

Effectiveness of Bupropion Sustained Release for Smoking Cessation in a Health Care Setting

A Randomized Trial

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Background: The efficacy of bupropion hydrochloride sustained release (SR) (Zyban) for smoking cessation has been evaluated in clinical trials that included frequent in-person behavioral counseling, but not in actual practice settings.

Objective: To determine the differential effectiveness of 2 doses of bupropion SR in combination with behavioral interventions of minimal to moderate intensity in an actual practice setting.

Design: Open-label randomized trial, with 1 year of follow-up.

Setting: A large health system (Group Health Cooperative) based in Seattle.

Participants: Adult smokers (N=1524) interested in quitting smoking.

Interventions: Participants were randomly assigned to receive 1 of 4 combinations of bupropion SR (150 or 300 mg) and behavioral counseling (minimal or moderate intensity).

Main Outcome Measures: The primary outcome measure was self-reported point-prevalence 7-day nonsmoking

status at 3 and 12 months following the target quit date. Secondary outcomes included adverse and abstinence effects reported since beginning treatment with bupropion SR.

Results: At 3 months, a significantly higher rate of nonsmoking was observed among those receiving the larger bupropion SR dose ($P=.005$). At 12 months, moderate intensity counseling was associated significantly with a higher rate of nonsmoking ($P=.001$). At 3 months, the higher dose was associated with a significantly increased frequency of self-reported symptoms such as difficulty sleeping ($P=.02$), difficulty concentrating ($P=.02$), shakiness/tremor ($P=.002$), and gastrointestinal problems ($P=.005$) and a decreased frequency of reported desire to smoke ($P=.001$).

Conclusions: In this actual practice setting, the combination of bupropion SR and minimal or moderate counseling was associated with 1-year quit rates of 23.6% to 33.2%. This suggests that existing health care systems can substantially decrease tobacco use rates among their enrollees if they provide these modest interventions.

Arch Intern Med. 2003;163:2337-2344

Author affiliations are listed at the end of this article. The authors have no relevant financial interest in this article, and received no financial support or medication from GlaxoSmithKline, which markets bupropion hydrochloride sustained release for smoking cessation under the trade name Zyban.

SEVERAL PLACEBO-controlled trials¹⁻⁵ of bupropion hydrochloride sustained release (SR) (Zyban) for smoking cessation have demonstrated it to be an efficacious agent to promote smoking cessation. Only Hurt et al,¹ however, used dosages other than 300 mg/d. In that study, abstinence rates for 150 and 300 mg of bupropion SR were higher than those for placebo at the end of treatment. Although abstinence rates were higher at the end of treatment for the 300-mg dose compared with the 150-mg dose, superior efficacy for the higher dose was not observed at 12 months. The published trials of bupropion SR also included intensive in-person behavioral

counseling during and/or following treatment, much more contact than individuals receiving a bupropion SR prescription from their physician will typically receive. To our knowledge, success rates for bupropion SR in combination with truly minimal counseling, as defined by recent guidelines,^{6,7} have not been reported. Therefore, recommendations based on the results from these studies^{8,9} are of unknown applicability to settings outside the context of a clinical efficacy trial. Evaluation of bupropion SR's effectiveness in a primary care-oriented health care system setting is important because it is the most likely form of delivery of this medication if it is included as a covered health care insurance benefit.

The present investigation crossed 2 dosage levels of bupropion SR, 150 or 300 mg/d, with 2 different counseling approaches of minimal or moderate intensity offered to smokers in a large primary care-oriented health system. The 2 counseling approaches both involved use of easily accessible means of support (one relying predominantly on tailored self-help mailed materials and the other predominantly on proactive telephone counseling) that reduced burden on the participants and the health care system. Participants were randomly assigned to 1 of 4 treatment groups and then surveyed twice during the year for smoking status following their target quit date.

METHODS

STUDY SETTING

Participants, all members of Group Health Cooperative (GHC), were enrolled during a 13-month period between April 9, 1998, and May 24, 1999. Group Health Cooperative is a nonprofit consumer-governed health care system, headquartered in Seattle, that serves approximately 600 000 residents of Washington State. The study was advertised in various publications mailed to GHC members and in brochures distributed to GHC clinics. Primary care physicians were informed of the study and were asked to refer eligible patients. Inclusion/exclusion criteria were modeled after the 2 previously conducted bupropion SR efficacy trials,¹⁰ and focused predominantly on conditions, including the use of medications, that may lower seizure threshold.

On calling the study center, individuals were screened for study inclusion entirely over the telephone, and were eligible for participation if they were at least aged 18 years, smoked 10 or more cigarettes per day, were motivated to stop smoking, were otherwise in good general health, had sufficient verbal and written command of English to provide informed consent and study responses, and were enrolled and planned to stay enrolled in GHC for the next 12 months. Exclusion criteria included the following: (1) any predisposition to seizure, as defined by a personal or family history of a seizure disorder, such as epilepsy, or a personal history of febrile seizures; (2) history of stroke or transient ischemic attack; (3) history of head injury resulting in loss of consciousness for longer than 1 hour; (4) current use of medications contraindicated to bupropion SR or known to lower the seizure threshold (complete list available on request); (5) history of or current diagnosis of anorexia nervosa or bulimia; (6) being of poor general health, as defined by the presence of severe and chronic cardiovascular disease (including myocardial infarction within the previous 3 months), severe and chronic pulmonary disease, renal or hepatic dysfunction, neurologic disease, uncontrolled hypertension, or uncontrolled diabetes mellitus; (7) participation in GHC's Free & Clear (FC) smoking cessation program in the previous 12 months (1 of the treatments included in the present study); (8) current depression; (9) current drinking of 14 or more alcoholic drinks per week and/or binge drinking 2 or more times in the past month; and (10) current pregnancy or plans to become pregnant or current nursing of a child. All protocols were reviewed and approved by the institutional review boards of GHC and SRI International.

If study screeners were unsure if a reported condition warranted exclusion based on the protocol, the case was reviewed and a study physician (T.M. or S.D.) and/or pharmacist (K.B.) made an inclusion decision. Review could include screener presentation of the medical history, examination of automated pharmacy data, medical record review, contact with the primary care physician, or further discussion with the potential participant. In most cases, the review process took only a few minutes.

TREATMENT PROTOCOL

In an actual practice setting, patients are prescribed active medication and know the dose they are prescribed. Therefore, to maintain fidelity with actual practice, the study did not include a placebo control group and was not blinded. Group Health Cooperative's pharmacy covered the cost of medication and, as a small incentive, participants did not have to pay the usual pharmacy copayment of \$5 to \$10. Other than this, neither patients nor physicians received reimbursement for their participation in this study.

All eligible volunteers were sent a pretreatment questionnaire and consent form. On receipt of the completed questionnaire and consent form, the participants were randomly assigned to treatment group by a procedure built into the study database that used a random-number generator. The computer code for the procedure calculated probabilities of group assignment that were dynamically modified based on the number of members in each group so that final group sizes were equal. No restrictions such as stratification or blocking were used as part of the randomization process.

Bupropion SR Regimens

Participants receiving 150 and 300 mg of bupropion SR were given instructions for use based on standard product information for the consumer, at randomization and when their prescription was mailed to them. Bupropion SR was taken for 1 week before the target quit date, and continued for 7 weeks after that date. Participants randomized to the 150-mg groups were prescribed 1 pill per day; those randomized to the 300-mg group were prescribed 1 pill twice per day.

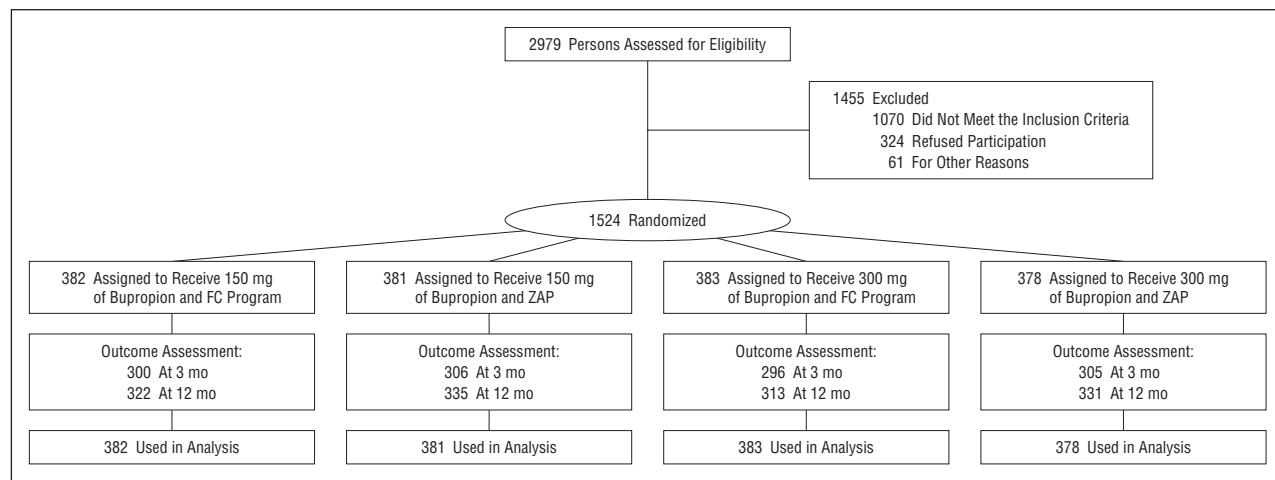
Behavioral Interventions

Participants randomized to the less-intensive behavioral counseling were automatically enrolled in the Zyban Advantage Plan (ZAP). Selected data from the pretreatment questionnaire, along with data from 4 brief progress questionnaires sent after the target quit date, were used to personalize the ZAP intervention materials. Patients also received a ZAP evaluation questionnaire and a 5- to 10-minute scripted call from a ZAP smoking cessation specialist on the day after their quit date. Participants in ZAP could return the progress questionnaires in provided postage-paid envelopes or they could complete the questionnaires using ZAP's automated telephone system. Participants also had access to a 24-hour automated toll-free question-and-answer and support line.

Participants randomized to receive higher-intensity counseling were enrolled in the FC telephone program,^{11,12} which is based on cessation strategies recommended by the US Public Health Service tobacco treatment guideline.^{6,7} This program included a mailing of self-help materials plus support materials for family and friends. In addition to an in-depth telephone assessment and counseling intervention and 4 brief prescheduled follow-up calls, participants had access to a toll-free Quitline for a full year. Counselors provided individualized counseling for participants on motivation, quitting, avoiding the return to smoking, and "recycling" (a return to nonsmoking following an episode of smoking within the follow-up period). The program version used in this trial was 1 year long, with outgoing call activity concentrated in the first 6 months.

MEASURES

The pretreatment questionnaire included the following: (a) smoking history, including the Fagerström Test for Nicotine Dependence¹⁰; (b) quitting history, including prior use of ces-



Study enrollment and follow-up. Bupropion was given as bupropion hydrochloride (Zyban). FC indicates Free & Clear; and ZAP, Zyban Advantage Plan.

sation aids; (c) depressive affect,¹³ lifetime history of depression, and family history of lifetime depression among all first-degree relatives; and (d) demographic characteristics, including date of birth, ethnicity, and educational level.

For the first follow-up, questionnaires were mailed to participants 3 months after the target quit date. A second copy of the questionnaire was mailed to all nonresponding participants 2 weeks after the initial mailing. Nonresponders were contacted to complete the questionnaire over the telephone. For the second follow-up, participants were contacted 12 months after their target quit date to complete the follow-up questionnaire over the telephone. At each of the 2 follow-ups, information on the smoking pattern within the past 7 days and since quitting (3-month follow-up) or during the past year (12-month follow-up) was collected. For the 3-month follow-up, participants also were asked whether they experienced any of a series of adverse or abstinence effects since taking bupropion SR.

STATISTICAL ANALYSIS

Overall group differences on the pretreatment characteristics of participants were examined using an analysis of variance (for continuous variables) or the χ^2 test of association (for categorical variables). For analysis of outcomes, nonsmoking was defined as the self-report of no smoking, not even a puff, within the 7 days before follow-up contact. An intention-to-treat approach was used, in which individuals who were unavailable for follow-up at either point were considered to be smoking. A logistic regression analysis,¹⁴ with terms for bupropion SR dose (150 or 300 mg), type of counseling (FC or ZAP), and a dose \times counseling interaction term, was used to evaluate their relationship to smoking outcome (nonsmoking or smoking) at each of the 2 follow-up points. Main effects for dose and type of counseling were tested for statistical significance in the presence and absence of a term for their interaction. The effectiveness (proportion of sample reporting nonsmoking) of the higher dose was expressed relative to that observed for the lower dose using the odds ratio (OR) at each follow-up. A similar approach was used to express the effectiveness of the more intensive counseling relative to the less intensive counseling. A number-needed-to-treat (NNT) estimate (and corresponding 95% confidence interval [CI]) was also computed for each significant main effect at each follow-up point to facilitate clinical interpretation. The NNT was calculated as follows: $1/(\text{proportion reporting nonsmoking following treatment with the more effective treatment} - \text{proportion reporting nonsmok-$

ing following treatment with the less effective treatment). The resulting NNT can then be interpreted as the number of smokers who, if treated with the more effective treatment rather than the less effective treatment, would yield 1 additional posttreatment nonsmoker (ie, 1 more posttreatment nonsmoker than the number expected from application of the less effective treatment). In general, more effective treatments are associated with smaller estimates of NNT.¹⁵

Pairwise group comparisons of nonsmoking rates used χ^2 tests of association. After combining counseling groups with similar dosages, χ^2 tests of association were used to evaluate the association between presence or absence of an adverse or abstinence effect and the 150- or 300-mg dose level at the short-term follow-up.

The present study had 80% power (with sample size ranging from 378-383 in each of the 4 treatment groups of the design) to detect an absolute difference of 3.2% or larger in percentage nonsmoking between groups at each of the 2 follow-up points.

RESULTS

PARTICIPANT CHARACTERISTICS

Participant disposition from initial screening to trial completion is shown in the **Figure**. Of the 2979 volunteers who participated in a screening interview, 1909 were considered eligible to participate. Consent forms and pretreatment questionnaires were received from 1524 persons (80.2%). Of those who were eligible but did not participate in the final sample, 324 (17.0%) did not return their enrollment materials or subsequently refused participation, 23 (1.2%) did not have proper coverage, and the remainder reported an exclusion criterion after screening ($n=16$), were excluded as a result of the pharmacy check ($n=11$), or were excluded by their personal physician ($n=11$). The most common reasons for exclusion among the 1070 individuals determined to be ineligible were as follows: current use of contraindicated medication (341 persons [31.9%]); participation in FC within the previous 12 months (155 persons [14.5%]); history of head injury, brain tumor, transient ischemic attack, or stroke (154 persons [14.4%]); current depression (145 persons [13.6%]); current heavy use of alcohol (139 per-

Table 1. Pretreatment Characteristics of 1524 Smokers at Randomization*

Characteristic	150 mg of Bupropion SR		300 mg of Bupropion SR	
	Plus the FC Program (n = 382)†	Plus ZAP (n = 381)‡	Plus the FC Program (n = 383)§	Plus ZAP (n = 378)
Age, y	46.1 (11.8)	45.0 (12.5)	44.6 (11.4)	44.5 (11.6)
Female sex¶	59.7	60.4	56.4	53.2
White race¶	90.6	90.3	87.0	91.0
Formal schooling, y	13.7 (2.0)	13.8 (2.0)	13.6 (2.0)	13.7 (2.2)
No. of cigarettes smoked/d	23.8 (10.2)	22.7 (10.2)	23.1 (9.5)	23.2 (9.1)
Time smoked, y	27.7 (12.0)	26.3 (12.4)	25.9 (11.3)	26.3 (11.7)
FTND score#	5.8 (2.1)	5.7 (2.1)	5.8 (2.0)	5.8 (2.0)
No. of previous attempts to quit	5.9 (11.4)	5.7 (8.3)	5.4 (9.5)	6.4 (10.5)
Previous use of the nicotine patch or gum¶	63.5	58.2	65.3	66.4
Quit for 24 h in the past year¶	44.0	47.5	41.4	46.3
Depression				
Score**	1.0 (0.7)	1.0 (0.7)	1.0 (0.6)	1.0 (0.7)
Ever in lifetime¶	45.3	40.4	41.6	46.8
% Of biological family ever depressed	15.5 (21.9)	14.3 (19.8)	15.7 (22.4)	14.1 (20.3)
Nonresponders to follow-up¶				
At 3 mo	21.5	19.7	22.7	19.3
At 12 mo	15.7	12.1	18.3	12.4

Abbreviations: FC, Free & Clear; FTND, Fagerström Test for Nicotine Dependence; SR, sustained release; ZAP, Zyban Advantage Plan.

*Data are given as mean (SD) unless otherwise indicated. No significant effect for group membership was observed for any of the measured characteristics.

Bupropion was given as bupropion hydrochloride (Zyban).

†Data available for 361 to 382 participants (94.5%-100.0%).

‡Data available for 362 to 381 participants (95.0%-100.0%).

§Data available for 363 to 383 participants (94.8%-100.0%).

||Data available for 353 to 378 participants (93.4%-100.0%).

¶Data are given as percentage of participants in each group.

#The range is from 0 to 10.

**The range for the 6-item depression scale, derived from the Hopkins Symptom Checklist-90, is from 0 to 4.

sons [13.0%]); wrong or no insurance coverage (126 persons [11.8%]); family history of seizure (72 persons [6.7%]); smoked too few cigarettes per day (68 persons [6.4%]); history of heart disease, myocardial infarction, or hypertension (53 persons [5.0%]); and history of serious pulmonary disease (52 persons [4.9%]). Some individuals reported having more than 1 reason for exclusion.

Pretreatment participant characteristics are shown in **Table 1**. There were no significant differences between the 4 treatment groups on any of the pretreatment characteristics (*P* range, .09-.85). Overall, the study sample was a mean age of 45.1 (SD, 11.8) years, was 57.4% female, and smoked an average of 23.2 (SD, 9.8) cigarettes per day.

PRIMARY EFFECTIVENESS OUTCOMES

The combined nonsmoking rates for groups receiving 150 and 300 mg of bupropion SR (collapsing on type of counseling) were 24.3% and 30.9%, respectively, at 3 months (OR, 1.18; 95% CI, 1.05-1.32), and 27.5% and 29.4%, respectively, at 12 months (OR, 1.05; 95% CI, 0.94-1.17). The combined nonsmoking rates for groups receiving FC and ZAP (collapsing on dose) were 29.7% and 25.4%, respectively, at 3 months (OR, 1.10; 95% CI, 0.99-1.24), and 32.3% and 24.6%, respectively, at 12 months (OR, 1.21; 95% CI, 1.08-1.35).

Nonsmoking rates at 3 and 12 months for each of the 4 treatment groups are shown in **Table 2**. Logistic

regression analyses of dose and type of counseling main and interactive effects at 3 months revealed a consistent significant effect for dose regardless of whether the interaction term was included in the model and none for type of counseling or the interaction between dose and counseling. Pairwise group comparisons revealed significantly more nonsmokers in the 300-mg FC group compared with those for the 3 other treatments at 3 months. Logistic regression analyses of dose and type of counseling main and interactive effects at 12 months revealed a consistent significant effect for type of counseling regardless of whether the interactive term was included in the model and none for medication dosage level or the interaction between dose and type of counseling. Pairwise group comparisons revealed a significantly higher rate of nonsmoking in the 300-mg FC group compared with the 2 ZAP groups. The nonsmoking rate for the 150-mg FC treatment increased from 24.4% at 3 months to 31.4% at 12 months, and was not significantly different from the nonsmoking rate for the 300-mg FC group at 12 months.

An NNT analysis of the 2 significant main effects revealed that 15 smokers (NNT, 15.1; 95% CI, 9.0-45.0) would need to receive 300 mg of bupropion SR to avoid 1 individual who would have returned to smoking within 3 months had they received the 150-mg dose. Thirteen smokers (NNT, 13.1; 95% CI, 8.2-31.8) would need to receive FC counseling to avoid 1 individual who would have returned to smoking within 12 months had they received the ZAP form of counseling.

Table 2. Primary Effectiveness Outcomes (7-Day Point Prevalence of Nonsmoking) at 3 and 12 Months*

Time Point	150 mg of Bupropion SR†		300 mg of Bupropion SR†		Dose (150 vs 300 mg)‡	Behavioral Counseling (FC Program vs ZAP)‡	Dose × Counseling Interaction‡
	Group 1: Plus the FC Program (n = 382)	Group 2: Plus ZAP (n = 381)	Group 3: Plus the FC Program (n = 383)	Group 4: Plus ZAP (n = 378)			
3 mo§	24.4	24.2	35.0	26.7	1.18 (1.05-1.32)	1.10 (0.99-1.24)	1.10 (0.98-1.23)
12 mo	31.4	23.6	33.2	25.7	1.05 (0.94-1.17)	1.21 (1.08-1.35)#	0.99 (0.88-1.11)

*Abbreviations are explained in the first footnote to Table 1. Bupropion was given as bupropion hydrochloride (Zyban).

†Data are given as percentage of participants in each group reporting nonsmoking.

‡Data are given as odds ratio (95% confidence interval).

§The following pairs of groups are significantly different from each other: 1 vs 3 ($P = .001$), 2 vs 3 ($P = .001$), and 3 vs 4 ($P = .01$).

|| $P = .005$.

$P = .001$. The following pairs of groups are significantly different from each other: 1 vs 2 ($P = .02$), 2 vs 3 ($P = .004$), and 3 vs 4 ($P = .02$).

Table 3. Adverse Reactions Reported at the 3-Month Follow-up by Bupropion Hydrochloride SR Dose*

Adverse Reaction	Bupropion SR Dose, mg		P Value
	150†	300‡	
Difficulty sleeping	41.0	48.0	.02
Difficulty concentrating	28.1	34.8	.02
Shakiness/tremor	16.9	24.3	.002
Dizziness	17.1	20.6	.13
Rhinitis	20.8	22.4	.52
Gastrointestinal problems	19.9	26.9	.005
Dry mouth	52.0	56.6	.11
Reported some adverse effects	67.9	76.1	.002
Deliberately took less medication	3.7	20.4	.001
Discontinued medication because of adverse effects	25.9	31.1	.07

*Participants were asked to indicate whether they had experienced each symptom since the beginning of treatment with bupropion SR (Zyban). The abbreviation is explained in the first footnote to Table 1.

†Data available for 495 to 577 of the 606 participants (81.7%-95.2%) randomized to receive this dose and who responded to follow-up.

‡Data available for 511 to 582 of the 601 participants (85.0%-96.8%) randomized to receive and who responded to follow-up.

ADHERENCE TO MEDICATION REGIMENS

Self-reported adherence to the prescribed pharmacotherapy regimen (total prescribed time to take bupropion SR, 56 days) was dose dependent. Those receiving 150 mg reported taking the medication for fewer total days than did those in the 300-mg groups (41.0 vs 45.3 days) ($P < .001$). Those receiving 300 mg were more likely to report taking fewer pills per day than prescribed than those taking 150 mg (13.1% vs 0.4%; $P < .001$), while those prescribed 150 mg were more likely to report taking more pills per day than prescribed (4.8% vs 0.7%; $P < .001$).

ADVERSE REACTIONS AND ABSTINENCE EFFECTS BY DOSAGE LEVEL

An analysis of adverse reactions (**Table 3**) revealed a higher rate of reported difficulty sleeping, difficulty concentrating, gastrointestinal problems, and shakiness and tremor in the groups receiving the higher dose. There were no seizures or deaths associated with medication use in this trial. An analysis of abstinence effects revealed that

Table 4. Abstinence Effects Reported at the 3-Month Follow-up by Bupropion Hydrochloride SR Dose*

Abstinence Effect	Bupropion SR Dose, mg		P Value
	150†	300‡	
Desire to smoke	68.2	57.2	.001
Irritability or anger	31.8	33.3	.58
Depression	15.8	18.7	.20
Confusion	16.3	15.0	.54
Tension or agitation	34.4	39.5	.07
Anxiety	31.3	32.9	.58
Increased appetite	28.6	32.9	.11
Decreased appetite	8.0	10.9	.09
Racing thoughts	13.6	16.1	.24

*Participants were asked to indicate whether they had experienced each symptom since the beginning of treatment with bupropion SR (Zyban). The abbreviation is explained in the first footnote to Table 1.

†Data available for 559 to 567 of the 606 participants (92.2%-93.6%) randomized to receive this dose and who responded to follow-up.

‡Data available for 565 to 571 of the 601 participants (94.0%-95.0%) randomized to receive and who responded to follow-up.

significantly fewer individuals randomized to take 300 mg reported a desire to smoke following treatment than did individuals in the lower-dose groups (**Table 4**).

ASSOCIATION BETWEEN NONRESPONSE AND TREATMENT GROUP

Three hundred seventeen participants (20.8%) were not reached at the 3-month follow-up. There was no association between 3-month response status and treatment group membership ($P < .63$). At 12 months, 223 participants (14.6%) did not complete the follow-up. As previously observed, the association between response status and treatment group was not significant ($P < .06$) (Table 1 provides nonresponse rates for each treatment group).

COMMENT

We found that there is an advantage associated with the higher dose of bupropion SR for short-term 3-month nonsmoking that is not evident at 12 months, results similar to those found in the clinical efficacy trials. The com-

bined point-prevalence nonsmoking rates at 3 and 12 months in the groups receiving 150 mg (24.3% and 27.5%, respectively) are similar to those reported by Hurt et al¹ (26.1% at 3 months and 22.9% at 12 months). The combined point-prevalence nonsmoking rate in the 300-mg groups at 3 months (30.9%) is also consistent with that reported by Hurt et al at 3 months (29.5%). At 12 months, the combined nonsmoking rate in the groups receiving 300 mg in the present study (29.4%) was somewhat higher than that reported by Hurt et al (23.1%), but was consistent with that reported by Jorenby et al² (30.3%).

While a nonsignificant 10.5% advantage for higher-intensity telephone counseling was apparent at 3 months, this advantage increased to 20.8% at 12 months and was significant. Inspection of the 12-month results for the 150- and 300-mg FC groups (Table 2) reveals that, while a high treatment effectiveness was maintained from 3 to 12 months in the 300-mg FC group, the point prevalence of nonsmoking actually increased during that interval for the 150-mg FC group, possibly because of the increased use of behavioral skills, a feature of the yearlong FC counseling. Given the equivalence across groups for contact rates at first follow-up, we do not believe this to be an artifact of coding those unavailable for follow-up as smokers under the intent-to-treat approach to analysis. The contact rates at 12 months were lower in the FC groups than in the ZAP groups and, if anything, coding those with missing outcomes as smokers would have biased results away from the conclusion of an increase in nonsmoking. Caution is warranted until the inference of increased recycling in this group is confirmed in an independent sample.

Although both counseling arms involved less contact than in previous studies, participants still received more careful screening, educational, and behavioral follow-up than most patients would receive in the course of obtaining a prescription from their physician. These study results provide a workable model for one way to ensure that patients using bupropion SR receive comparable safety and effectiveness outcomes to those obtained in the efficacy trials.

Compared with 150 mg, individuals receiving the 300-mg form of bupropion SR reported significantly more adverse reactions, including difficulty sleeping, shakiness/tremor, difficulty concentrating, and gastrointestinal disruption. Of participants, 48.0% in the higher-dose group reported experiencing difficulty with sleeping at some point after starting treatment. This rate is higher than that reported by Hurt et al¹ (34.6%), and may result from the method of assessment used in the present study (providing a list of adverse reactions to the participants and asking them to indicate whether they experienced them since starting to take the study medication). The proportion of those who indicated that they deliberately took less bupropion SR than prescribed was almost 7 times greater among those prescribed 300 mg compared with those assigned to receive 150 mg. This finding suggests the presence of an effort to reduce dosage in those taking 300 mg, possibly as a way to manage adverse effects. Most important, however, in this actual practice setting, bupropion SR was not associated with serious adverse events such as seizures or death.

Smokers taking the higher-dose bupropion SR were less likely to report a desire to smoke following treatment for smoking, a key variable in the possible explanation of the higher dose's relative success at 3 months. Other than this association, there was no evidence in favor of the higher dose for reported lower frequency of abstinence effects. This pattern is, overall, consistent with previously reported findings¹ in which few, if any, differences between the dosage groups were noted for abstinence effects over the course of treatment and follow-up.

The lack of blinding in this trial was a necessary aspect of conducting this work within the context of a large health care system in which ethical and practical concerns are of highest priority. Of course, lack of blinding can introduce biased estimates of treatment effects that emanate from the physician, the smoking cessation counselor, or the patient in the form of decreased or increased expectations for effectiveness depending on the dose and/or nature of adjunctive counseling to which the patient is randomized. Regarding the present study's estimates of point prevalence of nonsmoking, the comparability of the present results with those from Hurt et al¹ would suggest that the impact of not blinding on the primary conclusions of this analysis is small. Depending on bupropion SR dose, the lack of blinding could also lead to an overreporting or underreporting of adverse events and abstinence effects, as described earlier herein. Therefore, this portion of the analysis should be viewed with caution.

Because this study was conducted in an actual practice setting and relied entirely on telephone and mailed interaction between study participants and project staff, several methodological refinements (biochemical confirmation of nonsmoking, confirmation of medication adherence, measures of continuous abstinence, and placebo arms) usually found in clinical trials of efficacy were not logistically feasible and, thus, could represent limitations. The absence of biochemical confirmation of nonsmoking may have resulted in an overestimation of the true abstinence rate. Assuming that misreporting of nonsmoking would occur equally across all 4 treatment groups, the impact on conclusions derived would be minimal. Moreover, a comparison of nonsmoking rates obtained in the present trial with those reported from the 2 previous trials^{1,2} of bupropion SR suggests a consistency across the 3 studies. Previous analyses^{11,16-18} suggest that the rate of underreporting of smoking in a field trial of this type may be minimal. Another limitation of the present study stems from the lack of objective measurement of adherence to the therapeutic regimen. The use of automated pill counters or blood levels can provide accurate estimates of medication adherence,^{19,20} but their use in a field trial of this size was not feasible economically. A third limitation is related to our use of 7-day point prevalence of smoking at each of the follow-up visits as the outcome measure rather than an assessment of continuous abstinence. Our decision was based on a desire to minimize contact with the participants during the follow-up to maintain fidelity with actual practice. Therefore, all comparisons with previous studies are based on self-reported point-prevalence estimates of nonsmoking.

We experienced better rates of unavailability for follow-up (20.8% at 3 months and 14.6% at 12 months) than

those reported by the efficacy trials. Hurt et al¹ reported that 35.6% of participants failed to complete the 12-month follow-up, while this percentage was 34.8% in the study by Jorenby et al.² In the latter study, 19.8% of all participants provided no information about smoking status following treatment. In the present study, the convention of coding those unavailable for follow-up as smokers may have resulted in an underestimate of the nonsmoking rate in this effectiveness trial.²¹

While the randomized controlled trial remains the gold standard for determining the efficacy of new treatments, there is increasing concern about the generalizability of results from these trials to actual practice settings.²² The results from randomized controlled trials may have limited generalizability because of the unusual circumstances in which treatments are delivered, the often extreme nature of exclusion criteria that can result in homogeneous patient populations, and the use of generally higher doses of medication than what are likely to be prescribed by practicing physicians in the normal course of patient care. Policy decisions based on these trials could lead to inefficient use of resources, neglect of equally effective older treatments, or excessively high dosing levels.²² Recently published work lends support to the notion that use of pharmaceutical aids for smoking cessation in actual practice is much shorter in duration than prescribing regimens call for,²³ tends to occur in the absence of concurrent behavioral counseling,^{23,24} results in quitting at a lower rate than reported in clinical trials,²⁴ and/or demonstrates no long-term advantage for their use over nonpharmacological smoking cessation aids.²³ Sole reliance on data from randomized controlled trials of treatments such as bupropion SR for policy decisions concerning, for example, which pharmaceutical aids to include on the formulary of a managed care organization is not warranted in view of these findings. Results from the present analysis of the first effectiveness trial of bupropion SR to be conducted, in which the higher dose of bupropion SR does not demonstrate a clear advantage for long-term cessation, further suggest that caution be used in extrapolating the results of previously published randomized controlled trials of the agent to the millions of smokers who seek to quit.

It is important to place the overall results in the context of what is known about quit rates achieved through other behavioral methods likely to be encountered in a health care setting.²⁵ Quit rates for self-quiters are estimated to range from 2% to 5%. Brief physician advice alone to stop smoking results in an absolute increase in quit rates of 2%, which can be increased to 5% with additional assistance and written materials. Intensive behavioral counseling alone (such as that done in the placebo groups in the trials of Hurt¹ and Jorenby² and colleagues) results in quit rates ranging from 12% to 19%. Compared with the success rates achieved with behavioral treatment alone, the combination of bupropion SR and minimal adjunctive support can lead to a substantial improvement in quit rates. Even the least intensive treatment evaluated in the present study (150 mg of bupropion SR plus ZAP) resulted in a short-term quit rate of approximately 24%. Clinicians who treat smoking patients should be encouraged that prescribing bupropion

SR and enrollment of the patient in some form of minimally to moderately intensive treatment will result in a reduction of the overall number of smoking patients in their practice.

This trial successfully recruited and safely treated more than 1500 patients with bupropion SR without requiring an office visit. Although bupropion SR is a medication with serious adverse effects in higher-risk patients, we were able to safely and successfully screen patients entirely over the telephone based on a protocol that included medical backup.²⁶ Although similar results may not be obtained simply by writing a prescription in the course of an acute-care visit without any screening, education, or follow-up, this method provides a workable model to ensure that patients using bupropion SR receive comparable outcomes to those obtained in the efficacy trials. Since completion of this trial, GHC has incorporated this protocol into its integrated smoking cessation service and has successfully screened via the telephone and treated several thousand more patients with bupropion SR. This has proved extremely popular with physicians, because it allows them to focus on motivating patients to quit without requiring excessive office visits for counseling. This approach may hold considerable promise for increasing the reach of the most effective means of quitting, medication combined with behavioral counseling. Given the results of this study, it is reasonable for physicians to consider initiating and maintaining therapy with bupropion SR at 150 mg rather than 300 mg for many patients based on safety and adverse effect concerns, given their equal long-term efficacy. It is also important to emphasize with patients that they can significantly increase their likelihood of long-term success by including follow-up counseling of some form. The good news is that there are new models being developed that can accomplish this in a manner less burdensome to the busy practicing physician.

Accepted for publication December 19, 2002.

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This study was supported by grant CA71358 from the National Cancer Institute, Bethesda, Md.

We thank the GHC Pharmacy for providing the study medication; and Ella Thompson, BA, Casey Luce, MPH, Rachel Grossman, BA, Gaye Courtney, MPH, and Kymberli Hemberger, MA, for their assistance in the conduct of this study.

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