Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network

R Hubbard, S Lewis, J West, C Smith, C Godfrey, L Smeeth, P Farrington, J Britton

Background: Bupropion is an effective smoking cessation therapy but its use in the UK has been limited by concerns that it may increase the risk of sudden death.

Methods: Data for all patients prescribed bupropion within The Health Improvement Network (a computerised general practice database) were extracted and the self-controlled case-series method was used to estimate the relative incidence of death during the first 28 days of treatment. The incidence of seizures, a recognised adverse effect of bupropion, was also investigated during this period.

Results: A total of 9329 individuals had been prescribed bupropion (mean age 44 years, 48% male). The total person-time after the first prescription for bupropion was 17 586 years, and during this time 121 people died. Two people died within the first 28 days of treatment, which was less than expected in comparison with the remaining observation period by an incidence ratio of 0.50 (95% confidence interval CI 0.12 to 2.05). Twenty eight people were recorded as having a total of 45 seizures (23 before starting bupropion, two in the first 28 days of treatment, and 20 at a later point). The relative incidence of seizures during the first 28 days of treatment was 3.62 (95% CI 0.87 to 15.09), equivalent to one additional seizure per 6 219 first time bupropion users.

Conclusions: Bupropion use is probably associated with an increased risk of seizures, but no evidence was found to suggest that the drug is associated with an increased risk of sudden death.

Cigarette smoking is the most important preventable cause of morbidity and premature mortality in the UK, and smoking cessation interventions—including nicotine replacement therapy or bupropion—are among the most cost effective healthcare interventions available. Bupropion was launched in the UK in June 2000 and there was a rapid uptake in the use of this drug. In February 2001, however, a newspaper report suggested that bupropion caused an increased risk of sudden death, and this was followed by a series of other anecdotal reports in the tabloid press. The use of bupropion in the UK has since been very low.

Smoking cessation is the only intervention which has been shown to reduce the loss of lung function in people with chronic obstructive pulmonary disease. Given the limited range of treatments available for smoking cessation, we believe that more robust evidence on the association between bupropion and sudden death is required before this treatment option is discarded by health professionals in the UK. We have therefore analysed data from a new general practice database (The Health Improvement Network (THIN)) and, to prevent confounding resulting from inter-person comparisons, we analysed the data using the self-controlled case-series method which compares the incidence of an outcome during a “high risk” exposure time with the incidence during the remaining “control” time within person. The control time may include time both before and after the high risk time. Since the case-series method is based on exposed people with the outcome of interest, it is an efficient design which provides the same amount of statistical power as an analysis of an equivalent whole cohort and slightly more statistical power than an equivalent nested case-control study. The main advantage of the case-series method over a traditional cohort method for the present study is that it removes the problem of confounding caused by factors that vary between people, such as the extent of coronary artery disease. This means that the case-series approach allows for the fact that smokers prescribed bupropion may represent a select group who are more likely to have smoking related illnesses.

Initially we identified all people with at least one prescription for bupropion during their THIN data record, and this was the baseline cohort used for all subsequent analyses. Within this cohort for each person we identified the start of the computerised record, the date of all prescriptions for bupropion, the date of death where present, and the date of the last data collection. Using these data we calculated the crude death rate for the follow up period after the first prescription for bupropion and used Poisson regression (STATA version 7) to compare the crude death rate during the 28 days after the first prescription for bupropion with

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that in the remaining person-time. We chose 28 days as this is the duration of bupropion treatment currently recommended.1 For our case-series analyses we defined the high risk period as a period of 28 days after the first prescription for bupropion and the control time as the time between the end of the high risk period and the date of last data collection in the cohort. Since people had to be alive to receive a prescription for bupropion, we did not include any person-time before the first prescription for bupropion in this analysis and, since we were interested in the theoretical risk of dying at any point during the study period, each person who died was given the same end date of 11 November 2003, the date of last data collection. We compared the risk of dying during the high risk period with that during the control period using the case-series method (GLIM version 4.9), adjusting for the effects of age in 2 year age bands. Although we chose a 28 day “high risk period” to reflect current treatment recommendations,1 we also repeated our analyses using a 63 day high risk period, which corresponds to the maximum recommended duration of bupropion treatment, in order to check the robustness of our findings.

Since bupropion (in common with other antidepressants) is a recognised cause of seizures,9 we repeated our analyses during the high risk period with that during the control period using the case-series method (GLIM version 4.9), adjusting for the effects of age in 2 year age bands. Although we chose a 28 day “high risk period” to reflect current treatment recommendations,1 we also repeated our analyses using a 63 day high risk period, which corresponds to the maximum recommended duration of bupropion treatment, in order to check the robustness of our findings.

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Authors' affiliations

R Hubbard, J West, J Britton, Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

S Lewis, C Smith, Division of Respiratory Medicine, University of Nottingham, Nottingham, UK

C Godfrey, Centre for Health Economics, University of York, York, UK

L Smeeth, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, London, UK

P Farrington, Department of Statistics, Open University, Milton Keynes, UK

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Competing interests: RH is a member of The Health Improvement Network (THIN) advisory group. JB has received a honorarium from a third party organisation but originating from GlaxoSmithKline (the producers of bupropion) for speaking at an invited conference on smoking cessation management guidelines in 2002, and also received consulting fees from the manufacturers of nicotine replacement therapy and other novel smoking cessation therapies.

RH, JB and LS were responsible for the main study hypothesis and RH, SL, CS, CG, LS, PF and JB were responsible for the detailed study design and were applicants on the British Lung Foundation grant. The analysis was performed by RH, JW, SL, PF and CS. All authors contributed to the writing of the paper and all authors have had access to all of the data in the study.

Work attributed to Division of Epidemiology and Public Health, Nottingham University.

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Statistics and suggests that the validity of these data is high.3 There have been no specific studies of the validity of seizure diagnoses in THIN, so it is possible that these data are not as complete as those for death registration. However, given the concern in the media about the adverse effects of bupropion, it seems likely that the ascertainment of seizures during the period of treatment with bupropion will tend to be higher than that during other times so, if any variations in ascertainment exist, these will, if anything, lead to an overinflation of the adverse impact of bupropion on seizure rate.

Bupropion was first used for the treatment of depression in the late 1980s and at this time was only available in an immediate release form.11 In an open label trial of 3341 patients using up to 450 mg/day of this formulation, the risk of seizure during the first 8 weeks of treatment was 0.36%.12 In 1996 a sustained release formulation was introduced and, in a similar open label trial involving 3100 patients and a maximum daily dose of 300 mg, three people (0.1%) had a seizure.7 This increased risk of seizure is similar to that found for other commonly used antidepressants.11 In the UK for smoking cessation the sustained release preparation is used at a maximum dose of 300 mg and the suggested risk of seizure is 0.1%. Bupropion avoidance or a maximum daily dose of 150 mg is recommended if there is a risk of seizures, so it is likely that some selection is present in our cohort with people considered to be at high risk of seizures excluded. This exclusion was not complete, however, since 12 people had a total of 23 seizure diagnoses recorded before the first bupropion prescription. In our dataset there were two seizures during the first 28 days after starting treatment with bupropion and only 0.5 seizures were expected. This is equivalent to an additional one seizure per 6219 first time bupropion users, suggesting that bupropion has a better safety profile in relation to seizure than previously reported.

There are few data available on the association between bupropion and mortality, but a systematic review of the limited data available from clinical trials involving bupropion for smoking cessation has found no evidence to support an increase in mortality.14 In a questionnaire survey by the UK Drug Safety Research Unit, general practitioners were asked to provide information on bupropion users. Fourteen deaths were reported among 11 735 replies (response rate of 48%) during the first 12 weeks after starting bupropion treatment.15 Using data for American smokers as a comparator population, this was equivalent to a standardised mortality ratio of 0.77 (95% CI 0.42 to 1.28). Despite the differences in study design and the limitations of the control population, these results are similar to our own in demonstrating no increase in mortality in relation to the use of bupropion. In fact, both studies have shown a non-significant decrease in mortality in the period after starting bupropion treatment. The reasons for this are not clear, but may reflect a tendency for general practitioners to prescribe bupropion during times when patients are generally well and not to initiate treatment during periods of acute illness.

This study describes the experience of using bupropion in primary care in the UK. The results show that the drug is probably associated with a small increase in seizure rate, which is similar to that seen with most other antidepressants when used to treat depression. In a cohort of 9329 first time users of bupropion we found no evidence to suggest that the drug is associated with an increased risk of sudden death, and our findings suggest that a hesitancy to use the drug on these grounds is unfounded.
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