



TITLE: Use of Bupropion in Patients with Depression and the Associated Risk of Seizures: Safety

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CONTEXT AND POLICY ISSUES:

The prevalence of epilepsy ranges from 0.5% to 1%,^{1,2} and the incidence in adults varies from 0.03% to 0.1% depending on age.² In one case control study, depression was associated with an increased risk of seizures, even after controlling for age, sex, length of follow-up, and antidepressant medication use.³ No information was found on the incidence and prevalence of seizures among people with depression.

Bupropion is an antidepressant agent approved in Canada for the symptomatic relief of major depressive disorder and as a smoking cessation aid.^{4,5} Bupropion has been associated with a dose-related risk of seizures. According to the manufacturer, the incidence of seizures with Wellbutrin SR (sustained release) is 0.1% (1 per 1,000) with doses up to 300 mg/day, and 0.4% at 400 mg/day.⁶ In clinical trials of bupropion for smoking cessation, seven seizures were reported in approximately 8,000 patients treated.⁷ Estimated seizure rates from post-marketing adverse event monitoring in the UK, Canada, and France were lower than 0.1%. These rates, however, must be viewed with caution because serious adverse events are underreported up to 10 fold, and the total number of persons exposed to bupropion is not exactly known.⁷

Assessing the risk of seizures with antidepressants is challenging for a number of reasons. The prevalence of seizures in the general population is similar to the rates often reported among people treated with antidepressants.² Often patients who report seizures during antidepressant treatment have predisposing factors that may have contributed to the seizure.² Sample sizes of studies are often too small to detect differences in these rare events and patients are rigidly screened for inclusion in trials and, therefore, may not be reflective of those encountered in clinical practice. Incidence rates are frequently calculated without considering the length of therapy.²

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This report will explore evidence on the risk of seizures with bupropion in patients with depression. This information could be used to help inform formulary decisions about the coverage of bupropion and to make decisions about individual patient management.

RESEARCH QUESTIONS:

What is the risk of seizures in patients taking bupropion for depression compared to placebo or other antidepressants?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, PsycINFO, the Cochrane Library (Issue 3, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles. There was no date limit or filters applied to the search. Internet links were provided, where available.

SUMMARY OF FINDINGS:

No health technology assessment reports, randomized controlled trials (RCTs) or controlled clinical trials were found that provided information on the risk of seizures in patients taking bupropion for the management of depression. One systematic review⁸ and an update⁹ to that review met the inclusion criteria.

Additional studies of interest are listed in the appendix.

Systematic reviews and meta-analyses

The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review evaluating the effectiveness and safety of second-generation antidepressants when used for the treatment of adults with depression.⁸ A second publication provided an update of the harms data from this review.⁹ The authors' literature search was comprehensive and included multiple electronic databases, handsearching and a grey literature search. The search included English language studies from 1980 to February 2006⁸ or April 2007.⁹ They included meta-analyses, RCTs (of at least six weeks duration with sample size of at least 40 persons), and observational studies (minimum three month study duration and 100 patients sample size). Study selection and the quality of the studies were assessed by two independent reviewers. A total of 83 head-to-head RCTs and 21 observational studies were included in the evaluation of harms.^{8,9} Three studies assessed the risk of seizures, two of which were uncontrolled open label trials that included bupropion.⁸

The two studies that included bupropion enrolled 3,100 patients treated with sustained release bupropion (Dunner 1998) and 3,341 treated with regular release bupropion (Johnston 1991).⁸ The seizure rate reported in Dunner 1998 was 0.1%, and in Johnston 1991 was 0.4%.² Both Dunner and Johnston concluded that the rate of seizures for bupropion was within the reported range for other antidepressants.⁸ The review authors further concluded that the data were insufficient to conclude for or against an increased risk of seizures in patients taking bupropion.⁸

The two studies were rated as low quality by the systematic review authors because of their uncontrolled open label study designs.

Limitations

The authors of the systematic review reported several limitations to adverse event data in the studies they examined. They stated that it was difficult to determine if the methods used to assess harms were unbiased.⁸ Most studies did not pre-specify or define adverse events, nor did they use objective side effect scales or terminology. The open label uncontrolled studies providing data on the rate of seizures in patients treated with bupropion were rated as low quality.⁸

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The available evidence of an increased risk of seizures in patients treated with bupropion for depression was inconclusive. This evidence was, however, limited to uncontrolled studies rated as low quality by the authors of the AHRQ systematic review.

The absence of data from controlled trials may be a consideration when deciding on the criteria for use of bupropion in patients with depression.

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REFERENCES:

1. Benbadis SR, Allen HW. An estimate of the prevalence of psychogenic non-epileptic seizures. *Seizure*. 2000 Jun;9(4):280-1.
2. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract* [Internet]. 2005 Dec [cited 2010 Mar 18];59(12):1435-40. Available from: <http://www3.interscience.wiley.com/cgi-bin/fulltext/118711757/PDFSTART>
3. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. *Ann Neurol*. 2000 Feb;47(2):246-9.
4. *Wellbutrin® SR*. 2009 [cited 2010 Apr 1]. In: e-CPS [database on the Internet]. Ottawa: Canadian Pharmacists Association; 2007 - . Available from: <http://www.e-therapeutics.ca/> Subscription required.
5. *Zyban®*. 2009 [cited 2010 Apr 1]. In: e-CPS [database on the Internet]. Ottawa: Canadian Pharmacists Association; 2007 - . Available from: <http://www.e-therapeutics.ca/> Subscription required.
6. *Wellbutrin SR® (bupropion hydrochloride) sustained-release tablets* [Internet]. Research Triangle Park (NC): GlaxoSmithKline; 2009 [cited 2010 Mar 29]. Available from: http://us.gsk.com/products/assets/us_wellbutrinSR.pdf Prescribing information.
7. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2007;(1):CD000031.
8. Gartlehner G, Hansen RA, Thieda P, DeVaugh-Geiss AM, Gaynes BN, Krebs EE, et al. *Comparative effectiveness of second-generation antidepressants in the pharmacologic treatment of adult depression* [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2007 [cited 2010 Mar 29]. (Comparative effectiveness review, no. 7). Available from: http://effectivehealthcare.ahrq.gov/ehc/products/7/59/Antidepressants_Final_Report.pdf
9. Gartlehner G, Thieda P, Hansen RA, Gaynes BN, veaugh-Geiss A, Krebs EE, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. *Drug Saf*. 2008;31(10):851-65.

APPENDIX: Additional studies

Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry*. 1998 Jul;59(7):366-73. PM:9714265

Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, et al. A 102-center prospective study of seizure in association with bupropion. *J Clin Psychiatry*. 1991 Nov;52(11):450-6. PM:1744061