**RESEARCH LETTERS**

**Rapid Assessment of Cardiovascular Risk Among Users of Smoking Cessation Drugs Within the US Food and Drug Administration’s Mini-Sentinel Program**

In June 2011, the US Food and Drug Administration (FDA) issued a Drug Safety Communication indicating that varenicline tartrate, a drug prescribed for smoking cessation, may increase the risk of certain cardiovascular events in individuals with cardiovascular disease. The finding was based on the FDA’s review of a randomized placebo-controlled trial of 714 smokers. In July 2011, the FDA requested that the Mini-Sentinel program perform a rapid safety assessment of the drug.

Methods. Mini-Sentinel is part of the FDA’s Sentinel Initiative, a national system under development for monitoring medical product safety. The program has created a distributed network of electronic health care databases with more than 125 million lives and 350 million person-years of longitudinal observation time.

In this rapid assessment, we identified individuals who filled a first prescription for varenicline or the comparator drug, bupropion hydrochloride, between January 1, 2006, and the most recent date available at each data partner as of July 5, 2011. We further restricted the cohort to individuals who were 20 years or older on the date of first varenicline or bupropion dispensing (the index date) and who met the following criteria during the preceding 180 days: (1) continuously enrolled in the health plan with medical and drug coverage; (2) had no dispensing of either drug; (3) had no diagnoses of acute myocardial infarction (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 410.xx), intermediate coronary syndrome or unstable angina (411.1), acute coronary occlusion without myocardial infarction (411.81), or coronary atherosclerosis (414.0x); and (4) had a diagnosis code for tobacco use disorder (305.1).

The outcome of interest was a composite of 3 cardiovascular end points (ICD-9-CM codes 410.xx, 411.1, and 411.81) recorded as the primary diagnosis in an inpatient or emergency department setting. We bridged gaps that were 7 or fewer days between prescription periods, which began with the dispensing date and lasted for the number of days supplied, and extended the treatment episode for 7 days after the end of the last dispensing. The analysis followed up patients from the index date until the occurrence of the outcome or until the end of the first treatment episode, health plan enrollment, or data availability.

We estimated the incidence and incidence rate of the outcome, the crude incidence rate ratio (IRR) comparing varenicline with bupropion, and the Mantel-Haenszel IRR stratified on age group, sex, and data partner (analysis 1). As a secondary analysis, we compared all initiators of varenicline therapy with initiators of therapy with a bupropion product specifically approved for smoking cessation, that is, Zyban and its generic equivalents (analysis 2). In addition, we analyzed all initiators of varenicline and bupropion therapy and did not restrict the analysis to patients with a tobacco use disorder code or those who used a bupropion product approved for smoking cessation (analysis 3). Analysis 3 included the largest number of users but was expected to be more confounded because patients using bupropion for indications other than smoking cessation (eg, depression) would be included and may not be smokers.

Data partners ran a centrally developed and tested analytic program and returned output that consisted entirely of aggregate counts and no protected health information. Mini-Sentinel is a public health surveillance activity that is not under the purview of institutional review boards.

Results. Analysis 1—the primary analysis—identified 89 519 eligible individuals initiating varenicline therapy and 113 378 eligible individuals initiating bupropion therapy who had a tobacco use disorder code (Table); the adjusted IRR was 1.02 (95% CI, 0.71-1.47). The results did not vary substantially by age group or sex (not shown). In analysis 2, the adjusted IRR was 0.98 (0.43-2.23) when we compared all initiators of varenicline therapy (n=260 660) with initiators of therapy with bupropion products approved for smoking cessation (n=11 203). The adjusted IRR was 1.52 (1.21-1.91) in analysis 3 when we compared all initiators of varenicline therapy (n=260 660) with all initiators of bupropion therapy (n=745 004).

Initial results were provided to the FDA 2 days after the analytic specifications were finalized, and the final results were provided within 3 weeks. A report with data aggregated across sites is available on the Mini-Sentinel website.

Comment. Recent systematic reviews of randomized controlled trials provided conflicting results on the risk of adverse cardiovascular events associated with varenicline. This rapid assessment found no consistent evidence of increased cardiovascular risk during the first treatment episode of varenicline among individuals with no recent diagnosis of cardiovascular events when compared with bupropion use. The
analysis included patients treated with these drugs in actual clinical practice, thereby providing evidence complementary to findings from randomized trials and other sources.

This rapid analysis was not intended to be a comprehensive evaluation of causality. The results should be interpreted in the context of the goal to provide safety information quickly, the limitations of electronic health data, and the limited analytic approaches available at this early stage of implementation of the rapid assessment program (see the eAppendix [http://www.jamainternalmed.com] for discussion of the caveats of the analysis). However, the analysis demonstrates Mini-Sentinel's rapid response capability and illustrates how a large network of electronic health care databases can be used as part of a learning health care system to provide timely safety information about approved medical products.


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Table. Results from the Rapid Assessment of Cardiovascular Risk and Use of Smoking Cessation Drugs in the Mini-Sentinel Program

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of New Users</th>
<th>Follow-up Person-years</th>
<th>No. of Outcome Events</th>
<th>Incidence (95% CI) per 1000 Person-years</th>
<th>Incidence Rate (95% CI) per 1000 Person-years</th>
<th>Crude IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>89,519</td>
<td>11,197</td>
<td>56</td>
<td>0.63 (0.47-0.81)</td>
<td>5.00 (3.78-6.50)</td>
<td>0.97 (0.69-1.35)</td>
<td>1.02 (0.71-1.47)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>113,378</td>
<td>22,942</td>
<td>118</td>
<td>1.04 (0.86-1.24)</td>
<td>5.14 (4.26-6.16)</td>
<td>1 [Reference]</td>
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<tr>
<td>Analysis 1: Initiators of Therapy Who Had a Diagnosis of Tobacco Use Disorder‡</td>
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<tr>
<td>Varenicline</td>
<td>28,660</td>
<td>32,070</td>
<td>109</td>
<td>0.42 (0.34-0.51)</td>
<td>3.40 (2.79-4.10)</td>
<td>0.83 (0.57-1.23)</td>
<td>0.98 (0.43-2.23)</td>
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<tr>
<td>Bupropion</td>
<td>11,203</td>
<td>1,462</td>
<td>6</td>
<td>0.54 (0.20-1.17)</td>
<td>4.10 (1.51-9.93)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<tr>
<td>Analysis 2: Initiators of Therapy With Products Approved Specifically for Smoking Cessation§</td>
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<tr>
<td>Varenicline</td>
<td>260,660</td>
<td>32,070</td>
<td>109</td>
<td>0.42 (0.34-0.51)</td>
<td>3.40 (2.79-4.10)</td>
<td>1.58 (1.27-1.95)</td>
<td>1.52 (1.21-1.91)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>745,004</td>
<td>209,478</td>
<td>452</td>
<td>0.61 (0.55-0.66)</td>
<td>2.16 (1.96-2.37)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<tr>
<td>Analysis 3: All Individuals Initiating Therapy</td>
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Abbreviation: IRR, incidence rate ratio.

‡One cohort received varenicline tartrate and the other, bupropion hydrochloride.
§Identified by an inpatient or emergency department visit diagnosis code for acute myocardial infarction (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 410.xx), intermediate coronary syndrome or unstable angina (411.1), or acute coronary occlusion without myocardial infarction (411.81).
| Stratified on age group (20-44, 45-54, and $\geq$65 years), sex, and data partner using the Mantel-Haenszel method.
| Identifying by ICD-9-CM code 305.1.
| Restricted to all individuals initiating therapy with varenicline and those initiating therapy with bupropion products approved for smoking cessation (ie, Zyban and its generic equivalents).
Conflict of Interest Disclosures: None reported.

Funding/Support: The Mini-Sentinel program is funded by the FDA through the Department of Health and Human Services contract HHSF223200910006.

Role of the Sponsor: The FDA initiated the smoking cessation drug rapid assessment and participated in the choice of exposure, outcome, and cohort definitions; the interpretation of the data; and the preparation and review of the manuscript. The FDA was not involved in the collection and management of the data. Other aspects of the analysis highlighted in this article were proposed and performed by the Mini-Sentinel Investigators in collaboration with the FDA.


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Effect of the ACGME 16-Hour Rule on Efficiency and Quality of Care: Duty Hours 2.0

In July 2011, the Accreditation Council for Graduate Medical Education (ACGME) reduced the consecutive number of hours that postgraduate year-1 residents can work in a single shift, from 30 to 16.1 This rule was intended to improve patient safety by reducing residents’ fatigue. Many worry that the new duty hour policy increases patient care handovers, which may cause patient harm. The net effect of the 16-hour duty limits on patient outcomes is uncertain.

Methods. In April 2011, the Vanderbilt Internal Medicine Residency Program redesigned its rotations to reduce the maximum continuous on-duty period to 16 hours (eAppendix; http://www.jamainternalmed.com). We retrospectively examined the efficiency and quality of care for non—intensive care unit (ICU) medical inpatients under the 30-hour (July-December 2010) and 16-hour (July-December 2011) duty limits at Vanderbilt Uni-