Risk of Angle-Closure Glaucoma With Bupropion and Topiramate

Richard J. Symes, BSc(Hons), FRCOphth; Mahyar Etminan, PharmD, MSc; Frederick S. Mikelberg, MD, FRCSC

**Importance** Epidemiologic studies have shown that antidepressants may increase the risk of angle-closure glaucoma. We examined the risk of angle-closure glaucoma with bupropion hydrochloride, a unique, popular antidepressant also marketed as a smoking cessation aid.

**Observations** A nested case-control study was conducted using a large health claims database in the United States from January 1, 2006, to March 31, 2014. The database contained deidentified information pertaining to a cohort of 6,110,723 patients. Cases were defined according to the first coding for angle-closure glaucoma. For each case, 10 control participants were selected and matched to the cases using density-based sampling. Adjusted rate ratios were computed for bupropion, topiramate (positive control group drug), and esomeprazole (negative control group drug). The adjusted rate ratio was 1.09 (95% CI, 0.75-1.59) for bupropion and 2.59 (95% CI, 1.56-4.30) for topiramate. In a prespecified analysis of patients younger than 50 years, the adjusted rate ratio was 1.98 (95% CI, 1.02-3.84) for bupropion and 5.30 (95% CI, 2.54-11.04) for topiramate.

**Conclusions and Relevance** Both bupropion and topiramate are widely prescribed drugs. The risk of angle-closure glaucoma in patients younger than 50 years was twice as high in patients taking bupropion and more than 5 times higher in patients taking topiramate.

Bupropion hydrochloride, marketed as Wellbutrin or Zyban, is a novel norepinephrine and dopamine reuptake inhibitor-type antidepressant that is also approved by the US Food and Drug Administration as a treatment for smoking cessation. In 2011, more than 20 million prescriptions for bupropion were dispensed in the United States. One well-described case report has linked bupropion to choroidal effusion and secondary angle-closure glaucoma (ACG), as has been described for topiramate. Although most reports of choroidal effusion and ACG relate to topiramate, the same effects have been reported less frequently for other drugs, including selective serotonin reuptake inhibitor antidepressants and medications containing sulfa. Epidemiologic studies have also demonstrated a link between antidepressants and ACG; however, to our knowledge, no study to date has examined the risk of ACG specifically with bupropion.

Topiramate-associated ACG occurs secondary to choroidal effusion, with a consequential forward shift of the lens iris diaphragm that causes angle compromise. Typical associated features include bilateral involvement and younger age. In a case series of 86 patients who experienced this adverse effect, the mean age at presentation was 34 years and in a systematic review, 50% of affected patients were younger than 40 years. It has been suggested that topiramate may be a leading cause of bilateral ACG in younger patients.

Our group previously reported a positive association between topiramate and glaucoma. This study was limited by the inability to distinguish between open- and closed-angle forms of glaucoma. In the current study, it was possible to specifically identify cases with a code for angle closure. In addition, this method allowed topiramate to be used as a positive control for bupropion, for which the risk of ACG is unknown. It also enabled the relative frequency of the association for the 2 drugs to be compared.

**Methods**

**Data Sources and Cohort Description** LifeLink is a comprehensive health claims database that captures health-related information for approximately 150 million US individuals. LifeLink captures all physician visit diagnoses, hospitalizations, procedures, and outpatient prescriptions using the International Classification of Diseases, Ninth Revision, Clinical Modification. The deidentified data include a balanced sample of all regions of the United States. The cohort in this study consisted of participants aged 15 to 60 years who were randomly selected from January 1, 2006, to March 31, 2014, and who had at least 1 year of prescription drug data. The study was approved by the University of British Colum-
bria ethics board. Owing to the retrospective nature of the study and the use of anonymous data, participants were not required to provide written or verbal informed consent.

Study Design and Cohort Entry Definition
A nested case-control study (cohort study with a case-control analysis) was used to examine the risk of ACG with bupropion and topiramate. This design is especially useful in quantifying rare events with time-varying exposures, such as adverse events with prescription drugs.11 Cohort entry was defined as the first prescription of bupropion, topiramate (positive control group drug), and esomeprazole (negative control group drug not expected to be associated with ACG). Cohort members for each study drug were followed up to the first diagnosis of ACG or the latest date of data availability, whichever came first.

Case and Control Definition
Acute ACG was defined by the first physician visit for the condition through International Classification of Diseases, Ninth Revision code 365.22. The date of the first diagnosis was deemed the index date. A risk set of control participants that had the same length of follow-up, cohort entry time, and age of each case was created. From the risk set, 10 randomly selected control participants were matched to each case.

Exposure Definition and Statistical Analysis
All prescription drugs in the year prior to the index data were identified. Because the risk period from the onset of glaucoma has been estimated to be 14 days,6 the risk with current use of a study drug was examined. A current user was defined as having received a prescription where the initiation and termination of that prescription overlapped with the index date. Risk ratios (RRs) for the study drug were compared with those not taking the study drug. Risk ratios were adjusted for the following covariates, including sex and other drugs associated with ACG: selective serotonin reuptake inhibitors, inhaled respiratory medications, and sulfamethoxazole. Additionally, a prespecified subgroup of patients younger than 50 years was analyzed because younger age appears to be a feature of topiramate-associated ACG and younger patients would be at lower risk for primary ACG.8,12

At a Glance
- Bupropion and topiramate are both widely prescribed drugs that have been reported to cause angle-closure glaucoma via a choroidal effusion mechanism.
- This study investigates the association of angle-closure glaucoma with bupropion and topiramate.
- Both bupropion and topiramate were associated with angle-closure glaucoma, although the risk was greater for topiramate. This is consistent with a higher number of topiramate-associated cases reported in the literature.

Results
There were 6 110 723 patients in the cohort from which 1554 cases with acute ACG codes and 15 540 corresponding control participants were identified. Cases and control participants were comparable with respect to most covariates (Table 1). In the main analysis (Table 2), patients taking bupropion were not at a higher risk of developing ACG (RR = 1.09; 95% CI, 0.75-1.59) while patients taking topiramate had approximately 2.5 times the risk of developing ACG (RR = 2.59; 95% CI, 1.56-4.30). Patients taking esomeprazole were not at a higher risk of ACG (RR = 1.30; 95% CI, 0.94-1.79). In the prespecified analysis for patients younger than 50 years (Table 3), an increase in the risk of ACG with bupropion (RR = 1.98; 95% CI, 1.02-3.84) and topiramate (RR = 5.30; 95% CI, 2.54-11.04) was observed. The RR for esomeprazole was 0.85 (95% CI, 0.31-2.37). None of the patients with ACG who were taking bupropion or topiramate were dispensed a new prescription for these drugs after the angle-closure episode. We were unable to ascertain from the data whether cases were unilateral or bilateral.

Discussion
The results showed an increased risk of ACG with bupropion in patients younger than 50 years. This younger age group is known to be associated with topiramate-induced ACG and a lower rate of primary ACG.6,8,12 The risk was higher for topiramate, a finding consistent with the number of reported cases in the literature. Although the manufacturer’s full prescribing information for bupropion references the possibility of ACG occurring secondary to pharmacological pupillary dilation,13-15 it is possible that a choroidal effusion mechanism can also occur, similar to other antidepressants. In this analysis, no new prescriptions for bupropion were issued after the angle-closure event. This could imply that pupillary dilation with a predisposed narrow angle was less likely to be the mechanism of angle closure because laser peripheral iridotomy would have allowed treatment to be continued in such cases. For both topiramate and bupropion, 3.89% of eligible patients younger than 50 years not taking confounding drugs with a code for ACG were taking 1 of these drugs. For a given patient younger than 50 years presenting with ACG, the probability of an underlying drug-induced etiology is possible but relatively unlikely.

Table 1. Comparison of Cases and Control Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Control Participants</th>
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<tbody>
<tr>
<td>No.</td>
<td>1554</td>
<td>15 540</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54.6 (8.3)</td>
<td>54.6 (8.3)</td>
</tr>
<tr>
<td>Follow-up, mean (SD), y</td>
<td>2.3 (1.7)</td>
<td>2.3 (1.7)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>478 (30.8)</td>
<td>6791 (43.7)</td>
</tr>
<tr>
<td>Medications 1 year prior to glaucoma, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>210 (13.5)</td>
<td>2036 (13.1)</td>
</tr>
<tr>
<td>Respiratory drugs (salbutamol, pratropium, and tiotropium)</td>
<td>350 (22.5)</td>
<td>3030 (19.5)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>75 (4.8)</td>
<td>668 (4.3)</td>
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Abbreviation: SSRIs, selective serotonin reuptake inhibitors.
An increase in the risk of ACG was not identified with esomeprazole, although the upper limit of the confidence interval in both analyses did not exclude the possibility of a harmful effect. Epidemiologic evidence did not support a potential link between esomeprazole and ACG but it is possible that the sulfa-containing structure of the drug may have played a role. The results validate our previous findings and findings of others that topiramate increases the risk of glaucoma.

The strength of this study was the large sample size necessary to investigate a rare adverse drug reaction. As with all health claims databases, we did not have access to individual patient data; however, ACG is usually only diagnosed by an ophthalmologist and the specificity of the code makes a classification error unlikely. Another limitation was that our data set was limited to patients aged 15 to 60 years; however, as mentioned previously, younger patients appear to be particularly susceptible to drug-induced choroidal effusion.

Conclusions

Bupropion was associated with ACG in patients younger than 50 years, a finding that warrants further study. This association was stronger for topiramate.

**REFERENCES**