REVIEW ARTICLE

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Tolerability and Safety of Sustained-Release Bupropion in the Management of Smoking Cessation

Henri-Jean Aubin

Centre de Traitement des Addictions, Hôpital Emile Roux, Limeil-Brévannes, France

Abstract

Sustained-release bupropion (bupropion SR) was first launched in the US in 1997 as an aid to smoking cessation and has since been launched in many other countries. Adverse events associated with the use of bupropion SR at the recommended dosage of 150mg twice daily in clinical trials most commonly included insomnia, headache, dry mouth, nausea and anxiety; insomnia and anxiety are also recognised as symptoms of nicotine withdrawal. Only insomnia and dry mouth occurred significantly more frequently with bupropion SR than with placebo. Relative to placebo, no significant changes in mean values for heart rate, blood pressure or routine laboratory parameters have been reported in smokers using bupropion SR alone in clinical trials. When bupropion SR was compared with a nicotine transdermal patch in a clinical trial, insomnia predominated in the bupropion SR group, while dream abnormalities were more common in smokers using the nicotine patch. Bupropion SR and the nicotine transdermal patch in combination can be used safely (with appropriate monitoring) as an aid to smoking cessation.

Infrequent but clinically important adverse reactions to bupropion SR include seizures and hypersensitivity reactions: in controlled clinical trials of bupropion SR (300 mg/day), where smokers were carefully screened for risk factors for seizure, the incidence of both seizures and severe hypersensitivity reactions was ≈0.1% for each event. In order to avoid a risk of seizure of greater than 0.1%, smokers should be screened for predisposing risk factors and adhere to the manufacturer's dosage recommendations (maximum daily dose of 300mg).

Thus, bupropion SR is generally well tolerated, as seen by the low discontinuation rate due to an adverse event in clinical trials (6 to 12%). The most common adverse events (insomnia and dry mouth) are generally transient and often resolve quickly without therapeutic intervention; they can be managed if necessary by a reduction in bupropion dose.

Sustained-release bupropion (bupropion SR; Zyban®)[1] is the first licensed non-nicotine-based pharmacological therapy for smoking cessation. Since the launch of bupropion SR for smoking cessation in 1997 (and up to June 2001), some 9 million people worldwide have received bupropion SR treatment for this indication and 7000 smokers received the drug during clinical studies for this indication.[1] The clinical trial programme has

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

shown bupropion SR to be more effective than placebo in improving initial and long-term smoking cessation rates and in preventing relapse; quit rates (point prevalence) at 1 year are generally in the range of 25 to 30%. Approximately twice as many smokers who used bupropion SR rather than placebo had quit smoking a year after the start of treatment.[2,3] At the recommended dosage of 300mg daily, bupropion SR appears to be generally well tolerated, although it is often difficult to differentiate drug-specific adverse events from nicotine withdrawal symptoms such as agitation, anxiety, irritability and insomnia.

This article reviews the safety and tolerability of bupropion SR as an aid to smoking cessation, and compares the safety profile of bupropion SR with that of nicotine replacement therapy (NRT). Precautions to be taken when using bupropion SR in specific patient groups are also discussed.

1. Clinical Trial Programme: Tolerability and Safety Profile

Several large-scale placebo-controlled clinical trials of bupropion SR for smoking cessation have been conducted in the general population of smokers[2-7] as well as in smokers with tobacco-related cardiovascular and pulmonary diseases.[8,9] These clinical trials have typically been based upon a 7- to 12-week period of randomised, double-blind treatment with bupropion SR, with subsequent drug-free follow-up of patients for 6 or 12 months.

1.1 General Tolerability Profile of Sustained-Release Bupropion (Bupropion SR) in Clinical Trials

Controlled clinical trials of bupropion SR for smoking cessation have shown that it is generally well tolerated at dosages of 100 to 300mg daily over treatment periods of 7 to 45 weeks in the general population of smokers.[2-7] The most frequent adverse events relate to the gastrointestinal system [dry mouth (bupropion 1 to 13% *vs* placebo 0 to 10%) and nausea (bupropion 4 to 10% *vs* placebo 3 to 7%)] and the central nervous system [insomnia (bupropion 10 to 42% *vs* placebo 7 to 21%), headache (bupropion 7 to 32% *vs* placebo 9 to 33%) and anxiety (bupropion 6 to 9% *vs* placebo 5 to 11%)]. In these trials, the incidence of dry mouth and insomnia has proved to be significantly higher with bupropion SR 300 mg/day than with placebo (table I and table II). On the basis of evidence from clinical trials, bupropion SR has a favourable cardiovascular profile; tachycardia, hypertension, vasodilation and postural hypotension are reported at a frequency no greater than for placebo.[10,11]

The main safety considerations with bupropion SR are the risk of seizures and severe hypersensitivity reactions.[12-15] Although these are potentially serious complications (they are typically not life threatening), reports of these adverse events are rare (≈0.1% incidences in clinical trials). Seizures appear to be dose related,[16] and in order to avoid a risk of seizure greater than 0.1% the manufacturer's dosage recommendations should be strictly adhered to, and patients screened for predisposing risk factors (see section 3).

1.2 Comparative Tolerability Profile

The most commonly used pharmaceutical aid for smoking cessation is NRT, which is often given in the form of the nicotine transdermal patch. The adverse-event profile associated with nicotine patch use typically features delayed contact sensitisation reactions,[17] itching[18] and insomnia.[19] The tolerability of bupropion SR (150mg twice daily) was compared directly with that of the nicotine transdermal patch (initially 21mg nicotine, decreasing to 7mg at study end) and the combination of bupropion SR and the nicotine patch over a 9-week treatment period in a randomised, double-blind, placebo-controlled study involving 893 smokers.[3] In general, bupropion SR appeared to be as well tolerated as the nicotine transdermal patch: while insomnia tended to be more frequent with bupropion SR, dream abnormalities and application site reactions were more common with the nicotine patch (see table I). Bupropion SR, nicotine patch or these two therapies used in combination were associated with significantly higher rates of insomnia (42%, 30% and 48%, respec-

Table I. Summary of incidences (% of patients) of the most frequent adverse events reported in controlled clinical studies of sustained-release bupropion for smoking cessation in the general smoking population

	Hurt et al.[2] a		Jorenby et al.[3] b				Bolliger et al.[4] a		Puska et al.[7] a		Gonzales et al.[5] c	
	BUP 100-300 mg/d[d] (n = 462)	Pl (n = 153)	BUP 300 mg/d (n = 244)	NRT (n = 244)	BUP 300 mg/d + NRT (n = 245)	Pl (n = 160)	BUP 300 mg/d (n = 527)	Pl (n = 180)	BUP 300 mg/d (n = 501)	Pl (n = 166)	BUP 300 mg/d (n = 226)	Pl (n = 224)
Insomnia	31[e]	21	42[e]	30[e]	48[e]	20	25	14	39[e]	22	24	11
Headache	32	29	26	28	27	33	13	10	7	9	8	13
Nausea			10	8	12[e]	5	9	6	10	7		
Dry mouth	11[e]	5	11[e]	4	9	4	12	5	12	10	13	9
Anxiety	6	11	9	7	10	6			7	5		
Rhinitis	11	17	14	12	11	12						
Infection			15	15	15	16						
Application-site reaction			12[f]	19[e]	15[e]	17[f]						
Influenza-like syndrome			9	7	8	11						
Dizziness			11	3	8	6			7	7		
Dream abnormalities			5	18[e]	14[e]	3						
Viral infection			11	3	8	6	5	8			13	9
Restlessness			5	18[e]	14[e]	3						

a 7-week treatment phase; 52-week follow-up.

b 9-week treatment phase.

c 12-week treatment phase; 26-week follow-up.

d Mean incidence with 3 different doses of bupropion SR (100, 150 and 300 mg).

e Significant difference versus placebo, $p \leq 0.05$.

f Patients in these groups received placebo patch.

BUP = sustained-release bupropion; **NRT** = nicotine replacement therapy; **Pl** = placebo.

Table II. Incidence (% of patients) of the most frequent adverse events reported during the long-term (45-week) study of sustained-release bupropion (BUP) for smoking cessation (Reproduced from Hays et al.,[6] with permission from the American College of Physicians-American Society of Internal Medicine.)

	BUP 300 mg/day (n = 214)	Pl (n = 215)
Insomnia	10	7
Headache	24	17
Nausea	4	3
Dry mouth	1	0
Rhinitis	18	23
Influenza-like syndrome	16	17
Upper respiratory tract infection	17	24
Accidental injury	15	13
Viral infection	13	9

Pl = placebo.

tively) than placebo (20%). Application site reactions and dream abnormalities were significantly more frequent in smokers using the nicotine patch (either alone or in combination) than in those receiving placebo. The use of bupropion SR alone, but not in combination with the nicotine patch, was also associated with a significantly higher rate of dry mouth than placebo. Finally, smokers who used combination therapy reported a significantly higher rate of nausea than those on placebo; there were also reports of treatment-emergent hypertension (see sections 1.5 and 3.2.3).

1.3 Tolerability in Patients with Cardiovascular Disease

Bupropion SR was well tolerated in patients with pre-existing cardiovascular disease, exhibiting a similar tolerability profile to that seen in the general population of smokers.[8] This randomised, double-blind trial analysed 626 smokers with stable cardiovascular disease (previous myocardial infarction or cardiac surgery, angina, heart failure, or peripheral vascular disease with or without controlled hypertension), who received bupropion SR 150mg twice daily or placebo for 7 weeks.[8] The most common adverse events in the active treatment group were insomnia, dry mouth, nausea, headache and dizziness (table III), the incidences of which were within the ranges reported for the general population of smokers (see table I).

1.4 Tolerability in Patients with Chronic Obstructive Pulmonary Disease

Bupropion SR is also well tolerated by patients with pre-existing chronic obstructive pulmonary disease (COPD), as indicated by the results of a double-blind study in which 404 patients with mild or moderate COPD were randomised to treatment with bupropion SR 150mg twice daily or placebo for 12 weeks.[9] Insomnia was the most frequently reported adverse event with a 2-fold greater incidence in the bupropion SR than in the placebo group (table IV). The incidences of headache and dry mouth in the two treatment groups were similar.

1.5 Cardiovascular Safety Profile of Bupropion SR

No statistically significant mean changes in heart rate (figure 1) or systolic or diastolic blood pressure have been noted during treatment with bupropion SR 300mg daily for periods of 7 to 12 weeks in the general population of smokers[5] or those with pre-existing stable cardiovascular disease.[8] In a study in a general population of smokers using bupropion SR and NTP, elevation in blood pressure was seen in 15 of 244 patients (6.1%) in the combination (bupropion/NTP) group, but the incidence in this group was not significantly different from that in the placebo group (5 of 159; 3.1%).[3]

Table III. Incidence (% of patients) of the most frequent adverse events reported by patients with cardiovascular disease who received sustained-release bupropion (BUP) for smoking cessation for 7 weeks[8]

	BUP 300 mg/day (n = 313)	Pl (n = 313)
Insomnia	24	12
Headache	11	11
Nausea	13	6
Dry mouth	18	10
Dream abnormalities	8	5

Pl = placebo.

Table IV. Incidence (% of patients) of the most frequent adverse events reported by patients with chronic obstructive pulmonary disease who received sustained-release bupropion (BUP) for smoking cessation for 12 weeks[9]

	BUP 300 mg/day (n = 204)	Pl (n = 200)
Insomnia	24	12
Headache	6	6
Dry mouth	6	5

Pl = placebo.

Electrocardiographic data from studies of the bupropion immediate-release (IR) formulation in depressed patients have shown that it was not associated with orthostatic hypotension,[20] or with prolonged cardiac conduction intervals or exacerbation of pre-existing ventricular arrhythmias.[21] In elderly depressed patients, bupropion IR 150 to 450 mg/day did not significantly affect sinus rate, PR interval, QRS interval, or QTc interval.[22]

1.6 Premature Discontinuations Due to Adverse Events with Bupropion SR

In most controlled clinical trials of bupropion SR for smoking cessation, patient discontinuation rates due to adverse events have proved to be low and not greatly dissimilar between the bupropion SR (6 to 12%) and placebo (4 to 8%) treatment arms. Discontinuation rates due to adverse events in those receiving bupropion SR or placebo were similar in smokers with pre-existing cardiovascular disease (5% *vs* 6%, respectively),[8] and with COPD (7% *vs* 6%, respectively).[9] In one study in the general population of smokers, the discontinuation rate due to adverse events was significantly greater in the bupropion SR (12%) group than the placebo (4%) group.[3]

2. Post-Marketing Experience

Bupropion was first approved for smoking cessation in the US in 1997. It has now been approved in more than 50 countries, including Australia, Canada and most European countries. There have been an estimated 9 million patient exposures to bupropion SR for smoking cessation worldwide, and there is also extensive post-marketing experience with bupropion for the treatment of depression. Bupropion was marketed for depression in the US in 1989, and there have been over 31 million patient exposures for the two indications combined. At the time of writing, there were approximately 13 years of post-marketing experience for bupropion. As with any marketed product, adverse reactions have been added to the prescribing information as new information has been received. However, the basic safety profile of bupropion has not significantly changed since initial marketing.

With the launch of bupropion SR for smoking cessation, there has been extensive media coverage and rapid uptake of the product in some countries. Subsequently, there has been a high reporting rate of suspected adverse reactions. Several regulatory authorities have made information available on the post-marketing experience of bupropion received through their national spontaneous reporting schemes.[23-25] It is important to note that suspected reactions are not necessarily caused by bupropion and may be related to other factors such as nicotine withdrawal, other illnesses, or other medications taken concurrently.[23]

The reactions most commonly reported to regulatory authorities include the following: gastrointestinal events (e.g. dry mouth, nausea and vomiting); neurological events (e.g. dizziness, headache and tremor); psychiatric events (e.g. anxiety, de-

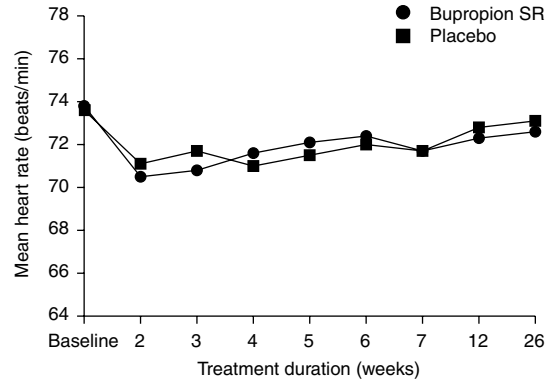

Fig. 1. Influence of sustained-release bupropion (bupropion SR)150mg twice daily or placebo on mean heart rate in patients with stable cardiovascular disease who had smoked ≥10 cigarettes daily in the past year.[8]

pression and insomnia); and skin events (e.g. angioedema, pruritus, rash and urticaria).[23,24] These adverse reactions are consistent with the findings from the clinical development programme for the smoking cessation indication, and the reactions are described in the prescribing information for bupropion.

There have also been reports of deaths in patients prescribed bupropion.[23,24] In many of the reports received by regulatory authorities, there is an alternative explanation for the patient's death, such as the patient's underlying condition.[23,24] In the UK, cardiovascular disorders (e.g. myocardial infarction), and cerebrovascular disorders, such as stroke, were the cause of death in 80% of reports;[23] these diseases are common in smokers. In addition, a number of patients were not taking bupropion at the time of death.[23]

As noted above, seizure is one of the medically important adverse reactions associated with bupropion SR. Seizures have also been reported during the post-marketing experience.[23,24] Evaluation of the reports of seizures received by the UK regulatory authority revealed that approximately 50% of seizures occurred in patients who had a past history of seizure(s) and/or risk factors for seizure.[23] This reinforces the need for physicians to carefully consider the prescribing information and to ensure that only appropriate candidates receive bupropion SR as an aid to smoking cessation.

The safety profile for bupropion is well established and the most commonly reported reactions are consistent with experience from clinical trials. Seizure and hypersensitivity reactions are the most frequently reported significant medical events known to be associated with bupropion treatment.

3. Dosage and Administration Considerations

3.1 Dosage Recommendations

It is recommended that bupropion SR be administered at an oral dosage of 150mg twice daily for smoking cessation in adults, and that this dosage should not be exceeded.[10,11] Patients are able to continue smoking while they take bupropion SR. Bupropion SR treatment should be initiated at a dosage of 150mg once daily followed by a dose increase as appropriate up to the recommended dose of 150mg twice daily. A target date for quitting smoking should be set to occur during the first 2 weeks (usually the second week) of treatment. It is recommended that patients should be treated with bupropion SR for up to 12 weeks; if by 7 weeks no progress towards smoking cessation has been made, bupropion SR should be discontinued. However, for those patients likely to benefit from more sustained treatment, bupropion SR has been shown to prevent relapse[6] and, where appropriate, continued treatment may be considered. Bupropion SR can be administered with a transdermal nicotine patch for smoking cessation, but it is advisable that smokers receiving this combination are monitored for possible treatment-emergent hypertension (see section 3.2.3).

3.2 Contraindications and Special Precautions

Bupropion SR is contraindicated in smokers with known hypersensitivity to the drug or its excipients, those with current or previous seizure disorders, bulimia, anorexia nervosa and those taking monoamine oxidase inhibitors. Furthermore, bupropion SR should not be administered while patients are undergoing abrupt withdrawal of alcohol or sedatives (seizure risk factors).

3.2.1 Seizures

Before prescribing bupropion SR, smokers should be assessed for any predisposition to seizure. Relevant predisposing risk factors include the following: a history of head trauma or seizures; tumours of the central nervous system; excessive alcohol use; and current use of drugs that can lower the seizure threshold (e.g. antipsychotics, antidepressants, theophylline and systemic corticosteroids). Other groups that may be at a higher risk of experiencing seizures while taking bupropion SR include patients with diabetes receiving insulin or hypoglycaemic agents, and users of sedatives, stimulants or anorectic products. In such circum-

stances, bupropion SR should be prescribed only with extreme caution.

The incidence of seizures with bupropion SR has been investigated in a prospective safety study in 3100 depressed patients. When the drug was used in accordance with the prescribing information at dosages that were titrated up to a maximum of 300mg daily (the recommended dosage), the seizure rate was reported to be approximately 0.1%.[16] Given these results, it is very important that physicians prescribe bupropion SR in accordance with the manufacturer's prescribing information.

3.2.2 Hypersensitivity Reactions

Symptoms of delayed hypersensitivity reaction (rash accompanied by arthralgia, myalgia and fever), in some cases resembling serum sickness, as well as anaphylactic-like reactions (pruritus, urticaria, angioedema and dyspnoea) have been reported at incidences of 0.1% in smokers receiving bupropion SR during clinical trials.[1]

3.2.3 Hypertension

In clinical practice, occasional cases of hypertension requiring acute treatment have been reported with bupropion SR in smokers both with and without evidence of pre-existing hypertension. Clinical trial findings suggest that the use of bupropion SR in conjunction with NRT may confer a higher risk of hypertension,[3] and for this reason blood pressure monitoring is recommended in smokers using this combination.

3.3 Special Patient Populations

For smokers with hepatic or renal insufficiency, it is recommended that the dosage of bupropion SR should be lower that that used for the general population of smokers.[10,11] These patients should be routinely monitored for adverse events, particularly dry mouth, insomnia and seizures, which may indicate high circulating levels of bupropion and/or its metabolites. A dosage reduction may also be necessary for elderly smokers, because of the high incidence of renal insufficiency in this patient population.

As no studies have fully assessed the safety of bupropion SR during pregnancy, its use is therefore not recommended. Depression has been shown to develop in some smokers who have used bupropion SR,[26] although this may relate to the fact that depression is commonly found in those giving up smoking,[27] and depression may also be a symptom of nicotine withdrawal. Furthermore, as with other antidepressants, bupropion SR may precipitate a manic episode in patients with bipolar disorder during the depressive phase of their illness and may activate latent psychosis in other susceptible patients.[10,11]

4. Conclusions

Bupropion SR is well tolerated by smokers, and the only adverse events that occurred significantly more frequently with the drug than with placebo in clinical trials were insomnia and dry mouth. No significant changes in mean vital signs or laboratory parameters have been noted either during or following the use of bupropion SR for smoking cessation compared with placebo treatment.

The most clinically significant adverse reactions with bupropion are seizure and hypersensitivity reactions. It is important that physicians carefully consider the prescribing information and ensure that only appropriate candidates receive bupropion SR.

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Correspondence and offprints: *Henri-Jean Aubin*, Centre de Traitement des Addictions, Hôpital Emile Roux, 1 Avenue de Verdun, 94456 Limeil-Brévannes, France.
E-mail: henri-jean.aubin@erx.ap-hop-paris.fr