

Clinical Efficacy of Bupropion in the Management of Smoking Cessation

Douglas Jorenby

Department of Medicine, Center for Tobacco Research and Intervention, University of Wisconsin Medical School, Madison, Wisconsin, USA

Abstract

Nicotine addiction is a chronic relapsing condition that can be difficult to treat. Until recently, pharmacological options for the treatment of tobacco dependence were primarily limited to nicotine replacement therapy (NRT). Sustained-release bupropion (bupropion SR) is the first non-nicotine pharmacological treatment approved for smoking cessation. Bupropion SR is recommended for first-line pharmacotherapy alongside NRT in the updated US Clinical Practice Guidelines and the UK Health Education Authority Guidelines. The UK National Institute of Clinical Excellence recommends NRT and bupropion SR for smokers who have expressed a desire to quit smoking. This review presents evidence that bupropion SR is an effective first-line therapy for smoking cessation in a wide range of patient populations. It is associated with significantly higher smoking cessation rates compared with placebo in patients with or without a history of prior bupropion SR or NRT use, and its effect is independent of gender. Bupropion SR treatment is effective in the prevention of relapse to smoking in those patients who have successfully quit, and re-treatment is effective in smokers who recommence smoking after a previous course of bupropion SR. Bupropion SR treatment relieves the symptoms of craving and nicotine withdrawal, and attenuates the weight gain that often occurs after smoking cessation. Data collected from motivational support programmes and employer-based studies provide strong evidence of the effectiveness of bupropion SR as an aid to smoking cessation in 'real life' situations, and confirm the efficacy seen in clinical trials.

Despite the introduction of the global Tobacco Free Initiative by the World Health Organization,^[1] smoking remains highly prevalent with serious consequences for public health. Cigarette smoking is the leading cause of preventable death, with more than 3 million smokers worldwide dying each year from smoking-related illnesses. Indeed, half of all lifelong smokers will die prematurely from tobacco-related causes.^[2] There are approximately 1.1 billion people worldwide who use tobacco products, and most of these want to stop.^[1] However, giving up permanently is difficult. Each

year, approximately 40% of the 50 million smokers in the US attempt to stop but only about 6% manage to do so,^[3] and the majority of people who do successfully stop smoking will relapse.^[3,4] In addition, most quit attempts are unassisted (will-power alone) and are associated with low success rates (3 to 5%).

Given that the health benefits of stopping smoking are enormous, and that significant morbidity, mortality and economic effects are attributed to smoking, clinical practice guidelines (e.g. US Public Health Service) have been published that pro-

vide recommendations for interventions and strategies to promote the treatment of tobacco dependence.^[4,5] US guidelines on smoking cessation advocate sustained-release bupropion (bupropion SR; Zyban®)¹ and nicotine replacement therapy (NRT) as first-line treatments for tobacco dependence.^[4] UK guidelines state that all healthcare professionals involved in smoking cessation should encourage and assist smokers (those smoking 10 or more cigarettes/day) in the use of NRT or bupropion SR where appropriate.^[5] The UK National Institute for Clinical Excellence recently recommended NRT and bupropion SR for smokers who express a desire to quit smoking.^[6] It is estimated that more than 2 million patients globally have successfully stopped smoking using bupropion SR (GlaxoSmithKline, unpublished data).

Bupropion SR was introduced for smoking cessation in 1997 and is the first non-nicotine pharmacological treatment approved for this indication. It is a norepinephrine and dopamine reuptake inhibitor, and is thought to work by enhancing dopaminergic activity in the mesolimbic system and the nucleus accumbens.^[7] A more detailed discussion of the mode of action of bupropion can be found in the second paper in this supplement.^[8] This review assesses the therapeutic efficacy of bupropion SR compared with placebo, NRT, and bupropion SR combined with NRT. The use of bupropion SR in the prevention of relapse to smoking and in the re-treatment of relapsed smokers, its effects on craving, withdrawal and weight gain, and its effectiveness in 'real-life' situations are also discussed.

1. Therapeutic Efficacy

Bupropion SR is an effective therapy for smoking cessation in the general population and is associated with significantly higher smoking cessation rates than placebo.^[9-12] Treatment with bupropion SR is effective in the prevention of relapse to smoking in patients who have successfully quit,^[13] and re-treatment with bupropion SR is also effective

in smokers who have returned to smoking after a previous course of bupropion^[14] or NRT.^[15]

Bupropion SR is effective in a diverse range of populations of smokers, including healthcare professionals,^[16,17] women,^[18] patients with chronic obstructive pulmonary disease (COPD),^[19] individuals with a history of alcoholism/depression,^[20,21] patients with post-traumatic stress disorder,^[22] patients with schizophrenia,^[23,24] and patients with cardiovascular disease.^[25] The effect of bupropion SR on these specific patient populations is discussed in more detail in another article in this supplement.^[26]

1.1 Clinical Studies with Sustained-Release Bupropion (Bupropion SR) in the General Population

Participants in placebo-controlled studies with bupropion SR were non-depressed individuals aged ≥ 18 years who smoked ≥ 10 cigarettes per day for the past year, and who were motivated to stop smoking. Bupropion SR was used in conjunction with motivational support – at weekly clinic visits during the treatment phase and periodic support during the follow-up phase. Subjects were randomised to receive bupropion SR 300 mg/day: they received 150 mg/day for the first 3 days and then up to 150mg twice daily thereafter. The treatment period was generally 7 to 12 weeks, and patients were followed up for 1 year. Efficacy assessments included the weekly point-prevalence rate (no smoking during a particular week of the study) and continuous abstinence rate (complete cessation over a period of time), as well as effects on craving, withdrawal symptoms and weight gain. In clinical trials abstinence was biochemically confirmed.

The efficacy of bupropion SR in promoting smoking cessation is directly proportional to dose. Bupropion SR at a dose of 300mg gave patients the best chance of quitting. Hurt and colleagues^[9] assessed the efficacy of bupropion SR for smoking cessation in a 12-month, parallel-group, double-blind, randomised, dose-response trial in 615 smokers. After 7 weeks of treatment, the week-7

1 Tradenames are used for identification purposes only and do not imply endorsement.

point-prevalence abstinence rates were 19% in the placebo group compared with 28.8% in the bupropion SR 100mg group ($p = 0.04$), 38.6% in the 150mg group ($p < 0.001$), and 44.2% in the 300mg group ($p < 0.001$). Continuous abstinence after 7 weeks of treatment (from target quit date to end of treatment) was 10.5% in the placebo group and 13.7%, 18.3% and 24.4% in the bupropion SR 100mg, 150mg and 300 mg/day groups, respectively. Weekly point-prevalence abstinence rates reported at 1-year follow-up were as follows: 12.4%, 19.6% ($p = 0.09$), 22.9% ($p = 0.02$) and 23.1% ($p = 0.01$), respectively. Johnston and colleagues^[27] carried out a retrospective pharmacodynamic/pharmacokinetic analysis of these data and confirmed that the efficacy of bupropion SR in facilitating smoking cessation was related to dose and also to the mean plasma bupropion concentration and metabolite concentration. Patients who received bupropion SR 100mg ($n = 126$), 150mg ($n = 131$) and 300mg ($n = 132$) per day were 1.42-, 1.69- and 2.84-times, respectively, more likely to stop smoking than patients ($n = 130$) receiving placebo.^[27] The predicted probability of quitting smoking increased linearly with increasing bupropion plasma concentration, from a probability of approximately 21% for patients receiving placebo to approximately 42% for patients receiving bupropion SR 300 mg/day. The likelihood of quitting smoking increased 1.01-times for every increase of 1 $\mu\text{g/L}$ in the bupropion metabolite concentration compared with placebo.^[27]

Tonstad and colleagues^[12] showed that, for smokers from the general population who received bupropion SR (300 mg/day) for 7 weeks with motivational support, the odds of quitting on bupropion SR were 2.82-times [95% confidence interval (CI): 1.89, 4.28] greater than for those on placebo. In addition, subjects treated with bupropion SR showed significantly greater 4-week continuous abstinence rates at the end of treatment (46% vs 23%; $p < 0.001$), 1-year continuous abstinence (21% vs 11%; $p = 0.002$), and weekly point-prevalence abstinence rates at 1 year (28% vs 14%; $p < 0.001$) compared with placebo (figure 1).^[12]

In an attempt to replicate a more true-to-life situation, Van der Molen and colleagues^[28] carried out an analysis of three multi-country studies using a 'slips allowed' approach. A 'slip' was defined as smoking on up to 6 consecutive days, or on a total of 9 days during the specified time period. As tobacco dependence is a chronic relapsing condition, analyses allowing slips are a more pragmatic method of measuring smoking abstinence, since they do not consider an occasional lapse or 'slip' to be a return to regular smoking, and so may be more reflective of a real-life situation. The authors showed that bupropion SR was superior to placebo, with almost one-third of subjects (25 to 30%)

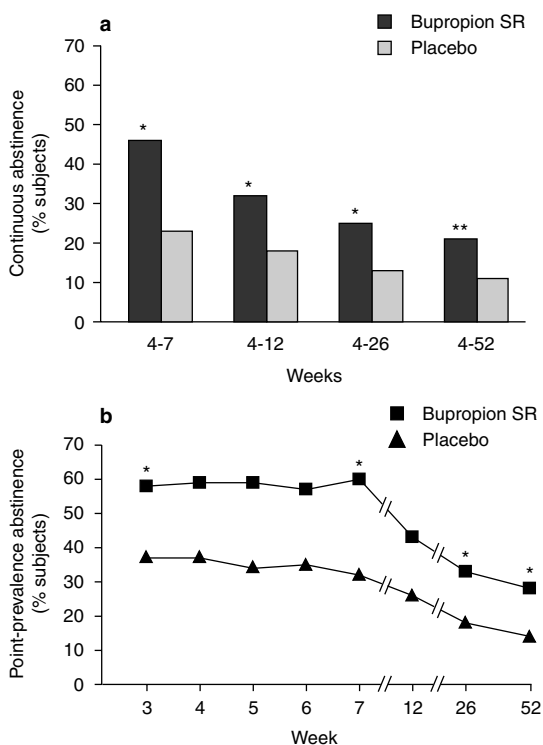


Fig. 1. Effect of treatment with sustained-release bupropion (bupropion SR) [150 mg/day for the first 3 days and 300 mg/day thereafter for a total of 7 weeks] on the following: (a) percentage of subjects continuously abstinent from smoking during the treatment phase and follow-up, * $p < 0.001$, ** $p < 0.002$; (b) percentage of subjects showing weekly point-prevalence abstinence, * $p < 0.001$. Statistical analyses were performed only at weeks 3, 7, 26 and 52.^[12]

being abstinent ('slips allowed') at 1 year, after short-term treatment.^[28]

1.2 Comparison of Nicotine Patch with Bupropion SR Alone and the Combination of Bupropion SR plus Nicotine Replacement Therapy (NRT)

In a large, double-blind study of 893 subjects, Jorenby and colleagues^[10] performed a placebo-controlled ($n = 160$) comparison of bupropion SR ($n = 244$), a nicotine patch (21mg daily for 6 weeks, 14mg daily for 1 week, 7mg daily for 1 week; $n = 244$), and bupropion SR plus a nicotine patch ($n = 245$) over a 9-week treatment period. Follow-up assessments and relapse counselling took place at weeks 10, 12, 26, and 52.

In this study, bupropion SR was significantly superior to a nicotine patch alone in facilitating smoking cessation, as assessed by both point-prevalence abstinence rates (6 and 12 months) and continuous abstinence rates over 12 months (figure 2). Four-week point-prevalence data did not differ significantly between the bupropion (60.2%) and nicotine patch groups (48%). However, by month 6, the point-prevalence abstinence was significantly greater in the bupropion group (34.8% of patients) than in the nicotine patch alone group (21.3%; $p = 0.001$). By 12 months these rates had fallen slightly, but bupropion SR (30.3%) was still significantly ($p < 0.001$) superior to a nicotine patch alone (16.4%) [figure 2 (a)]. Patients in the bupropion SR group also showed significantly ($p < 0.001$) higher rates of continuous abstinence at 12 months (18.4%) compared with the nicotine patch (9.8%) [figure 2 (b)].

Concomitant use of bupropion SR with a nicotine patch was also significantly superior to a nicotine patch alone. Four-week point-prevalence data did not differ significantly between the two groups (66.5% vs 48%). By month 6, significantly more patients in the combination group were abstinent compared with the nicotine patch group (38.8% vs 21.3%; $p < 0.001$) [figure 2 (a)]. This result was confirmed at 12 months (35.5% vs 16.4%; $p < 0.001$), and the continuous abstinence rate at 12

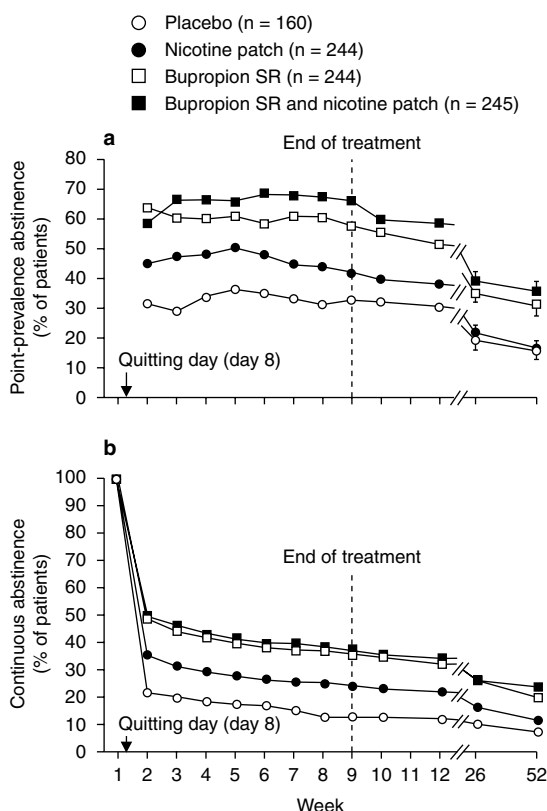


Fig. 2. The effect of treatment with sustained-release bupropion (bupropion SR) [150 mg/day for the first 3 days and 300 mg/day thereafter for a total of 9 weeks] with and without a nicotine patch (21 mg/day weeks 2-7; 14 mg/day week 8; 7 mg/day week 9) on (a) point-prevalence rates of abstinence, and (b) rates of continuous abstinence during treatment (weeks 1-9) and follow-up (weeks 10-52). (Reproduced with permission from 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: 685-91.^[10] Copyright© 1999 Massachusetts Medical Society. All rights reserved.)

months was also significantly higher in the combination group (22.5%) compared with nicotine patch alone (9.8%; $p < 0.001$) [figure 2 (b)].

At 4 weeks, all three active treatment groups showed significantly higher point-prevalence rates of abstinence (bupropion: 60.2%; nicotine patch: 48%; combination: 66.5%; $p \leq 0.005$) compared with placebo (33.8%), but only bupropion SR and the combination group had significantly higher

point-prevalence rates compared with placebo after that timepoint ($p < 0.001$ at 6 months and $p < 0.001$ at 12 months) [figure 2 (a)]. Bupropion SR alone did not differ significantly from combination therapy for any endpoint assessed.

Among the 467 patients in that study who failed to abstain from smoking within the first 3 weeks of treatment, continued therapy with bupropion SR, either alone or in combination with the nicotine patch, resulted in significantly ($p < 0.05$) higher short- and long-term smoking cessation rates compared with placebo or nicotine patch alone.^[29] Continuous smoking cessation rates for this population were as follows: during weeks 4 to 9 – 19% bupropion SR, 19% 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.^[29] These results suggest that, if patients remain motivated, bupropion SR should not be discontinued early in therapy despite initial failure to quit and may be considered for use in combination with the nicotine patch in such individuals.

2. Use of Bupropion SR for Re-Treatment and Relapse Prevention

Tobacco dependence is a chronic condition that often requires repeated intervention. Many people who attempt to stop smoking have made previous unsuccessful attempts to stop with and without pharmacological aids. An individual is likely to have tried an average of 6-times before successfully stopping smoking.^[4] An understanding of the impact of these previous attempts to stop is vital in selecting medications that may be more successful in a future attempt. Bupropion SR is an effective therapy for smokers who have previously attempted smoking cessation either with or without pharmacotherapy including bupropion SR or NRT.

2.1 Use of Bupropion SR in Smokers Previously Treated with Bupropion SR

Bupropion SR is effective in the treatment of relapsed adult smokers, even in those smokers who

have previously failed to stop smoking while using bupropion SR.^[14,30] Gonzales and colleagues^[31] investigated the effect of treatment with bupropion SR for 12 weeks, with follow-up at 6 and 12 months, in 450 smokers who had previously failed to stop smoking using bupropion SR. Compared with placebo, significantly more participants taking bupropion SR remained continuously abstinent from weeks 4 to 7 (27% vs 5%; $p < 0.001$), weeks 9 to 12 (28% vs 9%; $p < 0.001$), from week 4 to 6 months (12% vs 2%; $p < 0.001$), and from week 4 to 12 months (9% vs 2%; $p = 0.002$). Weekly point-prevalence rates were also consistently higher in the bupropion SR group than in the placebo group (21% vs 10% at 6 months and 19% vs 9% at 12 months).^[31] In a similar patient population, re-treatment with bupropion ($n = 141$) also resulted in significantly higher continuous abstinence rates compared with placebo ($n = 143$) between weeks 4 and 7 of treatment (29% vs 3%; $p = 0.002$) and weeks 4 to 12 (26% vs 8%; $p < 0.001$).^[30]

2.2 Use of Bupropion SR in Smokers Previously Treated with NRT

Re-treatment with NRT in smokers who have previously used NRT has been shown to be only moderately successful (abstinence rates ranging from 0 to 6.4% six months after stopping).^[32-34] However, a recent retrospective analysis of a placebo-controlled study showed that efficacy rates with bupropion SR or a nicotine patch were equivalent in both smokers who had used NRT previously ($n = 440$) and those who had not ($n = 453$).^[15] In an additional study, unmotivated smokers with at least two unsuccessful attempts to stop smoking in the past (at least one attempt with NRT), treatment with bupropion SR 150mg twice daily resulted in 14% of volunteers stopping smoking compared with 8% of the placebo-treated population ($p = 0.03$).^[35] Therefore, there may be a benefit in initiating bupropion treatment as an aid to smoking cessation among persons who have failed in previous quit attempts.

2.3 Use of Bupropion SR in the Prevention of Relapse

Relapse prevention remains a serious challenge in the treatment of tobacco dependence.^[4] Recent work suggests that bupropion SR may delay smoking relapse. In a large study in 784 smokers, participants received open-label bupropion SR 300mg daily for 7 weeks.^[13] Those who were abstinent during the last week of the 7-week treatment period were then randomised to receive either bupropion SR 300mg daily or placebo for a further 45 weeks, and were followed-up for a year after the end of pharmacotherapy. Participants were counselled briefly at all follow-up visits. Fifty-eight percent of participants ($n = 461$) stopped smoking during the open-label phase of the study. After randomisation, the percentage of subjects with continuous abstinence was significantly higher in the bupropion SR group than in the placebo group at week 5 (68.7% vs 58.1%; $p = 0.023$), week 17 (52.3% vs 42.3%; $p = 0.037$), but not through to week 52 or completion of the follow-up period.^[13] Smoking relapse was defined as a self-report of smoking confirmed by an expired air carbon monoxide level >10 ppm. The median time to smoking relapse from randomisation was significantly ($p = 0.021$) higher in the bupropion group (156 days) than in the placebo group ($n = 65$ days). The effect was maintained through 18 months (point prevalence) but was not seen at 2 years.

Women smokers often have low cessation rates and higher relapse rates when compared with men.^[36,37] Re-analysis of the relapse prevention study described^[38] revealed that treatment with bupropion SR, unlike some other pharmacotherapies,^[4,39,40] seems to decrease gender differences in initial abstinence and subsequent relapse rates. Women successful in achieving initial abstinence while taking bupropion SR were as likely as men to remain abstinent.^[38]

3. Effects on Craving, Withdrawal Symptoms and Bodyweight

One of the major reasons for relapse to smoking is nicotine craving and symptoms of nicotine with-

drawal. Bupropion SR is believed, at least in part, to work by alleviating nicotine cravings and by decreasing the physiological and psychological symptoms associated with nicotine withdrawal.^[7]

3.1 Craving and Withdrawal Symptoms

Several studies have reported that bupropion SR ameliorates some nicotine withdrawal symptoms.^[10,12,19,41-43] In a clinical pharmacology study of 91 smokers (who were not trying to stop smoking permanently), treatment with bupropion SR (300 mg/day) significantly ($p < 0.01$) reduced abstinence-associated increases in ratings of depression, difficulty concentrating, and irritability, and attenuated a decrease in positive affect compared with placebo or baseline.^[41] Teneggi and colleagues^[42] carried out a double-blind, randomised, 3-period crossover study in 21 healthy volunteers not intending to quit smoking. Subjects went through three 72-hour periods of free smoking, enforced smoking cessation with bupropion SR, and enforced smoking cessation with placebo. At pre-defined timepoints, three self-reported questionnaires were administered: the Tiffany Questionnaire of Smoking Urges Scale; the Schneider Smoker Complaint Scale; and the Shiffman-Jarvik Smoking Withdrawal Questionnaire. Craving was reported by 81% of patients in the placebo group compared with 55% in the bupropion SR group. Treatment with bupropion SR significantly reduced the intensity of craving but not the intensity of withdrawal symptoms compared with placebo. Craving and withdrawal symptoms could be sustained by different physiopathological pathways and are therefore separable.

In clinical trials bupropion SR has been shown to alleviate tobacco withdrawal symptoms, anger, anxiety, difficulty concentrating, craving and sadness, compared with placebo,^[12] and to attenuate symptoms of tobacco craving and withdrawal in COPD patients.^[19] Bupropion SR attenuated withdrawal symptoms when administered alone or in combination with the nicotine patch during the first week of treatment,^[10] and analysis of weekly means showed that it was significantly ($p \leq 0.05$)

more effective than placebo at reducing withdrawal symptoms in a dose-ranging study.^[9] Long-term bupropion SR recipients (open-label bupropion SR for 7 weeks, followed by randomisation to bupropion SR for 45 weeks), also reported significantly less craving than placebo recipients at weeks 12, 16, 20, 24, 48 and 52 of treatment ($p < 0.05$).^[25] A re-evaluation of the Hays study^[25] assessed the reasons why patients relapsed.^[43] For patients in the placebo group, the top five reasons were as follows: overwhelming craving (49.2%); stress (46.4%); presence of other smokers (44.5%); situation where I normally smoke (29.7%); and frustration (26.6%). Patients in the bupropion SR group showed a different pattern of relapse reasons. For bupropion SR patients, the presence of other smokers was the most frequently cited factor for relapse (49.2%) followed by stress (41.4%), situation where I normally smoke (26.7%), and frustration (23.3%). Overwhelming craving was cited by only 22.4% of bupropion SR patients. These data suggest that overwhelming cravings are a significant factor in relapse to smoking, and that bupropion SR reduces the craving associated with smoking cessation and continued craving contributing to subsequent relapses.

3.2 Effects on Bodyweight

Weight gain, actual or feared, is a major barrier to smoking cessation. In the 7- to 12-week treatment studies, attenuation of weight gain is seen while on treatment, but this benefit is not maintained in the follow-up phase.^[9,10] However, it may allow smokers in the early phase of smoking cessation to concentrate on quitting without excessive worry about diet/exercise. Hurt and colleagues^[9] showed that mean absolute weight gain was inversely related to the dose of bupropion SR. After 7 weeks of treatment, participants in the placebo group gained significantly ($p = 0.02$) more weight (2.9kg) than patients in the bupropion SR 100mg (2.3kg), 150mg (2.3kg) and 300mg groups (1.5kg). Further confirmation of the attenuating effect of bupropion SR on weight gain was found by Jorenby and colleagues.^[10] By week 7, the weight

gained by participants treated with bupropion SR was significantly lower (1.7kg; $p < 0.05$) than weight gained by participants receiving placebo (2.1kg). Patients on combined bupropion and nicotine patch therapy showed the least weight gain (1.1kg; $p < 0.05$).^[10] Others have shown that NRT attenuates the weight gain associated with smoking cessation.^[44,45]

Westlund and colleagues^[46] pooled the results of the Hurt et al. and Jorenby et al. trials,^[9,10] and showed that those patients with a sustained 4-week quit interval treated with bupropion SR gained significantly less weight at each week compared with placebo patients. The association between weight gain and treatment varied with gender. Female patients were 4-times more likely to experience low weight gain on treatment with bupropion SR, whereas male quitters were equally likely to experience low or high weight gain regardless of treatment assignment.^[46]

Long-term treatment with bupropion SR attenuates weight gain during treatment, and this effect is maintained after discontinuation of therapy. Hays and colleagues^[13] showed that participants who were treated with bupropion SR for 52 weeks and who remained abstinent for 1 year gained an average of 3.2kg less than the placebo group, who had remained abstinent for the same duration ($p < 0.001$). Bupropion SR-treated participants continued to have significantly lower weight gain 1 year after discontinuation of drug at the 2-year follow-up assessment (figure 3). Rigotti and colleagues^[47] evaluated these data and showed that the effect of long-term treatment with bupropion SR on attenuation of weight gain is more marked in women. In women, the bupropion SR-placebo difference in weight gain was 6.3kg at 52 weeks (95% CI: -8.8, -3.7) and -3.7kg at 18 months (95% CI: -7.0, -0.4). The bupropion SR-placebo differences that occurred in men did not reach statistical significance (-1.8kg at 52 weeks and -1.3kg at 18 months). In a large cohort, the mean bodyweight gain in those who abstained from smoking (without smoking cessation therapy) for >1 year ($n = 768$) was approximately 2.8kg in men and 3.8kg in

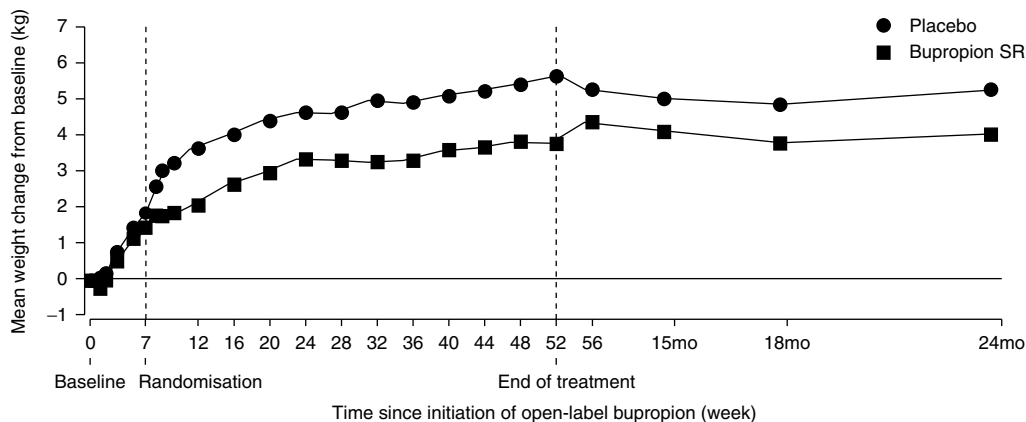


Fig. 3. The effect of treatment with sustained-release bupropion (bupropion SR) [300 mg/day] for 52 weeks on mean change in weight from baseline. (Reproduced from Hays et al.,^[13] with permission from the American College of Physicians-American Society of Internal Medicine.)

women.^[48] Bupropion SR may therefore prove particularly useful among patients who are concerned about weight gain, and who view this potential effect as a disincentive to stop smoking.

4. Real-Life Data

The effectiveness of bupropion SR as measured in clinical trials is well established, but data obtained in clinical trials may not always be indicative of the real-life situation of smoking cessation. Data collected from multiple sources, including real-life effectiveness studies, motivational support programmes, and employer-based studies, provide strong evidence of the effectiveness of bupropion SR as an aid to smoking cessation in clinical practice.

Holmes and colleagues^[49] carried out a prospective, non-randomised, observational study in UK general practices between November 2000 and September 2001 in order to estimate a real-life quit rate for bupropion SR in UK primary care. 529 subjects took part, 95% of whom had previously tried to quit. At 2 months, 7-day point prevalence and continuous abstinence rates were 41% and 34% respectively, which are consistent with results obtained in clinical trials. An interim analysis of an

open-label bupropion SR effectiveness study in Germany (primary care centres) revealed that 52% of patients were continuously abstinent for a 4-week period during treatment and experienced a reduction in the level of craving.^[50]

The data from these many sources consistently indicate that bupropion SR is an effective aid for smoking cessation when used in usual clinical practice settings. These results concur with the pattern of efficacy data observed in the clinical trials for bupropion.

5. Meta-Analyses

Clearly, a large number of randomised trials have examined bupropion SR combined with behavioural support as a treatment for smoking cessation. The body of evidence from these well conducted clinical trials confirms that bupropion SR significantly increases the likelihood of achieving smoking abstinence through to 12 months by at least 2-fold compared with placebo. The following meta-analyses used the most rigorous definition of abstinence for each trial, which in many cases was biochemically validated.

Jarvis and colleagues^[51] recently presented a meta-analysis in order to provide a pooled estimate

of the treatment effect for bupropion SR (300 mg/day) versus placebo in motivated-to-quit smokers. Major databases, trial registers and GlaxoSmithKline internal systems identified eight studies (five studies with 12-month data available) for inclusion in the meta-analyses. All studies included in the analyses were randomised, double blind and placebo controlled. Results showed that bupropion SR was associated with a significant increase in continuous abstinence from smoking for weeks 4 to 7 of the treatment period (odds ratio: 2.71; 95% CI: 1.88, 4.07) and for 12-month continuous abstinence (odds ratio: 2.10; 95% CI: 1.62, 2.73). Results for the 12-month point-prevalence abstinence were similar.^[51] Fiore and colleagues^[4] confirmed that the 6-month point-prevalence abstinence rate with bupropion SR is approximately 30% in clinical trials. The Cochrane Review also carried out a meta-analysis to assess the effectiveness of antidepressant medications in aiding long-term smoking cessation. Trials included in the meta-analysis were randomised trials comparing antidepressant drugs with placebo or an alternative therapeutic control for smoking cessation. They identified five trials. Pooling the rates of continuous abstinence at 12 months gave an estimated odds ratio of 2.73 (95% CI: 1.90, 3.94).^[52] Finally, the National Institute for Clinical Excellence (NICE) carried out a random-effects meta-analysis of ten randomised controlled trials involving 3800 smokers,^[6] and showed that the odds ratio for successful smoking cessation, comparing bupropion SR with placebo, was 2.16 (1.51-3.10). This result combines data for smoking cessation for 6 months and 12 months and, in all but one study, measures continuous abstinence. For 12 months of smoking cessation (3100 smokers; continuous abstinence in all but one study), the odds ratio was 2.05 (1.45-2.91). In terms of percentages of smokers quitting, the average over all trials shows that about 9% had not smoked for the 12 months after placebo therapy, and about 19% had not smoked after bupropion SR therapy. The results of these meta-analyses confirm that bupropion SR increases rates of smoking cessation.

6. Conclusions – the Place of Bupropion in the Management of Smoking Cessation

At the recommended dosage of 300 mg/day for 7 to 9 weeks, bupropion SR, in conjunction with motivational support, is significantly more effective than placebo as an aid to smoking cessation in patients with or without a history of prior bupropion SR or NRT use. The effect of bupropion SR as an aid to smoking cessation is independent of gender. Treatment with bupropion SR is effective for relapse prevention in patients who have successfully quit, and re-treatment is effective in smokers who have returned to smoking after a previous course of bupropion SR. Continued therapy with bupropion SR, despite initial failure, either alone or in combination with NRT, results in statistically significantly higher quit rates than placebo. Treatment with bupropion SR alleviates craving, withdrawal symptoms and attenuates the weight gain associated with smoking cessation. Real-life data confirm and support the efficacy seen in clinical trials. Bupropion SR is a highly effective therapy for smoking cessation and, as such, is recommended as first-line treatment in both the UK and US guidelines for smoking cessation. NICE further recommends bupropion SR as a treatment for those patients who express a desire to quit smoking. These data reinforce the efficacy and safety of bupropion SR and help to establish its utility in combating the adverse health effects of tobacco smoking, the leading cause of preventable death in the Western world.

Acknowledgements

Dr D. Jorenby has received research and continuing medical education support from GlaxoSmithKline.

References

1. World Health Organization (WHO). Tobacco or health: a global status report. Geneva: WHO, 1997
2. Royal College of Physicians. Nicotine addiction in Britain. London: Royal College of Physicians, 2000
3. Anonymous. Smoking cessation during previous year among adults: United States, 1990 and 1991. *Morb Mortal Wkly Rep* 1993; 42: 504-7
4. Fiore M, Bailey W, Cohen S, et al. Treating tobacco use and dependence: clinical practice guideline. Rockville (MD): US

- Department of Health and Human Services. Public Health Service, 2000 Jun
5. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Health Education Authority. Thorax 2000; 55: 987-99
 6. National Institute for Clinical Excellence. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. National Institute for Clinical Excellence Technology Appraisal Guidance No. 39. Available from: URL: <http://www.nice.org.uk> [Accessed 2002 Apr 16]
 7. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995; 56: 395-401
 8. Johnston AJ, Ascher J, Leadbetter R, et al. Pharmacokinetic optimisation of sustained-release bupropion for smoking cessation. Drugs 2002; 62 Suppl. 2: 11-25
 9. 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: 1195-202
 10. 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: 685-91
 11. Bolliger CT, Gilljam H, Lebarry F, et al. Burpropion hydrochloride (Zyban®) is effective and well tolerated as an aid to smoking cessation: a multicountry study. Eur Respir J 2001; 18 Suppl. 33: 11S
 12. Tonstad S, Aaserud E, Hjalmarson A, et al. Zyban® is an effective and well-tolerated aid to smoking cessation in a general smoking population: a multicountry study [poster no. 24]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
 13. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. Ann Intern Med 2001; 135: 423-33
 14. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. Clin Pharmacol Ther 2001; 69: 438-44
 15. Durcan MJ, White J, Jorenby DE, et al. Impact of previous nicotine replacement therapy on the efficacy of bupropion SR, nicotine transdermal system, and combination treatment for smoking cessation. Am J Health Behav 2002. In Press
 16. Puska PMJ, Brath H, Astbury CA, et al. Zyban® is an effective and well tolerated aid to smoking cessation in a health care professionals population: a multicountry study [poster no. 22]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
 17. Roussos C, Aigner K, Astbury C, et al. Involvement of healthcare professionals in a smoking-cessation programme positively benefits attitudes towards smoking [abstract]. European Society of Cardiology; 2001 Sep 1-5; Stockholm, Sweden
 18. Scharf D, Shiffman S. Are women less able to quit smoking than men? A pooled analysis of published trials of bupropion SR [poster no. RP-82]. 8th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2002 Feb 20-23; Savannah, Georgia
 19. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet 2001; 357: 1571-5
 20. Chengappa KN, Kambhampati RK, Perkins K, et al. Bupropion sustained release as a smoking cessation treatment in remitted depressed patients maintained on treatment with selective serotonin reuptake inhibitor antidepressants. J Clin Psychiatry 2001; 62: 503-8
 21. Hayford KE, Patten CA, Rummans TA, et al. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. Br J Psychiatry 1999; 174: 173-8
 22. Hertzberg MA, Moore SD, Feldman ME, et al. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. Clin Psychopharmacol 2001; 21: 94-8
 23. Evins AE, Mays VK, Rigotti NA, et al. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. Nicotine Tob Res 2001; 3: 397-403
 24. Weiner E, Ball MP, Summerfelt AA, et al. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry 2001; 158: 635-7
 25. Hays JL. Tobacco dependence treatment in patients with heart & lung disease: implications for intervention and review of pharmacological therapy. J Cardiopulm Rehabil 2000; 20: 215-23
 26. Tonstad S. Use of sustained-release bupropion in specific patient populations for smoking cessation. Drugs 2002; 62 Suppl. 2: 37-43
 27. Johnston JA, Fiedler-Kelly J, Glover ED, et al. Relationship between drug exposure and the efficacy and safety of bupropion sustained release for smoking cessation. Nicotine Tob Res 2001; 3: 131-40
 28. Van der Molen T, Raaijmakers JAM. Afkicken Met Bupropion. Medisch Contact 2001; 56 (37): 1333-6
 29. Jamerson BD, Nides M, Jorenby DE, et al. Late-term smoking cessation despite initial failure: an evaluation of bupropion sustained release, nicotine patch, combination therapy, and placebo. Clin Ther 2001; 23: 744-52
 30. Selby P, Brosky G, Baker R, et al. Zyban® is effective in the retreatment of relapsed adult smokers [poster no. 14]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
 31. Gonzales DH, Nides MA, Ferry LH, et al. Re-treating relapse: bupropion SR vs placebo in adult cigarette smokers previously treated with bupropion SR [poster no. 13]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
 32. Tonnesen P, Norregaard J, Sawe U, et al. Recycling with nicotine patches in smoking cessation. Addiction 1993; 88: 533-9
 33. Gourlay SG, Forbes A, Marriner T, et al. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. BMJ 1995; 311: 363-6
 34. Hughes JR, Grass JA, Pillitteri JL. Treatment resistant smokers: a pilot study of nicotine nasal spray and inhaler. J Addict Dis 2000; 19: 95-100
 35. Hatsukami D, Rennard S, Malcolm R, et al. A multi-center study examining the effects of Zyban® (bupropion HCl SR) vs placebo as an aid to smoking reduction leading to cessation among smokers unwilling and unable to quit smoking [poster no. 50]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
 36. Osler M, Prescott E, Godtfredsen N, et al. Gender and determinants of smoking cessation: a longitudinal study. Prev Med 1999; 29: 57-62

37. Royce J, Corbett K, Sorensen G, et al. Gender, social pressure and smoking cessation: the Community Intervention Trial for Smoking Cessation (COMMIT) at baseline. *Soc Sci Med* 1997; 44: 359-70
38. Gonzales D, Bjornson W, Durcan MJ, et al. Effects of gender on relapse prevention in smokers treated with bupropion SR. *Am J Prev Med* 2002; 22: 234-9
39. Swan GE, Jack LM, Ward MM. Sub-groups of smokers with different success rates after use of transdermal nicotine. *Addiction* 1997; 92: 207-17
40. Wetter DW, Kenford SL, Smith SS, et al. Gender differences in smoking cessation. *J Consult Clin Psychol* 1999; 67: 555-62
41. Shiffman S, Johnston JA, Khayrallah M, et al. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacol* 2000; 148: 33-40
42. Teneggi V, Squassante L, Iavarone L, et al. Craving and withdrawal symptoms, in a short term period (72 hours) of enforced smoking cessation in healthy volunteers [poster no. 4]. Third Annual Conference of the European Society for Research on Nicotine and Tobacco; 2001 Sep 20-22; Paris, France: Part II
43. Durcan MJ, Deener G, White J, et al. The effect of bupropion sustained-release on cigarette craving after smoking cessation. *Clin Ther* 2002; 24: 540-51
44. Dale LC, Schroeder DR, Wolter TD, et al. Weight change after smoking cessation using variable doses of transdermal nicotine replacement. *J Gen Intern Med* 1998; 13: 9-15
45. Hill AL, Roe DJ, Taren DL, et al. Efficacy of transdermal nicotine in reducing post-cessation weight gain in a Hispanic sample. *Nicotine Tob Res* 2000; 2: 247-53
46. Westlund R, Jamerson B, Glover E, et al. Bupropion hydrochloride sustained release tablets (BUP SR) is associated with reduced weight gain during quitting smoking: aggregated analyses of BUP SR vs placebo in quitters and non-quitters [abstract]. Abstracts of the World Conference on Tobacco OR Health (WCTOH) 2000; 1: 122
47. Rigotti NA, Thorndike AN, Durcan MJ, et al. Attenuation of post-cessation weight gain in smokers taking bupropion: the effect of gender [abstract]. Sixth Annual Conference of the Society for Research on Nicotine and Tobacco; 2000 Feb 18-20; Arlington, Virginia
48. Williamson DF, Madans J, Anda RF, et al. Smoking cessation and severity of weight gain in a national cohort. *N Engl J Med* 1991; 324: 739-45
49. Holmes S, Browning D, Powell S, et al. Real-World smoking cessation rates with bupropion SR in general practice in the UK [abstract]. Accepted by the 3rd European Conference on Tobacco OR Health; 2002 Jun 20-22; Warsaw, Poland
50. Bergman L. An open-label, multicentre study with general practitioners to assess efficacy and safety of bupropion SR (2 x 150mg per day) dependent on (sub-) depression and motivation. Presented at the 107th Congress of German Society of Internal Medicine; 2001 Apr 21-25; Wiesbaden, Germany
51. Jarvis MJ, Powell S, Marsh H, et al. A meta-analysis of clinical studies confirms the effectiveness of bupropion SR (Zyban®) in smoking cessation [abstract]. Presented at the Seventh Annual Conference of the Society for Research on Nicotine and Tobacco; 2001 Mar 23-25; Seattle, Washington
52. Hughes JR, Stead LF, Lancaster T. Anti-depressants for smoking cessation. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 4. Oxford: Update Software, 1997

Correspondence and offprints: *Douglas Jorenby*, Center for Tobacco Research and Intervention, University of Wisconsin Medical School, 1930 Monroe Street, Madison, Wisconsin 53711, USA.
E-mail: Dej@CTRI.medicine.wisc.edu