

Dear Colleague

The summary of product characteristics (SPC) for bupropion (*Zyban*[®]) has been updated since publication of the accompanying Bulletin. The initial dosage regimen has been modified and new safety precautions have been added to the SPC. It is important to consult the current SPC for full prescribing information. (The rINN has also been changed from amfebutamone to bupropion.)

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Bupropion (*Zyban*[®]) for smoking cessation

Cigarette smoking is the greatest cause of preventable death and disability in Wales. It is responsible for approximately one-fifth of deaths^{1,2} and an estimated cost to health services of £70 million per annum.² The effects of environmental tobacco smoke (passive smoking) are additional to this. The overall cost of smoking to society is even greater.

Government policy to combat smoking aims to prevent people, especially children, from starting to smoke; to help adult smokers to stop, particularly pregnant women and those in lower socio-economic groups; and to raise awareness of the dangers associated with passive smoking. Approximately one-quarter of the adult population in Wales smokes:¹ reducing this figure has been set as a national priority.

Smoking cessation is beneficial regardless of age or smoking history.³ In a 12-month period, about one in three smokers will attempt to stop,² of whom only 3% will be abstinent after 12 months using willpower alone.⁴ Supportive measures (including provision of self-help materials, and advice and counselling from health professionals) are effective in improving cessation rates.⁵ These are cost-effective healthcare interventions⁴ and guidelines for integrating effective smoking cessation measures through the healthcare system have been developed.^{6,7}

The use of nicotine replacement therapy (NRT) can raise success rates one and a half to two-fold over those achieved with motivational support alone (some level of support was always offered in the clinical trials of NRT).⁵ The various nicotine products are equally effective, with product choice primarily influenced by personal preference. However, even with NRT, the majority of dependent smokers rarely succeed in their first attempt to give up, many have to make several attempts and many never succeed.

Summary

- ♦ Bupropion can be an effective smoking cessation aid in appropriately selected patients who receive motivational support.
- ♦ Bupropion has only been studied in relatively heavy smokers who were otherwise healthy. Trials of bupropion were conducted in volunteers motivated to stop smoking, and treatment was combined with a structured support programme.
- ♦ Bupropion has not been studied in subjects below 18 years of age, those who are pregnant or breast-feeding, or those with serious or unstable medical or psychiatric disorders.
- ♦ Bupropion has been compared with a nicotine patch for smoking cessation in one trial; results were favourable.

This bulletin does not review all smoking cessation therapies but provides clinical information on the use of bupropion [amfebutamone (rINN)]. Bupropion hydrochloride sustained-release (*Zyban*[®]) is licensed in the UK for use with motivational support as an aid to smoking cessation in nicotine-dependent patients.

Increased knowledge of the effect of nicotine on neurotransmitters, and links between nicotine-dependence and depression, has led to the investigation of many pharmacological agents, including antidepressants, to aid smoking cessation.⁸ Observational reports and two early trials suggested that bupropion, an atypical antidepressant (used in the USA), may be effective. Bupropion has dopaminergic and noradrenergic properties but the precise mechanism by which bupropion aids smoking cessation is not firmly established.

Efficacy of bupropion: two clinical trials

Two randomised, double-blind, placebo-controlled, multi-centre trials of bupropion for smoking cessation have been conducted in the USA. The trials were conducted in adult volunteers who smoked at least 15 cigarettes per day and were motivated to stop.^{9,10} Subjects had no current depression. Other exclusions included recent use of NRT, a history of, or predisposition to seizures, eating disorders, pregnancy or breast-feeding, drug or alcohol abuse, dermatological disorders and serious or unstable medical or psychiatric disorders.

Both year-long studies included a treatment phase, with day 8 usually set as the “target quit date”. Subjects received supportive advice before starting treatment and individual 10-15 minute counselling sessions were provided each week during treatment. Subjects were also telephoned 3 days after the target quit date. During the follow-up period there were a further four counselling sessions and monthly telephone calls.

End-points included point-prevalence abstinence rates, which were based on the numbers of subjects who had not smoked for the previous week. Carbon monoxide testing was used to confirm self-reports of smoking abstinence. Continuous abstinence rates were based on the numbers of subjects who reported not smoking since the target quit date and who had negative carbon monoxide measurements at all preceding clinic visits. In addition to abstinence rates, body weight and symptoms of depression and withdrawal were monitored. The results were analysed on an intent-to-treat basis; subjects who did not complete the studies were considered to be smoking. Approximately 35% of subjects in both studies did not participate for a full 12-month period.

The first study of 615 smokers compared sustained-release bupropion taken at daily doses of 100 mg, 150 mg and 300 mg (150 mg twice daily) for 7 weeks.⁹ Point-prevalence or 7-day abstinence rates were determined at the end of treatment

(6 weeks after the target quit date) and at 3, 6 and 12 months. End-of-treatment and 12-month point-prevalence rates and 6-week continuous abstinence rates are presented in Table 1 (trial 1). Continuous abstinence rates at 12 months were not reported.

In the second study of 893 subjects, sustained-release bupropion 300 mg was compared with a nicotine 21-mg patch and a combination of bupropion and the patch.¹⁰ Bupropion treatment began 1 week before the target quit date and continued for a further 8 weeks. Patch treatment began on the target quit date and continued for 8 weeks, however, the dose was reduced in the final 2 weeks to 14 mg and then 7 mg.

Point-prevalence rates for smoking cessation were calculated for 6 and 12 months. The results at 12 months are given in Table 1 along with 12-month continuous abstinence rates (trial 2). Bupropion and the combined treatment were associated with significantly higher abstinence rates than the nicotine patch. The combined treatment appeared superior to, but not significantly better than, bupropion alone. With the nicotine patch, only the continuous abstinence rate differed significantly compared with placebo.

In the first trial, weight gain during treatment in subjects who were continuously abstinent (n=103) was significantly lower with bupropion 300 mg (1.5 kg) compared with placebo (2.9 kg). This difference had diminished at 6 months. In the second trial, weight gain in subjects at week 7 (n=666) was lower but not significantly different in the bupropion group (1.7 kg) compared with the placebo group (2.1 kg).

Withdrawal symptoms were experienced by subjects receiving bupropion 300 mg but not to the same degree as by those receiving placebo. Bupropion had no effect on measures of depressive symptoms in either trial.

Table 1 Smoking cessation rates*

	Point-prevalence (7-day abstinence) rates			Continuous abstinence rates	
	Trial 1		Trial 2	Trial 1	Trial 2
	7 weeks	12 months	12 months	7 weeks	12 months
Bupropion 300mg	44.2%	23.1%	30.3%	24.4%	18.4%
Placebo	19.0%	12.4%	15.6%	10.5%	5.6%

* Differences between rates for bupropion and placebo are statistically significant in both trial 1⁹ and trial 2.¹⁰

In the trials, dry mouth and insomnia were common adverse events that were reported significantly more frequently with bupropion than with placebo. In the first trial, 37 (6%) subjects withdrew because of adverse events (8 receiving placebo); tremor, headaches, rash and urticaria were the most common reasons.⁹ In the second trial, 79 (8.8%) subjects withdrew because of adverse events, with a significantly higher percentage withdrawing in the groups receiving bupropion (57 subjects in total) than in the placebo group (6 subjects).¹⁰ Serious adverse events included three cases of rash and pruritus, one of which occurred with shortness of breath and chest tightness.

One of the main concerns with bupropion use, which arose during post-marketing experience in the USA, is the incidence of seizures. The incidence of seizures is approximately 0.1%,¹¹ with risk strongly associated with the presence of predisposing factors. Higher doses of bupropion are associated with a greater risk of seizures.

Bupropion is contra-indicated in patients with a current or previous diagnosis of a seizure disorder or bulimia or anorexia nervosa, a history of bipolar disorder or those taking monoamine oxidase inhibitors. Bupropion is also contra-indicated in patients with severe hepatic cirrhosis. It should be used with caution in patients with hepatic impairment and renal insufficiency. A lower dose (150 mg daily) is recommended in these patients, and in the elderly.

Because bupropion can lower the seizure threshold, it should be administered with extreme caution in patients who may already be predisposed to a lower seizure threshold or a higher risk of seizures. For example, patients with a history of head trauma, those with central nervous system tumours, or those taking medicines such as antipsychotics, antidepressants, theophylline or systemic steroids. It should be used with caution in the presence of alcohol abuse, the abrupt withdrawal of alcohol or benzodiazepines, the use of stimulants or anorectic products, and diabetes treated with hypoglycaemics or insulin.

Relatively rare but serious adverse effects reported with bupropion include hypersensitivity reactions, serum sickness-like reactions, erythema multiforme and Stevens Johnson syndrome.¹¹⁻¹⁵ Since bupropion has become available in the UK,

suspected adverse reactions, including serious reactions, have been reported to the CSM. Bupropion carries the ▼ symbol; all suspected adverse reactions should be reported through the Yellow Card Scheme to CSM Wales.

Bupropion and smoking cessation have the potential to affect the metabolism of drugs by cytochrome enzymes and there are a number of medicines that can potentially affect blood levels of bupropion. The summary of product characteristics should be consulted about potential interactions between bupropion and other medications.

Patients with recent myocardial infarction or unstable heart disease were not included in clinical trials of bupropion, so care is advised in these groups. There have been reports of cardiovascular effects, including tachycardia, hypertension and postural hypotension, in patients receiving bupropion.¹¹ In the second trial,¹⁰ new or worsening hypertension was reported more frequently, although not significantly so, in subjects receiving bupropion combined with the nicotine patch than in those receiving placebo. In patients receiving combination treatment, caution must be exercised and blood pressure monitoring is advised.

The trials of bupropion for smoking cessation did not include patients with depression. The efficacy of bupropion for smoking cessation in the trials was not associated with an antidepressant effect, and a subgroup analysis of the first trial found bupropion was equally effective in patients with or without a history of major depression.¹⁶ Bupropion is not licensed in the UK for use in the management of depression and depression may occur during its use for smoking cessation.¹⁷

Discontinuation reactions were not observed in the trials of bupropion but gradual dose reduction may be considered.¹¹ As a centrally-acting drug, bupropion can affect the ability to perform tasks requiring judgement or motor and cognitive skills. Dizziness and light-headedness have been reported, and patients starting bupropion should be cautioned about driving and using machinery.¹¹

Bupropion has not been evaluated in subjects below 18 years of age and its safety in pregnant or lactating women has not been established. Bupropion has not been studied beyond 9 weeks for use as an aid to smoking cessation.

Prescribing bupropion

Healthcare professionals providing smoking cessation advice in primary care should **ask** about smoking at every opportunity; **advise** all smokers to stop; **assist** the smoker to stop and **arrange** follow-up.⁶ Before prescribing bupropion, GPs should be confident that patients are committed to quitting and be able to provide, or refer patients to, a source of face-to-face counselling.

Help with assessment of patients' motivation and provision of support may be available locally through community pharmacies or smoking cessation clinics. Information on how to contact your local smoking cessation co-ordinator can be obtained from the national telephone helpline. Additional telephone counselling for patients is available through this national helpline.

Smokers Helpline for Wales: 0800 169-0-169

The manufacturer of bupropion is also advertising a support programme that provides patients with self-help materials and access to telephone counselling. Contact details are provided in the patient information leaflet.

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The manufacturer's summary of product characteristics should be consulted for full prescribing information.

Prescribing in pregnancy is the topic for the next WeMeReC bulletin and GP distance-learning module. These will be issued in November.