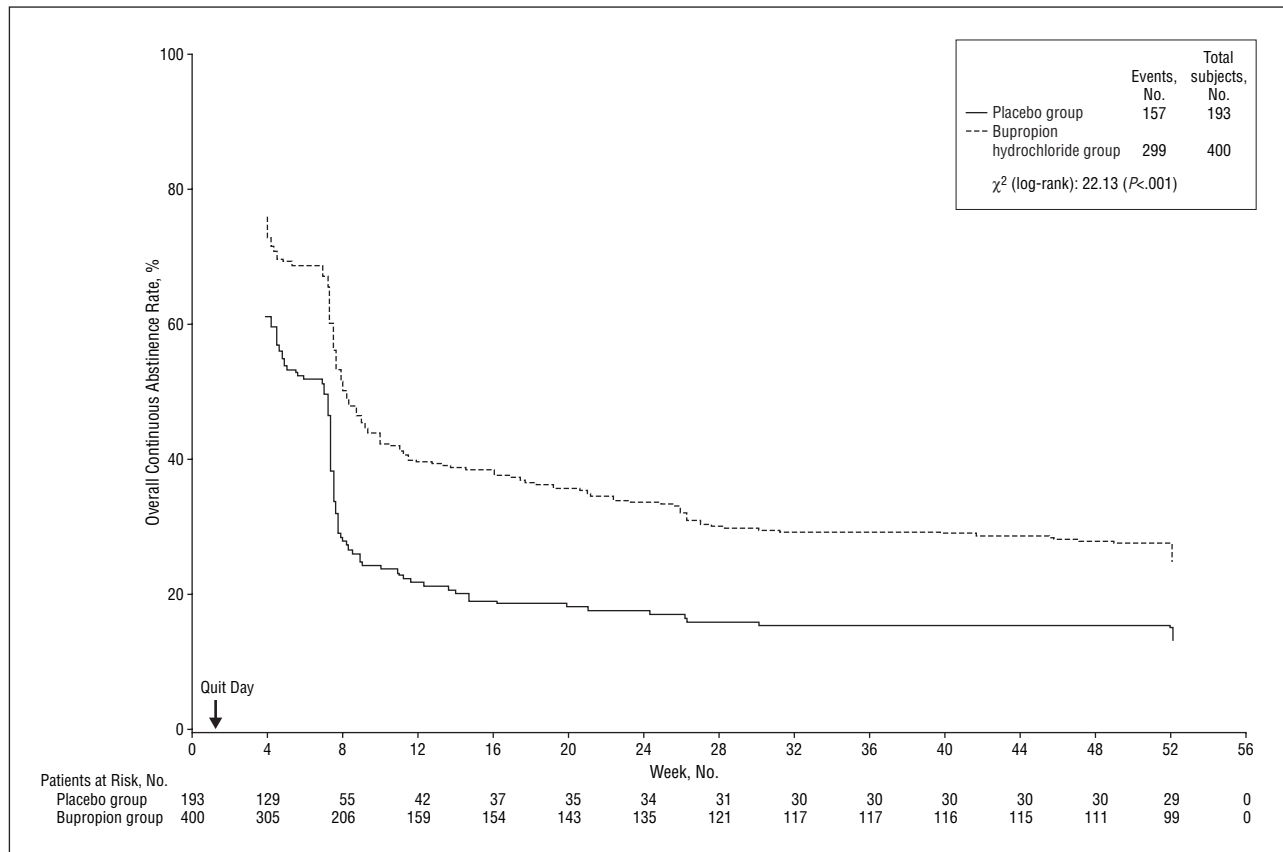


Figure 1. Kaplan-Meier curve of continuous abstinence. "Events" indicates the participants who started smoking again.

Table 3. Multivariate Associations of Treatment and Subject Characteristics With Continuous Abstinence

Variable	Continuous Abstinence During Weeks 4-7		Continuous Abstinence During Weeks 4-52	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Treatment (bupropion hydrochloride vs placebo)	2.37 (1.60-3.53)	<.001	2.11 (1.32-3.39)	.002
Female vs male	0.89 (0.63-1.28)	.54	0.84 (0.56-1.27)	.40
Age (per year)	1.01 (1.00-1.03)	.09	1.00 (0.98-1.02)	.86
Fagerstrom score (per point) <sup>a</sup>	0.89 (0.82-0.97)	.01	0.92 (0.83-1.01)	.08

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>The Fagerstrom Test for Nicotine Dependence includes 6 questions, and the score ranges from 0 (least-dependent smokers) to 10 (most dependent).<sup>3</sup>

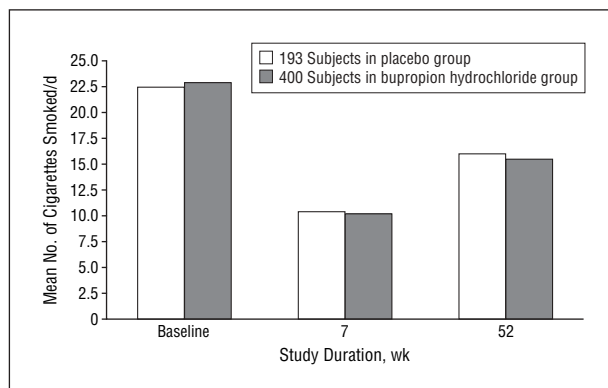


Figure 2. Mean number of cigarettes smoked by participants not in abstinence at baseline (visit 1), week 7 (visit 3), and week 52 (visit 5).

efit progressively decreased, and at week 52 the reduction was only 7 cigarettes less than baseline.

During the follow-up period, the subjects' weight increased, and the mean gain at week 52 was 4.09 kg for continuous abstainers in the bupropion group and 3.27 kg for continuous abstainers in the placebo group; weight gain was generally lower among noncontinuous abstainers who completed the 52-week study (0.76 kg). The mean weight gain at week 52 for continuously abstinent participants was 3.48 kg in women and 4.16 kg in men.

## SAFETY

Overall, 397 nonserious adverse events were recorded throughout the 7 weeks of drug treatment, and 230 par-



ticipants (39%) reported at least 1 adverse event: 51 in the placebo group (26.4%) and 179 in the bupropion group (44.8%) ( $\chi^2=18.4$ ;  $P<.001$ ). The GPs classified the severity of the adverse events as low, medium, and high, respectively, 46%, 43%, and 11% in the placebo group and as 37%, 46%, and 16% in the bupropion group ( $\chi^2=2.46$ ;  $P=.29$ ). Nonserious adverse events required specific treatment in 22% of cases in the placebo group and 21% in the bupropion group. The most frequently prescribed remedies for treatment-related symptoms were benzodiazepines for insomnia and anxiety (15 cases), lactulose for constipation (12 cases), antacids or proton pump inhibitors for nausea and dyspepsia (11 cases), and nonsteroidal anti-inflammatory drugs or paracetamol for headache (8 cases).

**Table 4** shows the adverse events reported by at least 5% of the participants according to group. Participants in the bupropion group were more likely to report insomnia, constipation, and xerostomia.

Ten serious adverse events were reported during the 52-week trial: 8 occurred in the bupropion group (suspected cholangitis, hypersensitivity reaction to insect stings, pemphigus, neck pain caused by acute cervical strain, breast cancer, brain tumor, cancer of the esophagus, and acute myocardial infarction) and 2 in the placebo group (possible acute pancreatitis and perforated colonic diverticula).

## COMMENT

Until recently, Italy was the only European country where research on drug efficacy in the primary health care setting was precluded.<sup>6</sup> The Italian Parliament enacted a law in 2001 that finally allowed and regulated primary health care research, and this protocol was the first to be approved by a specifically appointed central committee; it was also the first to be concluded.

We thought that the real therapeutic potential or impact of a pharmacologic approach to smoking cessation should be evaluated by GPs in the primary care setting and that the approach should address healthy smokers and use continuous abstinence at week 52 as the most valid outcome measure. This study was aimed at assessing the applicability of the results of early randomized trials to patients in general practice.<sup>7,8</sup>

Although bupropion increased rates of cessation in smokers attending a program involving high levels of specialized psychosocial support, there was still no evidence to support its routine use outside such intensive approaches. This study showed that bupropion can more than double the odds of continuous abstinence at both week 7 and week 52 vs placebo, even in the primary care setting.

To our knowledge, there have been no other randomized clinical trials of bupropion conducted strictly by GPs. Among randomized trials assessing bupropion use in healthy smokers, participants attended academic centers in 5 studies,<sup>7-11</sup> unspecified outpatient clinics in 1 study conducted in France,<sup>12</sup> and a community health care center for 1 study assessing a population of black subjects in the United States.<sup>13</sup> The participants in those

**Table 4. Adverse Events Occurring in at Least 5% of Subjects In Either Group During Treatment<sup>a</sup>**

Adverse Event	Bupropion Hydrochloride Group (n=400)	Placebo Group (n=193)
Headache	20 (5.0)	8 (4.2)
Insomnia	69 (17.3)	12 (6.2)
Constipation	44 (11.0)	7 (3.6)
Dizziness	21 (5.3)	14 (7.3)
Dry mouth	25 (6.3)	4 (2.1)

<sup>a</sup>Data are given as number (percentage).

studies were otherwise similar to those in our study, particularly in terms of smoking history, with most of the studies recruiting those who smoked approximately 21 to 22 cigarettes a day and had a Fagerstrom score of about 5. Only 2 studies<sup>7,8</sup> apparently recruited heavier smokers (those who smoked 25-27 cigarettes a day). Among the 4 trials that gave continuous abstinence rates at 1 year,<sup>8-11</sup> high percentages of participants failed to complete the study (range, 36%-45%). We had a better participation rate—only about 16% of participants failed to present at visit 5 in both groups—and this highlights the unique ability of GPs to provide very good long-term follow-up data because they can easily maintain contact with participants.

The OR of 2.11 for continuous abstinence vs placebo at week 52 was in keeping with the overall results of a Cochrane overview<sup>14</sup> (OR for abstinence at follow-up of  $\geq 6$  months, 1.94 [95% CI, 1.72-2.19]), but in the studies with a similar design, ORs could range from 3.79 (Jorenby et al<sup>8</sup>) to 1.50 (Jorenby et al<sup>10</sup>). Although relative measures of treatment effects, such as the ORs, are the most appropriate for comparisons across studies, absolute abstinence rates call for comment. The long-term continuous abstinence rates for the placebo group (14%) and for the bupropion group (25%) were higher than those reported in other studies with a similar design and target population. In other studies, the continuous abstinence rate at 1 year ranged from 5.6% (Jorenby et al<sup>8</sup>) to 11% (Gonzales et al<sup>9</sup>) for the placebo groups and from 14.6% (Jorenby et al<sup>10</sup>) to 21% (Gonzales et al<sup>9</sup>) for the bupropion groups. Two studies<sup>10,11</sup> recently compared the efficacy of varenicline as a new smoking cessation pharmacotherapy with bupropion and placebo. In 1 of these trials, varenicline showed a benefit compared with bupropion, although bupropion performed poorly both in absolute terms and in comparison with placebo (14.6% continuous abstinence rate at 1 year; OR of bupropion vs placebo, 1.50 [95% CI, 0.94-2.37]).<sup>10</sup>

An interesting by-product of our analysis is the interaction of body weight and treatment. Participants whose BMI was above the median seemed to respond better to bupropion than participants with a lower BMI. This interaction is worth exploring in other databases, and if confirmed, it might suggest a tailored pharmacologic approach to smoking cessation for lean or underweight smokers. In our study, the weight gain over time in continuously abstinent participants was the same in the placebo and bupropion groups, and it was limited (about 4

kg at week 52). Our results are in keeping with other randomized trials that found no difference in weight gain between the bupropion and placebo groups at week 26 or week 52; only 1 trial reported the absolute weight gain in abstainers at 1 year (5.5 kg for the bupropion group and 6.1 kg for the placebo group).<sup>9</sup>

The incidence of adverse effects (except constipation) was lower than in other studies, in which, for example, the incidence rates of insomnia, headache, and dizziness reached 42%,<sup>8</sup> 32%,<sup>7</sup> and 11%,<sup>8</sup> respectively. Because the risk of underreporting was negligible owing to the excellent compliance rates, we think that the lower rate of adverse effects was probably due to less frequent assessments of such events in the present study than in previous ones. No seizures were observed. Ten participants experienced serious adverse events during the entire 1-year period, but only 1 serious adverse event was thought to be related to the study medication (suspected cholangitis).

The GPs did not receive any guidelines on how to select subjects to be admitted to the trial, other than a simple eligibility criteria checklist, and no log was kept of patients who refused to participate. Therefore, nonmedical factors such as the doctor-patient relationship might have influenced the selection of the study population and, probably, the final outcome in terms of compliance with the protocol. How unpredictable these factors can be is clear from a comparison with other nicotine replacement therapy studies. In the most recent meta-analysis of these trials,<sup>15</sup> the setting in which such treatment was offered was one of the major determinants of its effectiveness. Nicotine gum and transdermal patches were more effective when offered to volunteer smokers recruited from the community or those attending specialized clinics than when offered to smokers in primary care. These findings were partly explained by the higher motivation to quit among the smokers attending specialized smoking cessation clinics than among those recruited in trials in primary care settings. In addition, the authors of that meta-analysis<sup>15</sup> reported that compliance rates with nicotine replacement therapy among smokers treated in primary care were lower than compliance rates in other settings.

The intervention program of our study (3 telephone calls and 5 visits in a year) might be deemed an excessive burden for most primary care clinics. We have shown that this schedule was indeed feasible in the daily routine of general practice facilities, with some GPs following more than 10 patients entered into the study over a few weeks. Moreover, it is possible that the late follow-up visits planned (at 6 months and 1 year) might be replaced in day-to-day practice with unscheduled contacts triggered by any other health or bureaucratic problem. We doubt that such a complex task as promoting smoking cessation can be further compressed in terms of work, time, and expertise.

In conclusion, the adherence of GPs and participants to the research protocol was excellent. Bupropion was efficacious, with an absolute 25% of participants continuously abstinent at 1 year; it doubled the odds of continuous abstinence from week 4 to week 7 and from week 4 to week 52 compared with placebo and was also well

tolerated. This study, conducted in the general practice setting, does not simply replicate previous studies undertaken in academic centers but also provides reliable data that physicians may use to make their best evidence-based decisions in the difficult task of helping people quit smoking.

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