ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (11): 1017-1026
0114-5916/08/0011-1017/$48.00/0

Serious Adverse Reactions of Bupropion for Smoking Cessation

Analysis of the French Pharmacovigilance Database from 2001 to 2004

Marie-Nöelle Beyens,[1] *Claire Guy*,[1] *Genevieve Mounier*,[1] *Sylvie Laporte*[2] and *Michel Ollagnier*[1]

1 Regional Pharmacovigilance Centre, Bellevue Hospital University, Saint-Etienne, France
2 Clinical Pharmacology Department, Bellevue Hospital University, Saint-Etienne, France

Abstract

Background: Bupropion was the first alternative to nicotine replacement therapy in the pharmacological treatment for smoking cessation. Its safety profile has been monitored in France via spontaneous reporting.

Objective: To describe all serious adverse reactions (SARs) reported in France since the marketing authorization for bupropion in September 2001, and to analyse risk factors for these SARs.

Design: We collected all spontaneous reports of adverse reactions to bupropion received by all French Regional Pharmacovigilance Centres and by GlaxoSmith-Kline, the manufacturer of bupropion, during the first 3 years of marketing of this agent. We identified the characteristics of the population to whom bupropion was prescribed from the Thales database, which contains information obtained from a representative sample of general practitioners in France. We then compared the population with SARs with the population prescribed the drug (exposed population) to identify possible risk factors such as sex, age and daily dose for the most frequent SARs.

Results: Bupropion was prescribed to 698 000 patients during the first 3 years of marketing in France. In these patients, 1682 cases of adverse reactions were reported; 28% of these involved SARs, mainly cutaneous or allergic reactions (31.2%), including angioedema and serum sickness-like reactions. Serious neurological reactions were frequent (22.5%), mostly comprising seizures; however, questioning revealed that almost half of these patients had a history of seizures or other risk factors. Of the serious neuropsychiatric adverse events reported (17.3%), suicide attempts/suicides were a cause for concern, although risk factors (history of depression, suicide attempts, etc.) were described for 66% of patients experiencing these events. Patients reporting angioedema and serum sickness-like reactions, and those involved in suicide attempts/suicides, were significantly younger than the exposed population. A dose-dependent effect was also apparent for angioedema and for seizures. Cardiovascular SARs, such as ischaemic heart disease (10.1%) or sudden death (2.3%), were very often associated with pre-existing coronary artery disease induced by smoking. All these SARs occurred within a median of 12–14 days after drug initiation.

Conclusion: To ensure safer use of bupropion, health professionals must respect the strict contraindications and warnings about use of this drug in patients with a history of seizures. Seizures, angioedema and serum sickness-like reactions were

the most frequently reported SARs to bupropion treatment in our study. Moreover, younger people appeared to be more at risk for cutaneous SARs generally, and younger women for angioedema in particular, perhaps because of weight-related differences in pharmacokinetics. A dose-dependent effect for angioedema and the results of skin tests were suggestive of a histamine liberation mechanism. Our analysis showed that taking more notice of the contraindications to use of bupropion could have prevented half the seizures reported to the database. The sex and age characteristics of patients with ischaemic heart disease and suicide attempts in the study population were similar to those of the French population as a whole. Whether bupropion is associated with an increase in these potential adverse effects of therapy can be determined only by epidemiological studies that take into account specific risk factors in the smoking population. Finally, the median time to onset of the SARs identified in this study suggests that prescribers should monitor patients exposed to bupropion more carefully during the first 2 weeks of treatment.

Background

Bupropion (amfebutamone) IR (immediate release) was approved in the US for treatment of major depression in 1985. The SR (sustained release) formulation of bupropion was the first pharmacological alternative to nicotine replacement therapy for smoking cessation and was approved for this indication in the US in 1997. Bupropion SR was launched in France only for the latter indication on 17 September 2001.

Bupropion is an aminoketone, structurally unrelated to other known antidepressants, that resembles amfepramone (diethylpropion), an anorectic agent. Bupropion inhibits norepinephrine (noradenaline) and dopamine reuptake with minimal effect on serotonin.[1] The possibility of an amfetamine-like effect of bupropion is a matter of considerable controversy,[2] but postmarketing data provide no evidence suggestive of a risk of dependency with use of this agent.

The exact mechanism of action of bupropion is not clearly understood. However, nicotine is known to activate the mesolimbic system, leading to release of dopamine in the nucleus accumbens. During abstinence from smoking, dopamine levels in this part of the brain decline. Bupropion may counteract this effect by inducing an increase in dopamine levels.[3]

In France, the initial dosage of bupropion SR is 150 mg/day for 6 days, after which the dose is increased to 150 mg twice daily. The total duration of treatment is 7–9 weeks.

Randomized clinical trials have shown higher rates of smoking cessation with bupropion than with placebo.[4-6] The most frequent adverse events reported were insomnia, headache, nausea and dry mouth; no seizures were reported in these trials,[7] whereas seizure risk in patients taking bupropion is estimated to be 0.1%.[8] There are few large studies analysing serious adverse reactions (SARs) in the literature, other than a prescription event monitoring study conducted in England.[9]

In much of the developed world, tobacco-related disease is the leading cause of preventable death, estimated to be one in every five deaths.[10] Introduction of bupropion SR led to a major change in the management of smoking cessation. The French Health Products Safety Agency also implemented a monitoring programme for this drug because of the risk of seizures, as well as the potential risk of abuse or dependency with this amfetamine-like product.

This study aimed to observe drug safety in the population exposed to bupropion, a newly marketed drug for smoking cessation in France. Here we describe SARs and analyse risk factors for those occurring more frequently.

Materials and Methods

Every month from September 2001 to September 2004 we extracted all medically confirmed spontaneous reports of adverse reactions for bupropion from the French Pharmacovigilance Database (data provided by 31 Regional Pharmacovigilance Centres)

and from GlaxoSmithKline, the manufacturer of bupropion. Individual cases were checked to identify duplicates, confirm the diagnosis, and assess causality by evaluating temporal relationships and other possible causes.

This article reviews only the SARs notified in the context of postmarketing surveillance. An adverse reaction was defined as serious if it resulted in death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistence or significant disability/incapacity or was life threatening.[11] All reports were reviewed by the authors for the purpose of assigning a severity level. These reports contained the following information relevant to identifying risk factors: patient age and sex, dose and duration of treatment (start and stop dates), adverse drug reactions and medical history.

Statistical analysis was performed only for the most frequently occurring SARs such as seizures, angioedema, serum sickness-like reactions, ischaemic heart disease, suicides and suicide attempts. The characteristics of the bupropion-exposed population were obtained in patients who were prescribed bupropion in France during the first 3 years of marketing using the Thales database. The latter is maintained by continuous epidemiological monitoring of a representative national sample of 1010 general practitioners and provides population characteristics such as sex, age and daily dose. Quantitative data are expressed as mean values ± SD and range (minimum–maximum). Median values are also provided for non-normal distributions such as time to onset. Statistical comparison between exposed patients and patients presenting with an SAR was performed using Fisher's exact test for qualitative data and Student's t-test for quantitative data. The statistical analysis was performed with Sphinx Plus2 software (Le Sphynx Development, Seynod, France).

Results

A total of 698 000 patients were treated in France during the 3 years following the introduction of bupropion SR in September 2001; in that time, 1682 adverse drug reactions were reported. The most frequent non-serious adverse reactions were insomnia, urticaria and pruritus, nausea and vomiting, and depressed mood. In 56% of these cases, bupropion was the sole suspected drug. There were 475 SARs, including 21 deaths; these are classified by body system in table I. The characteristics of patients with the most frequent SARs are shown in table II. The median time to onset is noteworthy; this ranged from 12 to 14 days and was almost the same for all SARs.

Skin Disorders

Angioedema (50 reports) and serum sickness-like reactions (40) were the most frequently reported reactions in this class.

Angioedema

Patients with angioedema had a significantly lower mean age than that of the total estimated population exposed to bupropion (37.5 vs 41.4 years, respectively; $p = 0.008$); this difference was related to the significantly younger mean age of female patients (35.6 vs 40.4 years, respectively; $p = 0.004$). These data also showed a dose-related effect ($p = 0.002$) [table II]. The reporting rate of angioedema was calculated as 0.07%.

All patients with angioedema were hospitalized, with 50% of affected patients presenting with serious symptoms of mucosal swelling (dyspnoea, pharyngeal oedema and dysphagia); however, epinephrine (adrenaline) was administered only twice. Cutaneous patch and prick tests were performed in one patient with negative results. There were four cases of recurrence after discontinuation of bupropion despite treatment with antihistamines and/or corticosteroids.

Serum Sickness-Like Reaction

The mean age of the 40 patients with serum sickness-like reactions was significantly lower than that of the total exposed population (35.2 vs 41.4 years, respectively; $p < 0.0001$), but there was no correlation with sex.

Oedema of the extremities was frequent, with the feet and hands almost always being involved. In four patients, purpura was associated with urticaria. Mucosal involvement with dyspnoea and/or dysphagia was described in 17.5% of cases. The joints most frequently affected were the knee (10 cases), hand (8), wrist (6) and ankle (5).

The outcome was invariably favourable following treatment with corticosteroids and/or antihista-

Table I. Serious adverse events, classified by body system, in patients taking bupropion sustained release (3-year postmarketing surveillance data)

Adverse event	No. of cases
Skin (31.2%)	
Angioedema	50
Serum sickness-like reaction	40
Urticaria	27
Bullous eruption	9
Psoriasis	5
Anaphylactic reaction	5
Others	12
Total	*148*
Nervous system (22.5%)	
Seizure	75
Loss of consciousness	16
Neuropathy	5
Others	11
Total	*107*
Neuropsychiatric status (17.3%)	
Suicide attempt/suicide	22 (3 deaths)
Suicidal ideation	19
Depressive syndrome	15
Mania	9
Others	17
Total	*82 (3 deaths)*
Cardiovascular system (10.1%)	
Ischaemic heart disease	22 (1 death)
Cerebrovascular disease	10
Others	16 (2 deaths)
Total	*48 (3 deaths)*
Hepatobiliary tract, pancreas and gastrointestinal tract (3%)	
Hepatitis	5
Pancreatitis	3
Others	6
Total	*14*
Musculoskeletal system (3%)	
Rhabdomyolysis, myalgia	11
Muscular rupture	3
Total	*14*
Sudden death (2.3%)	
Total	*11 deaths*
Endocrine and metabolic system (2%)	
Altered blood glucose levels	6
Others	3
Total	*9*
Others (8.8%)	
Overdose (nontreated patients)	10 (2 deaths)
Nonfavourable pregnancy outcomes[a]	11
Others	21 (2 deaths)
Total	*42 (4 deaths)*
Total	**475 (21 deaths)**

a Includes two birth defects (trisomy 21 and bilateral club foot), one extrauterine pregnancy, six spontaneous abortions and two fetal deaths.

mines. The mean time to recovery was 12 days for all but two patients, in whom serum sickness-like reaction persisted for several months. In four cases, arthralgia symptoms occurred several days (up to 10) after the onset of cutaneous symptoms, even when bupropion treatment had been stopped as soon as the first cutaneous signs appeared.

Other Skin Disorders

Nine cases of bullous eruption were reported, including three cases of Stevens Johnson syndrome and six cases of erythema multiforme, with a mean time to onset of 12 days and a favourable outcome in all cases. In six of these cases, the patients were taking no other medications.

Five cases of psoriasis were reported, including three of exacerbation of pre-existent disease.

Neurological Adverse Reactions

Seizures (75 reports), loss of consciousness (16) and neuropathies (5) were the most frequently reported SARs involving the nervous system (table I).

Seizures

Ninety-five percent of the seizures involved generalized convulsive seizures, the incidence of which was calculated to be 0.01%. Data analysis revealed a dose-related effect ($p = 0.0004$) [table II]. The risk of seizures appeared to be strongly increased by predisposing factors, with risk factors (e.g. history of seizures, alcoholism and use of drugs that induce seizures, mostly antidepressants) being identified in 50% of this group.

Other Neurological Adverse Reactions

Sixteen patients experienced loss of consciousness (mean age 37 years) at a mean time of 13 days (median 9 days) after the start of treatment.

Neuropsychiatric Adverse Reactions

Suicide and Suicide Attempts

Three suicides and 19 suicide attempts occurred during treatment with bupropion. These patients had a significantly lower mean age than that of the total estimated population exposed to bupropion (36.0 vs 41.4 years, respectively; $p = 0.011$). This difference was related to the significantly younger mean age of women (32.0 vs 40.4, respectively; $p = 0.0003$) [table II].

Table II. Characteristics of patients experiencing the most frequent serious adverse reactions of bupropion (3-year postmarketing surveillance data) compared with those of the total exposed population (p-values are for the comparison with exposed population)

Characteristic	Exposed population (n = 692 798)[a,b]	Seizures (n = 75)	Angioedema (n = 50)	Serum sickness-like reaction (n = 40)	Ischaemic heart disease (n = 22)	Suicides/suicide attempts (n = 22)
Male sex [n (%)]	382 568 (55%)	35 (48.6%); NS	27 (55.1%); NS	24 (61.5%); NS	18 (81.8%); p = 0.0163	10 (45.5%); NS
Age (y) overall [mean ± SD (range)]	41.4 ± 10.9 (18–104)	40.0 ± 11.3 (18–64); NS	37.5 ± 10.4 (20–68); p = 0.008	35.2 ± 8.4 (22–65); p < 0.0001	44.4 ± 9.1 (26–58); NS	36.0 ± 10.0 (22–54); p = 0.011
male [mean ± SD]	42.0 ± 11.0		39.1 ± 11.1; NS	35.2 ± 8.4; p = 0.0007		40.9 ± 9.5; NS
female [mean ± SD]	40.4 ± 10.6		35.6 ± 9.5; p = 0.004	35.2 ± 8.4; p = 0.001		32.0 ± 8.8; p = 0.0003
Daily dose [n (%)]						
unknown		16	12	8	3	8
150 mg	338 386 (48.8%)	15 (25.4%)	9 (23.7%)	15 (46.9%)	7 (36.8%)	9 (64.3%)
300 mg	354 412 (51.2%)	44 (74.6%) p = 0.0004	29 (76.3%) p = 0.002	17 (53.1%) NS	12 (63.2%) NS	5 (35.7%) NS
Median time to onset of adverse event (days)		13	14	14	12	14

a Thales database (accumulation of data provided by a representative national sample of 1010 general practitioners in France).

b Mean length of treatment 60 days.

NS = non-significant.

The total intake of bupropion at the time of the suicide attempt ranged from 1 to 80 tablets (150 mg to 12 g), which was associated with concomitant benzodiazepine ingestion in five patients and with alcohol in four patients. The three deaths included two suicides by hanging and one by drug overdose (total intake unknown). Risk factors were identified in 50% of the patients and included a history of depression (7 patients), history of alcohol abuse (4), previous suicide attempts (4) and schizophrenia (1).

Overdose

Eleven other cases of intentional overdose occurred in people who were not undergoing treatment with bupropion. These involved six men and five women, the median age of both men and women being 35 years. From 1 to 60 (150 mg to 9 g) tablets of bupropion were taken, in association with benzodiazepines in five people and with alcohol in four people. Two deaths occurred as a result of overdose, one following an intake of 60 tablets.

Analysis of the clinical characteristics of these people showed that the most frequent adverse reactions associated with overdose were seizures (9 cases, not including seizures occurring at the appropriate dosage), sleepiness (8), shivering (6), confusion (5), tachycardia (4) and mydriasis (3). Of the nine seizures reported, three recurred twice and one developed into status epilepticus. The total intake of bupropion in these four people with seizures was 15, 20, 45 and 80 tablets, respectively.

Other Neuropsychiatric Adverse Reactions

The most notable characteristics of depressive syndromes and suicidal ideation were the short mean time to onset (10 days for both) and the frequency of history of psychiatric illness (53% and 70%, respectively). Favourable outcomes were achieved rapidly, within a few days of stopping treatment, but antidepressants and/or benzodiazepines were needed in 30% and 50% of cases, respectively.

Anguish (8 cases), mania (4) and paranoia delusion (5), and hallucinations (4) were the main neuropsychiatric SARs, other than suicidality and depression, reported with bupropion treatment. Two cases of mania involved patients who had already experienced this event following corticosteroid therapy several years previously. Only two

serious cases of drug dependence and inability to stop treatment occurred; in one of these, concurrent medical conditions included abuse of methadone and amfetamine.

Cardiovascular Adverse Reactions

Ischaemic Heart Disease

Twenty-two cases of ischaemic heart disease were notified. These events comprised acute myocardial infarction (17), unstable angina (2) and angina (3). The patients concerned had a mean age of 44.4 years (range 26–58) and were predominantly men (82%); this rate was significantly higher than that of the exposed population ($p = 0.0163$). Sequelae (e.g. angina pectoris, cardiac impairment) were reported in eight cases and death in one. Risk factors other than smoking were identified in 73% of the patients, who often had more than one such risk factor; these included dyslipidaemia (10 cases), diabetes (4), familial history of ischaemic heart disease (4), obesity (3), hypertension (3), personal history of ischaemic heart disease (1) and use of hormonal contraception (1). Coronary angiography was performed in 77% of patients and 88% of these examinations revealed abnormalities.

Deaths

Unexplained sudden deaths accounted for the majority of fatal outcomes (11). The remainder (described in corresponding sections) resulting from suicide (3), overdose in nontreated patients (2), ruptured aneurysm (2) and myocardial infarction (1). One case of respiratory failure occurred in a patient with chronic respiratory insufficiency, and one case of serotonin syndrome was described in association with use of 'ecstasy' (3-4 methylenedioxymethamfetamine).

Cerebrovascular Disease

The ten cases of cerebrovascular disease included three cases of cerebral ruptured aneurysm, two of which were associated with hypertension and two resulting in death. Of the other seven cases, two were transient, all involved patients with at least one risk factor besides smoking, and four occurred in patients with dyslipidaemia.

Other Cardiovascular Adverse Events

Other cardiovascular adverse reactions comprised isolated hypertension (5 cases), dysrhythmia (5), transient thoracic pain (4), pericarditis (1) and venous thrombosis (1).

Discussion

This study provides information on the safety of bupropion SR obtained from stimulated spontaneous reporting of adverse effects on a national basis in France. The weakness of our system is mainly under-reporting; it is lower for SARs compared with all adverse drug reactions.[12] This method is useful for detecting mainly rare, unexpected adverse reactions.[13] The methodology used in this study differs from that of prescription event monitoring, which was used by Boshier and colleagues in a cohort study that evaluated the safety profile of bupropion SR in England.[9] Using the methodology of prescription event monitoring, Boshier and colleagues conducted a cohort study evaluating the safety profile of bupropion SR in England.[9]

The half-life of bupropion SR and its metabolites ranges from 20 to 37 hours.[14] Therefore, for all analysed SARs, the median time to onset of 12 to 14 days after commencement of therapy coincided with the time to steady state pharmacokinetics after the increase in dose at the beginning of the second week of treatment. This is suggestive of a dose-related risk for bupropion SR SARs and the first 14 days of treatment with this agent appear to represent the maximum risk period.

Cutaneous Adverse Reactions

In clinical trials of bupropion, hypersensitivity reactions (urticaria, angioedema, serum sickness-like reaction, etc.) have been reported with an incidence of 3%.[15] The incidence of urticaria alone was estimated at 0.56% in a prescription event monitoring study conducted in England.[9] In our study, we calculated a rate of 0.2% for all cutaneous SARs.

We have no obvious hypothesis to explain the younger age of patients with serum sickness-like reaction and angioedema, and the higher incidence in females and dose-related nature of angioedema (table II). Pharmacokinetic data for bupropion and its metabolites show that the values of several para-

meters such as half-life, area under the concentration-time curve and maximum concentration are significantly greater in females than in males and this may be explained by the higher doses per unit weight administered to women relative to men because of the lower bodyweight of women.[16-18] All these results indicate a possible risk of relative overdosage in women and secondarily of dose-related effects. They also suggest that patients taking bupropion SR may need weight-related dose adjustments.

Eleven cases of urticaria with bupropion have been reported in the literature.[19-21] The five patch tests performed in those cases were negative and the prick tests yielded at most an equivocal result (in one case). The existence of an allergic mechanism responsible for urticaria in patients taking bupropion is consequently not evident and both an increase in histamine level, as is known to occur with amfetamines, and an action on central serotonin pathways have been postulated to explain these reactions.[19]

Various authors have described a total of 15 cases of serum sickness-like reaction, three of these being associated with coagulation disorders, elevated hepatic enzymes and proteinuria, respectively.[15,22-29] Angioedema could also be regarded as a minor form of serum sickness-like reaction, similar to isolated arthralgia.[20,26] The high proportion of serum sickness-like reactions is of concern, as it is normally an infrequent reaction and it appears that bupropion could increase this risk,[1] perhaps by a histamine release mechanism, as is the case with amfetamines.[19-21]

Neurological Adverse Reactions

Like other antidepressant drugs, bupropion can lower the seizure threshold. The incidence of seizures during antidepressant therapy in general at therapeutic doses ranged from 0.1% to 0.6% with a dose-dependent response, whereas the annual incidence of a first unprovoked seizure in the general population is 0.07% to 0.06%.[30] Bupropion SR at a dosage of 300 mg/day has been associated with a seizure incidence ranging from 0.08% to 0.36%.[8,31] In our study, the seizure incidence was ten times lower (0.01%), probably because of under-reporting of this labelled SAR. Our results confirmed the well recognized dose dependency of this adverse effect of bupropion ($p = 0.0004$) [table II]. However, risk factors for seizures were present in 50% of our patients, as was observed in the UK, where 184 seizures have been reported among approximately 500 000 patients.[32] Contraindications to or precautions concerning use of bupropion were not adhered to in 30% of patients with seizures in our population, emphasizing the need to respect the Summary of Product Characteristics (SPC) for this drug.[14]

Neuropsychiatric Adverse Events

In France, two-thirds of suicide attempts, in contrast to completed suicides, are committed by women and mostly involve women less than 40 years of age.[33] Our sample was therefore similar to the general French population in terms of the sex (57.9% female for attempted suicides) and age (mean 36 years) of those attempting suicide.

However, psychiatric disorders are more prevalent among smokers than in the general population,[34,35] and any assessment of neuropsychiatric adverse reactions to bupropion therefore needs to take into account effects related to smoking cessation and previous history of depression or psychiatric disorder (which were present in 50% of our cases). Smokers with a history of major depressive disorders who achieve abstinence have a significantly higher risk of developing a new depressive episode.[36] Independently of psychiatric morbidity, studies report a higher rate of suicidal thoughts/attempts or suicide) in smokers, compared with non-smokers.[37,38] Moreover, bupropion, as with all antidepressants, is known to potentially induce worsening of pre-existent depression or suicidal tendencies, especially at the start of therapy.[39] In 2002, 'suicidal ideation' was added to the undesirable effects listed in the European SPC for bupropion, under the heading of postmarketing adverse events.

The most likely effect in acute bupropion overdose are nausea, vomiting, tremors, seizures, sinus tachycardia, agitation, hallucination and confusion.[40-42] Five case reports of fatal overdose involved intakes ranging from 66 to 153 tablets.[43-45]

Cardiovascular Adverse Events and Deaths

In our study, 50% of the fatalities were unexplained sudden deaths occurring in a middle-aged population. Although no autopsy was performed, these events probably resulted from coronary disease, which is the main cause of sudden death among smokers in this age bracket.[46] Sudden death can be the first manifestation of coronary angiopathy and is 2- to 4-fold more frequent for young male smokers than non-smokers. The high proportion of men (82%) in the subgroup of patients with ischaemic heart disease was significantly different to the proportion of men in the exposed population ($p = 0.0163$), a finding that was consistent with French data about this disease. In the English prescription-event monitoring study,[9] the median age of patients presenting with ischaemic heart disease was 53 years compared with 44.4 years for our study. The median age of the total cohort is also higher (47 years vs 41.4 years).[9]

The high rate of cardiovascular risk factors (73%) other than smoking and the high frequency of angiographic changes (88%) in patients who underwent this investigation make it difficult to assess the exact role of bupropion in cardiovascular disease. Smoking is a very well recognized risk factor for ischaemic heart disease and sudden death (resulting in a 4-fold increase in risk for heavy smokers), as well as for cerebrovascular disease, for which the increase in risk is lower but still important.[10] A self-controlled case-series analysis that estimated the relative incidence of sudden death during the first 28 days of treatment with bupropion reported an incidence ratio of 0.50 (95% CI 0.12, 2.05), suggesting that the drug is not associated with an increased risk of sudden death.[47] The main advantage of this self-controlled study was that it limited prescription bias, as the incidence during a 'high-risk' period was compared with the incidence during the remaining 'control' time in the same person. In England, mortality after starting bupropion was compared through indirect standardization between the PEM cohort and smokers from the Cancer Prevention Study – II (USA); the standard mortality ratio was 0.77 (95% CI 0.42, 1.28).[9] Meanwhile, under-reporting of patient age in the US cohort (unknown for 10 patients in 14 deaths) may have resulted to overestimation of expected deaths.[48] Moreover, the time window of exposure to bupropion was not defined and could have resulted in an overestimation of expected deaths.

In a randomized clinical trial of 626 smokers with cardiovascular disease, seven and four cases of angina pectoris occurred in the bupropion and placebo groups, respectively, over a follow-up period of 52 weeks, but only two during treatment.[49] The two deaths in the bupropion group occurred during the follow-up phase. Neither this study,[49] nor any of those discussed above,[9,47] showed any increase in cardiovascular risk with use of bupropion.

Conclusion

Seizures, angioedema and serum sickness-like reactions were the most frequently reported SARs to bupropion treatment in our study. Moreover, younger people appeared to be more at risk for cutaneous SARs generally, and younger women for angioedema in particular, perhaps because of weight-related differences in pharmacokinetics. A dose-dependent effect for angioedema and the results of skin tests were suggestive of a histamine liberation mechanism. Our analysis showed that taking more notice of the contraindications to use of bupropion could have prevented half the seizures reported to the database. The sex and age characteristics of patients with ischaemic heart disease and suicide attempts in the study population were similar to those of the French population as a whole. Whether bupropion is associated with an increase in these potential adverse effects of therapy can be determined only by epidemiological studies that take into account specific risk factors in the smoking population. Finally, the median time to onset of the SARs identified in this study suggests that prescribers should monitor patients exposed to bupropion more carefully during the first 2 weeks of treatment. To ensure safer use of bupropion, health professionals must respect the strict contraindications and warnings about use of this drug in patients with a history of seizures.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors would like to thank all members of the network of French Regional Centres of Pharma-

covigilance and AFSSAPS (Health Products French Safety Agency). The authors would also like to thank Maryse Dudu for her help in administrative organization and Dr B. Daury from GlaxoSmithKline. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Aronson JK, editor. Meyler's side effects of drugs. 15th ed. Oxford: Elsevier, 2006
2. Rush CR, Kollins SH, Pazzaglia PJ. Discriminative-stimulus and participant-rated effects of methylphenidate, bupropion, and triazolam in d-Amphetamine-trained humans. Exp Clin Psychopharmacol 1998 Feb; 6 (1): 32-44
3. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995; 56: 395-401
4. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997; 337: 1195-202
5. 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
6. 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
7. Aubin HJ. Tolerability and safety of sustained-release bupropion in the management of smoking cessation. Drugs 2002; 62 Suppl. 2: 45-52
8. Johnston JA, Lineberry CG, Ascher JA, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry 1991; 52 (11): 450-6
9. Boshier A, Wilton LV, Shakir S. Evaluation of the safety of bupropion (Zyban) for smoking cessation from experience gained in general practice use in England in 2000. Eur J Clin Pharmacol 2003; 59: 767-73
10. Fagerstrom K. The epidemology of smoking: health consequences and benefits of cessation. Drugs 2002; 62 Suppl. 2: 1-9
11. The Uppsala Monitorig Center. Practical pharmacovigilance [online]. Available from URL: http://www.who-umc.org/DynPage.aspx [Accessed 2008 Sep 1]
12. Hazell L, Shakir S. Under-reporting of adverse drug reactions. Drug Saf 2006; 29 (5): 385-96
13. Kennedy D, Goldman S, Lillie R. Spontaneous reporting in the United States. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley and Sons, 2000: 151-74
14. Summary of product characteristics for Zyban (bupropion). GlaxoSmithKline, 9 July 2002
15. Benson E. Bupropion-induced hypersensitivity reactions. Med J Aust 2001; 174: 650-1
16. Stewart JJ, Berkel HJ, Parish RC, et al. Single-dose pharmacokinetics of bupropion in adolescents: effects of smoking status and gender. J Clin Pharmacol 2001; 41 (7): 770-8
17. Findlay JW, Van Wyck Fleet J, Smith PG, et al. Pharmacokinetics of bupropion, a novel antidepressant agent, following oral administration to healthy subjects. Eur J Clin Pharmacol 1981; 21 (2): 127-35
18. Hsyu PH, Singh A, Giargiari TD, et al. Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. J Clin Pharmacol 1997; 37: 737-43
19. Fays S, Trechot P, Schmutz JL, et al. Bupropion and generalized acute urticaria: eight cases. Br J Dermatol 2003; 148: 171-92
20. Chiaverini C, Baldin B, Chichmanian RM, et al. Urticaire au bupropion (Zyban®): 2 cas. Ann Dermatol Venereol 2003; 130: 208-9
21. Loo WJ, Alexandroff A, Flanagan N. Bupropion and generalized acute urticaria: a further case [letter]. Br J Dermatol 2003; 149 (3): 660
22. Davis JS, Boyle MJ, Hannaford R, et al. Bupropion and serum sickness-like reaction. Med J Aust 2001; 174 (9): 479-80
23. Kanani AS, Kalicinsky C, Warrington RJ, et al. Serum sickness-like reaction with bupropion sustained release. Can J Allergy Clin Immunol 2000; 5 (1): 27-9
24. MacCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. Ann Pharmacother 2000; 34 (4): 471-3
25. Muller G, Bielefeld P, Ramanantsoa M, et al. Maladie sérique et coagulopathie de consommation sous bupropion [abstract]. Rev Med Intern 2002; 23 Suppl. 2: 704s
26. Ornetti P, Disson-Dautriche A, Muller G, et al. Joint symptoms in patients on bupropion therapy. Joint Bone Spine 2004; 71 (6): 583-5
27. Peloso PM, Baillie C. Serum sickness-like reaction with bupropion [letter]. JAMA 1999; 282 (19): 1817
28. Tripathi A, Greenberger PA. Bupropion hydrochloride induced serum sickness-like reaction. Ann Allergy Asthma Immunol 1999; 83: 165-6
29. Weber EA, Knowles SR, Tsao S. Bupropion-induced serum sickness-like reaction [abstract no. 30]. J Allergy Clin Immunol 2001; 107 (2): S331-9
30. Pisani F, Oteri G, Costa C, et al. Effects of psychotropic drugs on seizure threshold. Drug Saf 2002; 25 (2): 91-110
31. Dunner DL, Zisook S, Billow AA, et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998; 59 (7): 366-73
32. Medicines Control Agency. Zyban (bupropion hydrochloride): safety update. 29 Jul 2002 [online]. Available from URL: http://www.mca.gov.uk [Accessed 2002 Jan 20]
33. Réseau Sentinelles, Unité INSERM 707 [online]. Available from URL: http://Sentiweb.org [Accessed 2005 Mar 5]
34. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet 1995; 25: 95-101
35. Hall SM, Munoz RF, Reus VI, et al. Nicotine negative affect and depression. J Consult Clin Psychol 1993; 61 (5): 761-7
36. Glassman AH, Covey LS, Stetner F, et al. Smoking cessation and the course of major depression: a follow-up study. Lancet 2001; 357: 1929-32
37. Breslau N, Schultz LR, Johnson EO, et al. Smoking and the risk of suicidal behaviour. Arch Gen Psychiatry 2005; 62: 328-34
38. Miller M, Hemenway D, Bell NS, et al. Cigarette smoking and suicide: a prospective study of 300,000 male active-duty army soldiers. Am J Epidemiol 2000; 151: 1060-3
39. US Food and Drug Administration. Worsening depression and suicidality in patients being treated with antidepressant medications. Media release: 22 Mar 2004 [online]. Available from URL: http://www.fda.gov [Accessed 2005 Sep 12]
40. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. Med J Aust 2003; 178: 61-3
41. Tracey JA, Cassidy N, Casey PB, et al. Bupropion (Zyban) toxicity. Ir Med J 2002; 95 (1): 23-4
42. Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. J Emerg Med 2004; 27 (2): 147-51
43. Friel PN, Logan BK, Fligner CL. Three fatal drug overdoses involving bupropion. J Anal Toxicol 1993; 17 (7): 436-8
44. Harris CR, Gualtieri J, Stark G. Fatal bupropion overdose. J Toxicol Clin Toxicol 1997; 35 (3): 321-4
45. Rohrig TP, Ray NG. Tissue distribution of bupropion in a fatal overdose. J Anal Toxicol 1992; 16 (5): 343-5
46. Holbrook JH. Nicotine addiction. In: Harrison T, Fauci AS. Harrison's principals of internal medicine. 14th ed. New York: McGraw-Hill, Health Professions Division, 1998

47. Hubbard R, Lewis S, West J, et al. Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network. Thorax 2005; 60: 848-50
48. Thun MJ, Day-Lally C, Myers DG, et al. Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959 through 1965) and II (1982 through 1988). In: Changes in cigarette-related disease risks and their implication for prevention and control. Smoking and tobacco control monograph 8. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Cancer Institute, 1997: 305-82
49. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J 2003; 24 (10): 946-55

Correspondence: Dr *Marie-Nöelle Beyens*, Regional Pharmacovigilance Centre, Bellevue Hospital University, 42055 Saint-Etienne Cedex 2, France.
E-mail: m.noelle.beyens@chu-st-etienne.fr