

# Chest pain during use of bupropion as an aid in smoking cessation

L. de Graaf & W. L. Diemont

Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, the Netherlands

**Aims** To investigate the cause of chest pain during the use of bupropion as an aid to stop smoking.

**Methods** The Netherlands Pharmacovigilance Centre received 22 reports of chest pain, associated with the use of bupropion as an aid to smoking cessation. Additional information about long-term follow up was collected to analyze whether these complaints herald manifest cardiac disease.

**Results** All but one patient recovered after withdrawal of bupropion. Seven patients were additionally investigated and in six of them, a cardiac cause could be excluded. During long-term follow-up, no coronary heart diseases were diagnosed.

**Conclusions** These reports indicate that chest pain seems to be associated with the use of bupropion, but its origin remains unclear.

**Keywords:** bupropion, chest pain, pharmacovigilance, smoking cessation

## Introduction

In December 1999, the Netherlands was the first country in Europe to grant a marketing authorization for bupropion (Zyban<sup>®</sup>) as an aid in smoking cessation. In the USA, bupropion has also been approved as an antidepressant. It is chemically and pharmacologically not related to any other known antidepressant. The mechanism responsible for the effect in smoking cessation is unknown, yet a pharmacological relation between smoking and depression has been demonstrated [1]. Bupropion selectively inhibits the re-uptake of norepinephrine and dopamine, two monoamines. It has minimal effects on the reuptake of serotonin and no anticholinergic properties or effects on MAO-A and B activity. The Summary of Product Characteristics (SPC) of bupropion mentions chest pain as a possible adverse drug reaction (ADR), but an underlying mechanism is not specified [2].

The Netherlands Pharmacovigilance Centre Lareb is responsible for collecting and analyzing reports concerning possible ADRs from health professionals on behalf of the Dutch Medicines Evaluation Board.

Since chest pain may be a manifestation of coronary heart disease, especially in high-risk patients like smokers, it is important to know whether such complaints indeed herald manifest coronary disease or have another origin [3].

## Methods

The database of the Netherlands Pharmacovigilance Centre Lareb was searched for the period between approval of bupropion SR on the Dutch market and 31 December 2001. Information about latency, additional reported ADRs, recovery, additional investigations and long-term follow-up was collected, partly by an additional questionnaire to be answered by the reporting physician or pharmacist.

## Results

We received 591 ADRs associated with the use of bupropion SR, of which 45 dealt with cardiac disorders. A total of 22 reports concerned chest pain or a feeling of pressure on the chest. In accordance with the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>, a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA)), chest pain and feeling of pressure on the chest are arranged under 'general disorders' and not under cardiac disorders. Reported cardiac ADRs included palpitations (21), arrhythmia (7), oedema (4), myocardial infarction (3), anginal pain (2) and cardiac arrest (1). The reporting odds ratio of the association between bupropion and chest pain was 8.25 (95% confidence interval 4.97, 13.68). This implies that in our database chest pain is significantly associated with bupropion in comparison with other associations.

The mean age of the patients experiencing chest pain was 42.2 years, varying between 21 and 63 years. Ten patients were female. Mean latency time was 6 days (range 1–27) with a median of 4 days. The SPC recom-

Correspondence: L. de Graaf pharmD, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, the Netherlands. Tel.: + 31 7364 69700; Fax: + 31 7364 26136; E-mail: l.degraaf@lareb.nl

Received 14 January 2003, accepted 17 April 2003.

mends to quit smoking only 7 days after the start of bupropion. If the chest pain occurs in the first 7 days of use, a relation between nicotine withdrawal and chest pain can be excluded. During the research period, the dose recommendation included an increase after 3 days. In three patients, the dose was decreased, resulting in disappearance of the complaints in one patient. Bupropion SR was withdrawn in all other patients, resulting in disappearance of the complaints, except in one patient, whose outcome is unknown.

In four patients, the initial data were sufficient to confirm or exclude a cardiac origin. One of them appeared to have a coronary stenosis >70%, three had a normal ECG including one without a beneficial reaction on sublingual nitroglycerin.

In the other 18 reports data were insufficient; therefore a questionnaire was sent to the 18 reporters and returned by 16. The mean follow-up period was 392 days (range 68–752 days). In 12 patients, no additional investigations were performed. Nevertheless, in one of them a hiatus hernia with reflux oesophagitis grade I was diagnosed 4 months later. In three other patients, additional investigations revealed no causes for the chest complaints, including two normal ECGs. In one patient, information on additional investigations was not available.

## Discussion

Our data suggest that chest complaints are associated with use of bupropion SR, and especially following the previously recommended dose increase after 3 days. A dose decrease might therefore resolve the complaints, as demonstrated in one patient. Taking into account an elimination half-time of 20 h, it may be questionable whether patient and physician want to wait for the possible beneficial effect of a dose decrease.

The nature of the chest complaints seems not related with coronary heart disease. The finding of coronary heart disease in one patient may be coincidental, since the ECG during chest pain showed no evident ischaemia (flattening of repolarization). In five other patients the ECGs, although at rest and not during chest pain, were

normal. During the long follow-up period, no coronary heart diseases were diagnosed.

A total of 18 patients (82%) experienced simultaneous ADRs like dyspnoea (six patients), tachycardia or palpitations (five patients) and increased sweating (four patients). Although these complaints fit within nicotine withdrawal, most symptoms appeared before smoking cessation on day 7. Most of these ADRs resolved as well after bupropion withdrawal.

The noncardiac origin of chest pain is supported by the reporters. First, they reported chest pain and not angina pectoris. Second, the questionnaire on 16 patients revealed that in 12 patients no additional investigations had been performed. Apparently, no coronary heart disease was suspected despite the fact that these patients have a risk factor for coronary heart disease.

Chest pain has been associated with other medicines. An example is sumatriptan [4]. Due to its pharmacological vasoconstrictive action, the occurrence of chest pain in response to sumatriptan administration caused fear for cardiac ischaemia due to coronary vasoconstriction. However, a case-control study demonstrated no differences in abnormal exercise tests in patients with sumatriptan-induced chest pain and patients without chest pain after sumatriptan administration.

In conclusion, chest pain seems associated with use of bupropion SR 150 mg twice daily. Its origin is unclear, although coronary heart disease seems not responsible. Generally, withdrawal of bupropion resulted in recovery.

## References

- Berlin I, Said S, Spreux-Varoquaux O, Olivares R, Launay JM, Puech AJ. Monoamine oxidase A and B activities in heavy smokers. *Biol Psychiatry* 1995; **38**: 756–761.
- Dutch Summary of Product Characteristics of Zyban®. <http://www.cbg-meb.nl/nl/prodinfo/index.htm>, access date 13.12.2002.
- Bass C, Mayou R. ABC of psychological medicine. Chest pain. *Br Med J* 2002; **325**: 588–591.
- Ottervanger JP, Hoorntje JC, Valkenburg HA, Grobbee DE, Stricker BH. Exercise testing in patients with chest pain to sumatriptan. *Neth J Med* 1998; **53**: 245–248.