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Use of Sustained-Release Bupropion in Specific Patient Populations for Smoking Cessation

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Abstract

Smoking cessation trials of sustained-release bupropion (bupropion SR) were initially conducted in a general population of smokers who were motivated to quit smoking. Bupropion SR has also been found to be a useful treatment of tobacco dependence in various special populations of smokers who often experience difficulty in overcoming tobacco addiction.

Point-prevalence quit rates at 6 months were higher in those treated with bupropion SR than in those receiving placebo in studies on smokers with chronic obstructive pulmonary disease (23% *vs* 16%) and in those with cardiovascular disease (34% *vs* 12%). Abstinence from smoking after treatment with bupropion SR was not affected by a history of major depression or alcoholism. Women treated with bupropion SR were just as likely as men to abstain from smoking. Approximately one-third of a study population who were initially unwilling or unable to quit smoking were able to reduce their smoking by 50% or more during therapy with bupropion SR; 14% of these went on to achieve abstinence.

Bupropion SR was well tolerated in these trials; importantly, it had no clinically significant effect on mean blood pressure in smokers, including those with hypertension, and attenuated the weight gain associated with smoking cessation, particularly in women.

It is estimated that only 3 to 5% of smokers manage to quit smoking unaided.[1] Clinical trials have shown that sustained-release bupropion (bupropion SR; Zyban®)[1], in combination with motivational support, is an effective and well tolerated, non-nicotine, first-line treatment of tobacco dependence and a preventive of relapse in general smoking populations who are motivated to quit smoking.[2-4]

Initially, randomised, double-blind, placebo-controlled trials of bupropion SR for the treatment of tobacco dependence were conducted in a general population of smokers who were motivated to stop smoking. This review focuses on clinical trials of bupropion SR as a treatment of tobacco dependence in special populations of smokers who face varying and often additional barriers to becoming smoke-free.

1. Smokers with Smoking-Related Diseases

Smoking is the major cause of cardiovascular disease and chronic obstructive pulmonary disease (COPD), both of which are major causes of mor-

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

bidity and mortality. Long-term prognosis is improved in patients with cardiovascular disease or COPD who quit smoking,[5,6] and it is highly desirable from a health and economic viewpoint that these people stop smoking. However, compared with general populations of smokers, individuals who have developed smoking-related cardiovascular disease or COPD are generally older, have a higher pack-year history and higher nicotine-addiction scores, and may have a history of depression, all of which reduce the probability of successfully quitting.

The efficacy of treatment with bupropion SR (7 or 12 weeks) for smoking cessation has been assessed in 6- to 12-month double-blind, placebo-controlled, randomised trials in chronic, motivated-to-quit smokers with stable cardiovascular disease[7] or mild-to-moderate COPD.[8]

In smokers with mild-to-moderate COPD,[8] absolute cessation rates in patients receiving bupropion SR were lower than those previously obtained in general populations of smokers.[2,3] Nevertheless, 28% of bupropion SR patients were continuously abstinent from weeks 4 to 7 of the 12-week treatment period, compared with 16% of those receiving placebo ($p = 0.003$), and the 26-week continuous abstinence for bupropion SR (16%) was almost double that with placebo (9%) [table I].[8]

The efficacy of bupropion SR in the study conducted exclusively in smokers with stable cardiovascular disease[7] was comparable to that observed in trials conducted in general populations of smokers (see table I).[2,3] Forty-three percent of bupropion SR recipients remained continuously abstinent from weeks 4 to 7 of the 7-week treatment period, compared with 19% of placebo recipients [$p < 0.001$; odds ratio (OR) 3.27; 95% confidence interval (CI): 2.24 to 4.84] (see table I).[7] Compared with placebo, abstinence rates were consistently more than doubled with bupropion SR right through follow-up to week 26, when continuous abstinence rates were 27% for bupropion SR and 11% for placebo ($p < 0.001$; OR 3.09; 95% CI: 1.96 to 4.96) [see table I].[7] There was no change in mean blood pressure or mean pulse rate during treatment with bupropion SR compared with placebo, either in subjects with normal blood pressure or in treated hypertensive subjects.

2. Smokers with a History of Depression or Alcoholism

Psychiatric disorders are more prevalent among smokers than in the general population.[14,15] As many as 30% of patients seeking help to stop smoking may have a history of depression and 20% or more may have a history of alcohol abuse or dependence.[16] Depressive symptoms can hamper attempts to quit smoking,[17] and a history of depression[18] or alcoholism[19,20] has been associated with poor outcomes for smoking treatment.

Subpopulation analyses from one of the first trials examining bupropion SR for smoking cessation[2] showed that bupropion SR was effective in aiding smoking cessation in smokers with a history of major depression or alcoholism (see table I).[11] Logistic regression analysis revealed that abstinence after the 7-week treatment period and at 1 year were unaffected by a history of depression or alcoholism. At the end of treatment, the dose-response effect seen with bupropion SR in smokers with a history of depression (OR 1.63; $p = 0.027$) was consistent with that found in smokers with no history of depression or alcoholism (OR 1.50; $p < 0.001$).[11] The estimated dose-response effect of bupropion SR at 1 year in smokers with a history of depression (OR 1.50; $p = 0.127$) was consistent with that found in smokers without a history of depression or alcoholism (OR 1.29; $p = 0.021$). Separate logistic regression was not performed in those with a history of alcoholism because of the small sample size. Smokers with a history of depression or alcoholism in this subpopulation analysis were more severely dependent on nicotine than smokers without such histories. However, the fact that the study excluded smokers with current depression and alcoholism – i.e. within the past year – may limit the significance of the results, as it is possible that the recency of comorbidities may impact on treatment outcome.[11]

Table I. Summary of clinical trials and secondary analyses assessing the efficacy of sustained-release bupropion (BUP) as an aid to smoking cessation in specific populations

Patient population	Treatment	Treatment duration (weeks)	Number of patients	7-day point prevalence[a] (%)			Continuous abstinence (%)		
				end of treatment	6 months	12 months	end of treatment	6 months	12 months
Primary analyses of clinical trials									
General[2] (db)	BUP[b]	7	156	44.2[c]	26.9[c]	23.1[c]	24.4[d]	12.2[d]	NR
	PL	7	153	19.0	15.7	12.4	10.5[d]	5.9[d]	NR
General[3] (db)	BUP[b]	9	244	57[c]	34.8[c]	30.3[c]	36[c,d]	26[c,d]	18.4[c,d]
	PL	9	160	32	18.8	15.6	13[d]	11[d]	5.6[d]
CVD[7] (db)	BUP[b]	7	313	53[c]	34[c]	NR	43[c,e]	27[c,e]	NR
	PL	7	313	24	12	NR	19[e]	11[e]	NR
COPD[8] (db)	BUP[b]	12	204	29[c]	23	NR	18[c,e]	16[c,e]	NR
	PL	12	200	17	16	NR	10[e]	9[e]	NR
Medicaid[9] (ol)	BUP[b]	7	106	NR	NR	NR	19.8[e]	NR	NR
female		7	74	NR	NR	NR	17.6[e]	NR	NR
male		7	32	NR	NR	NR	25.0[e]	NR	NR
Black		7	63	NR	NR	NR	20.6[e]	NR	NR
White		7	29	NR	NR	NR	20.7[e]	NR	NR
Unwilling/unable to quit[10] (db)	BUP[b]	7[f]	113	NR	NR	NR	14[c,e]	NR	NR
	PL	7[f]	101	NR	NR	NR	8	NR	NR
Secondary analyses of clinical trials									
History of depression[11] (db)	BUP[b]	7	22	36	NR	18	NR	NR	NR
	PL	7	31	16	NR	10	NR	NR	NR
History of alcoholism[11] (db)	BUP[b]	7	12	42	NR	17	NR	NR	NR
	PL	7	15	27	NR	27	NR	NR	NR
History of depression[3,12] (db)	BUP[b]	9	51	NR	NR	29	NR	NR	NR
	PL	9	25	NR	NR	8	NR	NR	NR
Males[13]	BUP[b] (ol)	7	361	61.8	NR	NR	NR	NR	NR
	BUP (db)	45[g]	98	54.1	NR	NR	37.8	NR	NR
	PL (db)	45[g]	112	42.9	NR	NR	36.6	NR	NR

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table I here

These data are, however, further supported by subpopulation analyses from another bupropion SR study.[3] Compared with placebo, bupropion SR approximately tripled year-long abstinence in smokers with a history of depression (see table I).[12] A history of depression predicted a worse smoking cessation outcome when smokers were receiving placebo or a nicotine patch, but not when they were receiving bupropion.[12]

3. Female Smokers

The urgency to stop smoking is amplified in women because of the additional health risks that smoking poses, including reproductive health risks,[21] increased risk of stroke in those using oral contraceptives,[22] and greater risk of osteoporosis.[23] However, females often have lower smoking cessation rates[24-26] and higher relapse rates[27] than male smokers. Possible weight gain associated with smoking cessation may deter women from making and/or maintaining a quit attempt.[28]

3.1 Efficacy

An analysis of data obtained from a trial of long-term (1 year) bupropion SR treatment in a general population of smokers who were motivated to quit[4] indicated that women who achieved initial abstinence were just as likely as men to remain abstinent for 1 year (see table I).[13] Smokers received bupropion SR during an initial 7-week open-label phase, and those who achieved abstinence were randomised to continue with bupropion SR or to receive placebo for 45 weeks of double-blind therapy. The median time to relapse from continuous abstinence in both males and females receiving long-term bupropion SR was 32 weeks, compared with 20 weeks for both sexes receiving placebo. In addition, there was no significant difference between males and females in 7-day point-prevalence abstinence rates after 7 weeks of open-label bupropion SR treatment (61.8% and 55.6%, respectively) [see table I].[13]

A subpopulation analysis of data from a trial in which smokers received short-term (9 weeks) therapy[3] showed that, compared with placebo, buprop-

Table I. Continued.

Patient population	Treatment	Treatment duration (weeks)	Number of patients	7-day point prevalence[a] (%)			Continuous abstinence (%)		
				end of treatment	6 months	12 months	end of treatment	6 months	12 months
Females[13]	BUP[b] (ol)	7	423	55.6	NR	NR	NR	NR	NR
	BUP (db)	45[g]	118	55.9	NR	NR	36.4	NR	NR
	PL (db)	45[g]	104	41.3	NR	NR	29.8	NR	NR
Females[3,12] (db)	BUP[b]	9	126	NR	NR	26	NR	NR	NR
	PL	9	94	NR	NR	8	NR	NR	NR

a Patients who had not smoked during the previous 7 days.

b Patients received sustained-release bupropion (bupropion SR) 150 mg/day for 3 days then bupropion SR 300 mg/day (twice daily) for the remainder of the study, and treatment was usually started 1 week before the target quit date.

c $p < 0.05$ *vs* comparator.

d From target quit date (1 week).

e From week 4.

f ≤ 6 months of smoking reduction therapy + 7 weeks of smoking cessation therapy.

g Patients had received a 7-week period of open-label bupropion SR before being randomised to double-blind therapy with placebo or bupropion SR.

CVD = cardiovascular disease; **COPD** = chronic obstructive pulmonary disease; **db** = double blind; **NR** = data not reported; **ol** = open label; **PL** = placebo.

ion SR approximately tripled year-long abstinence in female smokers (see table I).[12] Female gender predicted a worse smoking cessation outcome when smokers were receiving placebo or a nicotine patch, but not when they were receiving bupropion.[12]

In their study of patients with COPD, Tashkin et al. observed that slightly fewer females than males were continuously abstinent during weeks 4 to 7 of treatment with bupropion SR (25% *vs* 30%).[8] Nevertheless, the equivalent placebo-adjusted response rate to bupropion SR was more favourable in women than in men (ORs of 2.7; 95% CI: 1.2 to 6.0 *vs* 1.7; 95% CI: 0.9 to 3.2, respectively).[8]

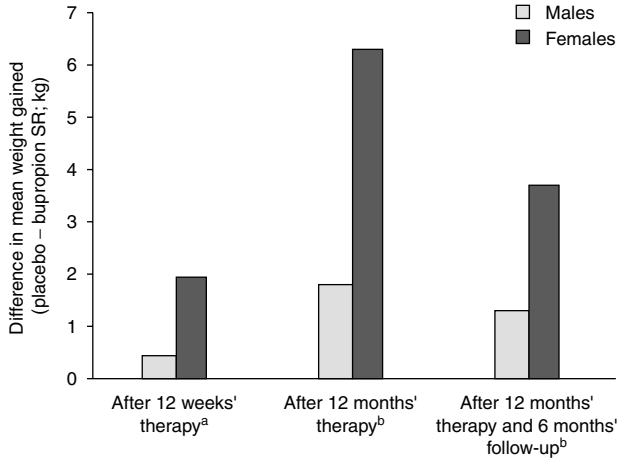
A pooled analysis of clinical trial data from 1163 people found that females had lower quit rates than men regardless of treatment with bupropion SR or placebo. Logistic regression analyses did not reveal a treatment-gender interaction and males and females benefited equally from bupropion SR (OR 1.03, NS).[29]

3.2 Effects on Bodyweight

Concern about possible weight gain resulting from smoking cessation may have an especially negative effect on a female smoker's resolve to quit.[28] Results from several studies have shown that bupropion SR is able to attenuate weight gain after smoking cessation.[2-4,7,8] In a relapse prevention study in which treatment was continued for 1 year,[4] a reduction in weight gain was most marked in those who remained abstinent through week 52 and this was maintained through an additional 1 year of follow-up. When analysed according to gender, the advantage of long-term bupropion SR relative to placebo in attenuating weight gain was greater in women than in men (figure 1).[30] In the shorter-term studies (see figure 1),[2,3,7,8] the advantageous effect of bupropion SR on weight gain attenuation was limited to the duration of the treatment period. However, bupropion treatment may be of benefit in the short-term when it is the quit attempt, and not necessarily diet and exercise, that will be the focus.

4. Medicaid Population

Compared with that in the general population, the prevalence of smoking tends to be greater in indigent populations,[31] such as those with poor



a From a study population with mild-to-moderate COPD.
b From a general smoking population study.

Fig. 1. Difference in mean weight gained in male and female smokers receiving placebo relative to mean weight gained with bupropion SR (300 mg/day) in those who remained abstinent after short-term[8] or long-term[30] therapy. **COPD** = chronic obstructive pulmonary disease.

education, those in unskilled manual employment, and those in single-parent households. Medicaid is a publicly funded US health insurance programme that provides coverage for certain low-income people.

In an open-label trial, motivated-to-quit smokers receiving Medicaid were given 7 weeks of therapy with bupropion SR to aid smoking cessation.[9] Cessation rates were lower than those observed in predominantly white, middle-class populations (see table I).[2,3] In smokers who continued to smoke during weeks 4 to 7 of treatment, average daily cigarette consumption was consistently reduced throughout the treatment and 1-year follow-up phases.[9] These results are particularly encouraging, since it is known that smoking cessation rates tend to show a strong direct relationship with socioeconomic status.[32]

5. Smokers Unwilling or Unable to Quit

The smokers discussed in previous sections were motivated to quit smoking; however, some smokers are initially unwilling to attempt to quit.[33] Such smokers may be unaware of the harmful effects of smoking, may lack the financial resources to seek help, may have concerns about quitting or may feel demotivated because of previous unsuccessful attempts to quit.[16] Nevertheless, smokers who are initially unwilling to quit may be willing to reduce their intake rather than quit or as a precursor to quitting.[34]

5.1 Efficacy

In a randomised, double-blind, placebo-controlled study, bupropion SR was shown to aid smoking cessation in a population of smokers who were initially unwilling or unable to quit but were willing to reduce their cigarette consumption (see table I).[10] Approximately one-third of the total study population, after reducing their smoking by 50% or more, were willing to make a quit attempt and entered a cessation arm in the study. Fourteen percent of smokers randomised to bupropion SR were continuously abstinent from weeks 4 to 7 of the 7-week cessation period, compared with 8% of those randomised to placebo ($p = 0.03$) [see table I]. Although the majority of study participants continued to smoke,[10] they successfully reduced their tobacco consumption.

6. Conclusions

Smoking is a complex, multifactorial addiction, and the presence of various social and clinical factors can make it harder for some smokers to quit than others. For example, a poorly educated female with COPD and a history of depression would generally find it much harder to cease smoking than a 40-year old, healthy, well educated male, even if the two had a similar daily smoking rate.

Clinical trial results indicate that bupropion SR is an effective treatment of tobacco dependence in various populations of smokers who may experience difficulty in quitting smoking. Bupropion SR is as effective and well tolerated in smokers with stable cardiovascular disease or mild-to-moderate COPD as it is in general populations of smokers.[7,8] The efficacy of bupropion SR as an aid to smoking cessation does not appear to be compromised in smokers with a history of depression or alcoholism.[11,12] Male and female smokers benefit equally from this agent.[8,12,13,29] Furthermore, bupropion SR attenuates the weight gain associated with smoking cessation,[2-4,8] particularly in women.[8,30] Bupropion SR appears to be useful as an aid to smoking cessation in socially and economically disadvantaged populations.[9] Moreover, it may be beneficial in aiding smoking cessation in smokers who are motivated to reduce their smoking and who then make a concerted effort to quit.[10]

In conclusion, bupropion SR is a useful first-line treatment of tobacco dependence in smokers with smoking-related comorbidities such as pulmonary or cardiovascular disease, as well as those with a history of depression or alcoholism, females, indigent populations, and those who are unwilling or unable to quit.

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References

1. Hughes JR, Gulliver SB, Fenwick JW, et al. Smoking cessation among self-quitters. Health Psychol 1992; 11 (5): 331-4
2. 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 (17): 1195-202
3. 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 (9): 685-91
4. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. Ann Intern Med 2001; 35 (6): 423-33
5. Rosenberg L, Kaufman DW, Helmrich SP, et al. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 1985; 313 (24): 1511-4
6. Scanlon PD, Connett JE, Waller LA, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med 2000; 161 (2 Pt 1): 381-90
7. Tonstad S, Murphy M, Astbury C, et al. Effectiveness and tolerability of Zyban in smokers with cardiovascular disease - week 26 follow-up phase results [oral presentation]. European Society of Cardiology; 2001 Sep 1-5; Stockholm: abstract no.: 1460
8. Tashkin DP, 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
9. Olopade CO, Colah JJ, Wilken L, et al. Bupropion SR as an aid to smoking cessation in cigarette smokers receiving medicaid [abstract]. Sixth Annual Conference of the Society for Research on Nicotine and Tobacco; 2000 Feb 18-20; Arlington (VA)
10. Hatsukami D, Rennard S, Malcolm R, et al. A multicentre study examining the effects of Zyban (bupropion SR) vs placebo as an aid to smoking reduction leading to cessation among smokers unwilling or unable to quit smoking [abstract]. Eighth Annual Conference of the Society for Research on Nicotine and Tobacco; 2002 Feb 22; Savannah (GA)
11. 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
12. Smith SS, Jorenby DE, Leischow SJ, et al. Targeting smokers at high risk for relapse: treating women and those with a history of depression [poster]. Eleventh World Conference on Tobacco OR Health; 2000 Aug 6-11; Chicago (IL)
13. Gonzales D, Bjornson WM, Buist AS, et al. Effects of gender relapse prevention in smokers treated with bupropion SR. Am J Prev Med 2002; 22 (4): 234-9
14. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet 1995; 25: 95-101
15. Hall SM, Munoz RF, Reus VI, et al. Nicotine, negative affect, and depression. J Consult Clin Psychol 1993; 61 (5): 761-7
16. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical Practice Guideline. Rockville (MD): US Department of Health and Human Services. Public Health Service, 2000 Jun
17. Glassman AH, Covey LS, Stetner F, et al. Smoking cessation and the course of major depression: a follow-up study. Lancet 2001; 357 (9272): 1929-32
18. Glassman AH, Stetner F, Walsh BT, et al. Heavy smokers, smoking cessation, and clonidine: results of a double-blind, randomized trial. JAMA 1988; 259: 2863-6
19. Covey LS, Glassman AH, Statner F, et al. Effect of history of alcoholism or major depression on smoking cessation. Am J Psychiatry 1993; 150 (10): 1546-7
20. Hurt RD, Dale LC, Offord KP, et al. Nicotine patch therapy for smoking cessation in recovering alchoholics. Addiction 1995; 90 (11): 1541-6
21. Windham GC, Elkin EP, Swan SH, et al. Cigarette smoking and effects on menstrual function. Obstet Gynecol 1999; 93 (1): 59-65
22. Petitti DB, Sidney S, Bernstein A, et al. Stroke in users of low-dose oral contraceptives. N Engl J Med 1996; 335 (1): 8-15
23. Hollenbach KA, Barrett-Connor E, Edelstein SL, et al. Cigarette smoking and bone mineral density in older men and women. Am J Public Health 1993; 83 (9): 1265-70
24. Bjornson W, Rand C, Connett JE, et al. Gender differences in smoking cessation after 3 years in the Lung Health Study. Am J Public Health 1995; 85 (2): 223-30
25. Swan GE, Jack LM, Ward MM, et al. Subgroups of smokers with different success rates after use of transdermal nicotine. Addiction 1997; 92 (2): 207-17
26. Wetter DW, Kenford SL, Smith SS, et al. Gender differences in smoking cessation. J Consult Clin Psychol 1999; 67 (4): 555-62
27. Royce JM, Corbett K, Sorensen G, et al. Gender, social pressure, and smoking cessations: the Community Intervention Trial for Smoking Cessation (COMMIT) at baseline. Soc Sci Med 1997; 44 (3): 359-70
28. Meyers AW, Klesges RC, Winders SE, et al. Are weight concerns predictive of smoking cessation?.: a prospective analysis. J Consult Clin Psychol 1997; 65 (3): 448-52
29. 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]. Eighth Annual Meeting of the Society for Research on Nicotine and Tobacco; 2002 Feb 20-23; Savannah (GA)
30. Rigotti NA, Thorndike AN, Niaura R, et al. 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 (VA)
31. Anonymous. Cigarette smoking among adults: United States, 1992, and changes in the definition of current cigarette smoking. Morb Mortal Wkly Rep 1994; 43: 342-6
32. Jarvis MJ. Patterns and predictors of smoking cessations in the general population. In: Bolliger CT, Fagerstom KO, editors. The tobacco epidemic. Basel: Karger, 1997: 151-64
33. DiClemente CC, Prochaska JO, Fairhurst SK, et al. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991; 59 (2): 295-304
34. Cinciripini PM, Wetter DW, McClure JB. Scheduled reduced smoking: effects on smoking abstinence and potential mechanisms of action. Addict Behav 1997; 22 (6): 759-67

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