Late-Term Smoking Cessation Despite Initial Failure: An Evaluation of Bupropion Sustained Release, Nicotine Patch, Combination Therapy, and Placebo

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ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy of long-term use of bupropion sustained release (SR), the nicotine patch, and the combination of these 2 treatments in patients who initially failed treatment.

Methods: This was a post hoc analysis of a multicenter, double-blind, randomized, placebo-controlled clinical trial in 893 smokers. Patients were randomly assigned to 9 weeks of treatment with placebo (n = 160), bupropion SR (n = 244), nicotine patch (n = 244), or a combination of nicotine patch and bupropion SR (n = 245). The study was originally designed with a follow-up period of 52 weeks. In this analysis, short-term success was defined as smoking cessation after 14 or 21 days of therapy and long-term success was defined as smoking cessation after >21 days of therapy. Patients who did not achieve short-term success were evaluated for long-term success at week 9 (end of treatment), 6 months, and 1 year after the start of the study.

Results: The mean age of the smokers was 44 years. The majority (93%) of patients were white, and 52% were female. The study subjects smoked an average of 27 cigarettes per day. Among the 467 patients who initially failed treatment in the first 3 weeks, treatment with bupropion SR alone and in combination with the nicotine patch produced significant increases in successful smoking cessation rates from weeks 4 to 9 (19% bupropion SR or combination, 7% nicotine patch, 7% placebo), at month 6 (11% bupropion SR, 13% combination, 2% nicotine patch, 3% placebo), and at month 12 (10% bupropion SR, 7% combination, 2% nicotine patch, 1% placebo) ($P < 0.05$ for bupropion SR and combination vs nicotine patch or placebo).

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Conclusion: Among patients who initially failed treatment, continued therapy with bupropion SR, either alone or in combination with the nicotine patch, resulted in significantly higher short- and long-term smoking cessation rates than treatment with the nicotine patch alone or placebo.

Key words: bupropion SR, nicotine patch, smoking, smoking cessation. (*Clin Ther.* 2001;23:744–752)

INTRODUCTION

Smoking cessation usually requires several attempts before long-term success is achieved. Each year ~40% of the 50 million smokers in the United States attempt to quit, and ~6% are successful.[1] Of those who initially succeed, up to 80% will experience a relapse over a 12-month period.[2] Pharmacologic therapy, in combination with a behavioral counseling program, has been moderately successful in achieving smoking cessation rates that are ~2 times those achieved with placebo.[3] Therapy with bupropion sustained release (SR), compared with placebo, has been shown to result in statistically significantly higher end-of-treatment (7-week) and 12-month cessation rates (7-week: 38% vs 19%; 12-month: 23% vs 12%).[4] In addition, a number of currently marketed products containing nicotine, including chewing gum, patches, inhalers, and nasal sprays, have shown efficacy, although the success rates vary with each. Early relapse is common in studies using nicotine replacement therapy and is often predictive of an unsuccessful cessation attempt.[5,6] A recent study found that cigarette re-exposure to smokers who had decided to quit resulted in 100% relapse within 2 days after exposure.[7] However, the efficacy of continued pharmacologic treatment in individuals who resume smoking shortly after choosing to quit has not been examined.

A MEDLINE® literature search from 1966 to the present combining *smoking cessation* and *prediction* as search terms and a second literature search combining the search terms *smoking relapse* and *prediction* revealed no reports of smoking abstinence among patients who were still smoking in early therapy.

The efficacy of placebo, bupropion SR, nicotine patch, and a combination of bupropion SR and nicotine patch were compared in a randomized, double-blind clinical study.[8] The treatment period lasted 9 weeks; day 8 (second week of treatment) was targeted as the quit date. Efficacy was based on continuous abstinence rates, weekly point-prevalence abstinence rates from day 22 through week 10, and 6- and 12-month abstinence rates. Continuous abstinence was defined as no cigarette smoking (not a single puff). Smoking cessation was verified by cigarette count recorded in the patient diary and exhaled carbon monoxide concentrations ≤10 ppm. Point prevalence was defined as no smoking since the previous clinic visit. All 3 active treatments were shown to be effective, although only bupropion SR and combination therapy were consistently and statistically significantly superior to placebo in all primary outcome measures.[4]

The present report is a post hoc analysis of these trial data to determine whether patients who initially fail a smoking cessation attempt should continue to use bupropion SR, the nicotine patch, or both to eventually achieve successful cessation. Therefore, the primary objective of this analysis was to determine whether continued treatment with bupropion SR, nicotine patch, or a combination of the 2 results in higher ces-

sation rates compared with placebo in patients who initially fail treatment.

METHODS

The original investigation was a multicenter, double-blind, randomized, placebo-controlled clinical trial conducted between August 1995 and March 1997 (Figure).[8] A total of 893 patients were randomly assigned to 1 of 4 treatment groups: placebo (n = 160), bupropion SR (n = 244), nicotine patch (n = 244), and combination therapy with nicotine patch plus bupropion SR (n = 245). All patients were ≥18 years of age, smoked ≥15 cigarettes per day at the time of enrollment, weighed ≥100 pounds, and wanted to quit smoking. Patients with unstable medical and psychiatric disorders (including cardiovascular disease, seizures, and major depression) were excluded from the study. The study protocol was approved by an institutional review board or ethics committee at each study site, and all patients provided written informed consent. In the original study, the mean age across treatment groups ranged from 42 to 44 years; 49% to 59% were female. The majority of patients were white (92%–94%), and the average number of cigarettes smoked per day ranged from 25 to 28.[8]

The primary outcome measurement in the original study was the point-prevalence rate of abstinence at 6 and 12 months. Patients were considered to be abstinent if they reported in their patient diaries that they had not smoked since the previous clinic visit and if they had an expired carbon monoxide concentration ≤10 ppm in the clinic. Patients were considered to be continuously abstinent if they had not smoked after the target quit date, as reported in their patient diaries and confirmed by carbon monoxide concentrations of ≤10 ppm at all clinic visits during the 12-month study. Adverse events were based on spontaneous reporting.

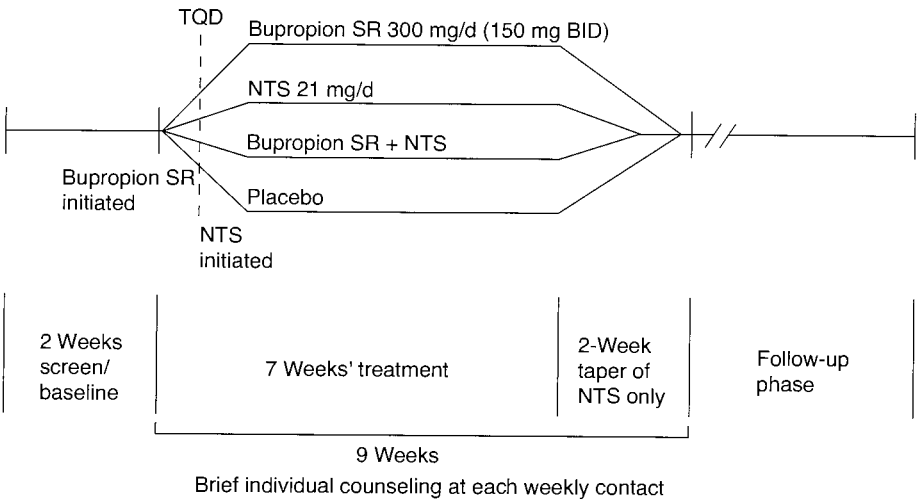

Figure. Study diagram.[8] TQD = target quit date; SR = sustained release; NTS = nicotine transdermal system (Habitrol®, Novartis Consumer Health, Inc, Summit, New Jersey).

After the 9-week active-treatment phase, follow-up continued until 52 weeks after the start of the study. Patients were assessed for rate of point prevalence and for continuous abstinence each week during the first 9 weeks of treatment and then at 10, 12, 26, and 52 weeks after the start of the study. At each visit, smoking status was evaluated based on self-report (from patient diaries) and confirmed by expired carbon monoxide concentration (≤10 ppm was indicative of nonsmoking status).

All patients who received bupropion SR were administered 150 mg each morning for the first 3 days, then 150 mg twice daily (morning and evening) on days 4 through 63. Patients in the nicotine patch group received a patch containing 21 mg of nicotine for weeks 2 to 7 (no treatment was given in the first week); the dose was tapered to 14 mg and then 7 mg for the final 2 weeks of treatment. The target quit date for all patients was set for the second week of treatment, usually day 8. All patients received standardized weekly behavioral counseling and scheduled telephone calls at specific intervals during the treatment phase of the study. Jorenby et al[8] provide a complete summary of these methods.

In this post hoc analysis, the primary outcome measurement was the number of patients who were still smoking 21 days after the start of the study (ie, initial treatment failures). These patients were assessed for point-prevalence rate of abstinence at weeks 4 through 9, at 6 months, and at 1 year after the start of the study. The end point for these patients was the development of late-term success, defined as continuous smoking abstinence at any point after week 4. Therapy was continued until the end of the treatment phase (ie, end of week 9) or until the patient discontinued therapy (resumed smoking), whichever came first.

In an additional analysis, logistic regression was used to predict late-term success as a function of cigarette counts and nicotine-craving scores in those patients who initially failed treatment but had late-term success. This was based on the hypothesis that those patients who missed their target quit date but still experienced a reduced level of smoking or a decrease in nicotine craving between the initiation of drug/placebo and week 3 may have had a better rate of success in late-term abstinence.

Statistical Analysis

Statistical analyses were performed on the intent-to-treat population, assuming that all patients (treated and control) who did not complete the study had not given up smoking and therefore failed treatment.

Chi-square analysis and analysis of variance were used to test for differences in baseline demographics. Comparison of continuous cessation rates was carried out via 2-tailed Fisher exact tests. An α level < 0.05 was considered statistically significant.

RESULTS

Withdrawal data and baseline demographic characteristics of the study population (ie, age, sex, race, body weight, education, smoking habits, previous smoking cessation attempts, baseline laboratory values, and psychological profiles) have been published previously.[8] In the original study,[8] 10% of the study population reported ≥1 adverse event. Insomnia was the most frequent adverse event (47.5% combination, 42.5% bupropion SR, 30% nicotine patch, 19.5% placebo). In the nicotine patch group, common adverse

events included dream abnormalities (18.1% vs 2.5% in the placebo group) and application site reactions (18.5% vs 6.9% in the placebo group). In the bupropion SR group, dry mouth was also reported frequently (10.7% vs 4.4% in the placebo group).

There were no significant differences among the 4 treatment groups in demographic or withdrawal characteristics. Potential risk factors for long-term failure in smoking cessation, such as age, sex, history of depression, and other factors, were found to be equally distributed among patients with early failure.

Of the 893 patients enrolled in the original study, 467 failed initial treatment and 426 were termed initial successes (Table I). Of the patients who failed initial treatment, 58 achieved late-term success by week 9. The specific demographic characteristics of patients evaluated in this analysis are shown in Table I. There were no statistically significant differences in demographic characteristics between the initial-failure group and either the original study group or the group that achieved initial success, or among the 3 initial-failure groups. The 3 initial-failure groups had moderately high cigarette use and high addiction scores (Fagerstrom tolerance scores). Although none of the patients had been diagnosed with current major depression, per the exclusion criteria, ~20% had a history of depression.

Initial Failure/Late-Term Success

For this analysis, initial failure was defined as smoking at the end of week 3. A confirmatory analysis, with initial failure defined as smoking at the end of week 2, was conducted to determine whether failure to quit smoking at an earlier time point (ie, end of week 2) predicted long-term failure. Treatment and counseling were continued for all patients with initial fail-

Table I. Baseline characteristics of the total study population and those who experienced initial success, initial failure, initial failure/late-term success, and initial failure/late-term failure.

Characteristic	All Patients (N = 893)	Initial Failure (n = 467)	Initial Success (n = 426)	Initial Failure/ Late Success (n = 58)	Initial Failure/ Late Failure (n = 409)
Mean age, y	44	43	45	45	43
Race, %					
White	93	93	93	93	93
Other	7	7	7	7	7
Sex, %					
Female	52	56	48	59	56
Male	48	44	52	41	44
History of depression, %	18	20	17	21	19
Mean Fagerstrom score*	7.36	7.54	7.17	7.17	7.59
Mean no. cigarettes/d	27	27	25	25	27

*Scale: Possible score of 0 to 11, with scores ≥6 indicating higher levels of addiction.

ure, as well as for those who had successfully quit. Periodic reassessments were made in the same manner as for those patients who had initial success. Continuous cessation rates for patients who were still smoking at the end of week 3 were calculated at the end of weeks 4 through 9, at 6 months, and at 1 year (Table II). Compared with the placebo group, each of the active-treatment groups had significantly fewer patients who were smoking at the end of week 3 ($P < 0.01$). However, among the 3 active-treatment groups, significantly fewer patients in the bupropion SR group (47%; $P < 0.05$) and combination therapy group (39%; $P < 0.01$) were still smoking at the end of week 3, compared with those who received the nicotine patch (56%).

Of the patients who failed initial treatment at week 3, bupropion SR alone and in combination with the nicotine patch resulted in significant increases in smoking cessation at weeks 4 to 9 and at 6 months compared with placebo or patch alone ($P < 0.05$ for all comparisons) (Table II). At the end of 1 year, cessation rates for bupropion SR were significantly higher than those for both placebo and nicotine replacement therapy ($P < 0.01$). There was no difference between the nicotine patch and placebo in producing late-term success at any time. A similar statistically significant result ($P < 0.05$ for all comparisons) was obtained when initial failure was defined as smoking at the end of week 2.

Cigarette Reduction and Nicotine Craving as Predictors of Late-Term Success

To determine surrogate markers that would be predictive of late-term success despite early failure, we examined the data for any correlation between fewer cigarettes smoked in initial treatment failures and eventual success. We also examined whether lower craving scores occurred in patients who achieved late-term success in quitting (ie, during weeks 4 through 7). There were no differences in either variable between those who successfully quit and those who did not, either in the group as a whole or in any treatment group within the study.

Table II. Late-term success of patients who were still smoking at the end of week 3 (initial failure).

	Initial Failure	Cessation at Weeks 4 to 9	Cessation at 6 Months	Cessation at 1 Year
Placebo, no. (%)	119/160 (74)	8/119 (7)	3/119 (3)	1/119 (1)
NRT patch, no. (%)	138/244 (57)*	10/138 (7)	2/138 (1)	3/138 (2)
Bupropion SR, no. (%)	115/244*† (47)	22/115*‡ (19)	13/115*‡ (11)	11/115*‡ (10)
Combination NRT + bupropion SR, no. (%)	95/245*‡ (39)	18/95*‡ (19)	12/95*‡ (13)	7/95§ (7)

NRT = nicotine replacement therapy (ie, nicotine patch); SR = sustained release.
*$P < 0.01$ versus placebo.
†$P < 0.05$ versus patch.
‡$P < 0.01$ versus patch.
§$P < 0.05$ versus placebo.

DISCUSSION

This post hoc data analysis of a smoking cessation trial is the first analysis comparing the nicotine patch with bupropion SR for both short- and long-term success. Results demonstrated that of the 3 treatments, only bupropion SR alone and in combination with the nicotine patch produced effective late-term success in patients who experienced early failure.

Previous work has demonstrated that long-term success with the patch was directly related to both the dose of nicotine administered and the degree of nicotine addiction of the subject,[9] although this may not be a uniform finding.[10,11] Other investigators have shown that any smoking within the first 2 to 3 weeks after initiating treatment is a powerful predictor of both short- and long-term failure with the nicotine patch, even with the use of a higher-strength (21- or 22-mg) patch.[5,6,12]

In contrast, treatment with bupropion SR or the bupropion/nicotine patch combination resulted in significantly higher abstinence rates for late-term smoking cessation (continued cessation through 52 weeks) in subjects who failed initial treatment (ie, subjects who were still smoking at week 3 of treatment). We also found a statistically significant result when failures were defined as smoking at week 2, a result that was consistent with that in the primary analysis; however, because some patients may not have fully engaged in a cessation attempt at week 2, we chose week 3 for the primary analysis.

To explore the mechanism for late-term success with bupropion SR treatment, we hypothesized that smoking reduction or attenuation in craving may help smokers to quit. However, we did not find any difference in smoking reduction or attenuation in craving in subjects who initially failed treatment but eventually quit smoking. These negative findings may be the result of the small sample size, which prevented the gathering of adequate data to examine craving effects, or the design of the trial, which prohibited examination of abstinence as the primary success end point. Therefore, a smoking reduction hypothesis merits further testing in a prospectively defined population and using specific measures of craving.

A potential limitation of this analysis is that this was a screened and selected study population composed of chronic smokers who were motivated to quit and had volunteered for the study. It has been previously shown that efficacy in smoking cessation studies is greater when using self-referred and screened smokers than in studies using unrestricted recruiting of successive smokers.[13] Therefore, the internally generated motivation and homogeneity of this population may have produced results that might not be representative of the general population of smokers.

The efficacy of continued treatment with bupropion SR, either alone or in combination with the nicotine patch, in producing success in smokers who had failed early in their attempt at smoking cessation is a new finding. It suggests that patients receiving bupropion SR (either alone or in combination) should continue to receive treatment even if they initially fail treatment. Since it is generally known that smokers do not make a serious smoking cessation attempt more than once per year, it is important for them to understand how to optimize their chances of success during the attempt.

The primary findings of this report are based retrospectively on patients who initially failed treatment, and these patients

were not rerandomized to treatment. Therefore, specific causality of effect based on the treatments evaluated here should be interpreted cautiously. Additional studies powered to detect differences between the use of bupropion SR alone and the use of bupropion SR in combination with the nicotine patch are needed.

CONCLUSIONS

Previous reports have demonstrated that early relapse in smoking cessation studies is predictive of lower overall smoking cessation rates. Although this study confirmed this finding with use of the nicotine patch alone, it also illustrated that continued therapy with bupropion SR, either alone or in combination with the nicotine patch, resulted in significantly higher cessation rates than did treatment with placebo. These results were sustained at 1-year follow-up. The results of this study suggest that bupropion SR should not be discontinued early in therapy and may be considered for use in combination with the nicotine patch in individuals who initially fail to quit.

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REFERENCES

1. Smoking cessation during previous year among adults—United States, 1990 and 1991. *MMWR Morb Mortal Wkly Rep.* 1993;42:504–507.

2. Hunt WA, Bespalec DA. An evaluation of current methods of modifying smoking behavior. *J Clin Psychol.* 1974;30:431–438.

3. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence. A US Public Health Service report. *JAMA.* 2000;283:3244–3254.

4. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195–1202.

5. Kenford SL, Fiore MC, Jorenby DE, et al. Predicting smoking cessation: Who will quit with and without the nicotine patch? *JAMA.* 1994;271:589–594.

6. Westman EC, Behm FM, Simel DL, Rose JE. Smoking behavior on the first day of a quit attempt predicts long-term abstinence. *Arch Intern Med.* 1997;157:335–340.

7. Chornock WM, Stitzer ML, Gross J, Leischow S. Experimental model of smoking re-exposure: Effects on relapse. *Psychopharmacology.* 1992;108:455–500.

8. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999; 340:685–691.

9. Daughton DM, Fortmann SP, Glover ED, et al. The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. *Prev Med.* 1999;2:113–118.

10. Hughes JR, Goldstein MG, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. *JAMA.* 1999; 281:72–76.

11. Jorenby DE, Smith SS, Fiore MC, et al. Varying nicotine patch dose and type of smoking cessation counseling. *JAMA.* 1995;274:1347–1352.

12. Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: Results of a randomised placebo-controlled trial. *Med J Aust.* 1994;161:130–135.

13. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med.* 1995;155:1933–1941.

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