New Reports Examine Psychiatric Risks of Varenicline for Smoking Cessation

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A new analysis by the US Food and Drug Administration (FDA) downplays the psychiatric risks of the smoking cessation drug varenicline, but an independent analysis of the agency’s adverse event reports suggests the drug dramatically increases the risk of suicide and suicide-related behavior compared with other cessation medications.

Reports of an array of serious adverse events, including suicide, other violence, cardiac problems, and crashes, have dogged varenicline for several years. Such reports led the FDA in 2009 to require that the drug’s label carry a black box warning of the risk of severe neuropsychiatric adverse events in patients taking the drug and earlier this year to update the drug’s label to warn of increased risk of cardiac adverse events in patients with cardiovascular disease. Now the new analysis from the FDA concludes that varenicline does not increase the risk of hospitalization for psychiatric problems. Meanwhile, though, the independent analysis found an alarmingly high rate of suicide-related adverse events—predominantly events that would not involve hospitalization.

REPORTS DELAYED

Since the FDA’s approval of varenicline in 2006, a growing number of adverse event reports involving patients who experienced suicidal thoughts or behaviors or serious aggression while taking the drug have led to close scrutiny of the drug’s safety profile by the agency and other organizations.

In 2009, the FDA required Pfizer, the manufacturer of the drug, to add a black box warning alerting physicians to the risk of suicidal thoughts or aggressive behavior in patients taking the drug and to prepare a medication guide for patients. The label changes also noted that patients with mental health problems were excluded from premarketing studies of the drug, so the safety of the drug in this population has not been established. This exclusion occurred despite the high rate of smoking among individuals with mental health disorders; such individuals consume nearly half of all cigarettes in the United States and are twice as likely to smoke as individuals without such disorders, according to the National Alliance on Mental Illness.

At the time, according to the Institute for Safe Medication Practices (ISMP) (http://www.ismp.org/newsletters/acuteCare/articles/20110519.asp), the agency was missing more than 1000 adverse event reports involving varenicline, including 150 completed suicides, dating as far back as 2007, because Pfizer had classified them as less serious events and submitted them in a paper format that delayed their entry into the Adverse Events Reporting System (AERS). Manufacturers are required to report serious adverse events to the FDA electronically within 15 days. In a spring 2011 quarterly report on the drug (http://www.fda.gov/Drugs/DrugSafety/ucm255918.htm), the FDA insisted that these reports would not have changed the agency’s 2009 action; however, it noted that the agency required Pfizer to resubmit the reports.

But the ISMP has called for a reevaluation of the drug’s safety in light of the new information and has also urged the FDA to investigate why these reports were not made sooner and whether manufacturers are correctly identifying and submitting serious adverse events within the 15-day time frame. “We believe varenicline is unsafe for widespread clinical use and encourage FDA to reassess this drug’s safety profile based on this new information and take the necessary steps to mitigate harm,” said ISMP earlier this year in its QuarterWatch report on AERS data submitted in the third quarter of 2010.

### Suicidal and Self-injurious Behavior

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>Varenicline (n=1819) No. (%)</th>
<th>Bupropion (n=155) No. (%)</th>
<th>Nicotine (n=50) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed suicide</td>
<td>272 (15.0)</td>
<td>19 (12.3)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1135 (62.4)</td>
<td>73 (47.1)</td>
<td>40 (80.0)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>323 (17.8)</td>
<td>56 (36.1)</td>
<td>2 (4.0)</td>
</tr>
</tbody>
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*Preferred terms from the Medical Dictionary for Regulatory Activities (http://www.meddramso.com).

In June 2011, the FDA issued another safety warning about the drug, notifying patients and physicians that it may increase the risk of cardiovascular adverse events in patients with cardiovascular disease. The warning was based on an FDA review of a randomized controlled trial of 700 smokers that found that, compared with placebo, varenicline raised the risk of nonfatal heart attack, need for coronary revascularization, and new diagnosis of peripheral artery disease or admission for treatment of peripheral artery disease (http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm).

An update from the agency in October 2011, however, downplayed the neuropsychiatric risks of the drug (http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm). The update was based on the results of 2 retrospective cohort studies conducted by the Department of Veterans Affairs (VA) and the Department of Defense (DOD). The VA study, which included 14,131 varenicline users and as many users of nicotine replacement therapy, found no significant difference in hospitalization rates for neuropsychiatric conditions between the 2 groups (16 hospitalizations in the varenicline group vs 21 in the nicotine replacement group). The DOD analysis, which involved 11,978 varenicline users and the same number of nicotine replacement users, found 18 psychiatric hospitalizations among varenicline users vs 16 in the nicotine replacement group, again not a significant difference.

The FDA noted the studies “do not rule out an increased risk of other neuropsychiatric events” with varenicline.

But Curt D. Furberg, MD, PhD, a professor of public health sciences at Wake Forest University, said that by examining only neuropsychiatric hospitalizations, these 2 studies would have missed the majority of serious neuropsychiatric events reported in varenicline users. Furberg, who has analyzed the FDA adverse events data in his role as senior medical advisor for ISMP’s QuarterWatch report and as a researcher, explained that 82% of the reports of serious adverse events involving varenicline do not involve hospitalization. For example, he said that individuals who successfully commit suicide would not be counted in such a study, nor would those who experience suicidal ideation or who attempt a suicide but are treated in the emergency department and then released.

### SUICIDE RISKS ELEVATED

In a recent analysis of adverse event reports to the FDA that focused on suicidal behavior and depression among patients using varenicline or other smoking cessation aids, Furberg and colleagues from the ISMP, Harvard Medical School, and Johns Hopkins University School of Medicine found that varenicline use is associated with a substantially elevated risk of suicidal behaviors (Moore TJ et al. *PLoS ONE*. 2011;6(11):e27016). The analysis found elevated rates of suicidal or self-injurious behavior or depression among patients using any cessation aid compared with a comparison group of patients taking antibiotics. Additionally, it found that patients taking varenicline were more than 8 times as likely as those using nicotine replacement products to experience such adverse events. Patients using buproprion to quit smoking had data in the middle, with about 3 times the risk of such an adverse event compared with nicotine replacement users.

The findings may help clarify whether quitting smoking itself may trigger depression or suicidal behaviors. Furberg noted that the study confirms that such risks are elevated among smokers trying to quit, but also shows that the risks associated with varenicline are much higher than those associated with other cessation drugs, suggesting the drug itself also plays a role.

Varenicline was associated with 90% (2925) of the cases of suicidal or self-injurious behavior or depression identified by Furberg and colleagues among smokers trying to quit. By comparison, buproprion was associated with 7% (229) of the cases, and nicotine replacement was associated with 3% (95). Particularly concerning were the high numbers of completed suicides and reports of suicidal ideation among varenicline users compared with other groups. The analysis found 272 completed suicides among varenicline users, compared with 19 among those taking buproprion, 4 taking nicotine replacement, and 3 taking antibiotics. Suicidal ideation followed a similar pattern, with 1135 such reports among varenicline users, compared with 73 in buproprion users, 40 in nicotine replacement users, and 7 in antibiotic users.

Furberg said the actual number of neuropsychiatric adverse events is likely much higher than the number reported to the FDA. He said that typically, only 10% of adverse events are reported to the agency.

Furthermore, Furberg noted that varenicline has consistently had high rates of serious adverse event reports, including such alarming events as loss of consciousness, seizures, and loss of vision. Such reports led the Federal Aviation Administration and the DOD to limit or ban its use in certain personnel.

“This is one of the most harmful drugs on the US market,” Furberg said. Varenicline’s adverse event profile is particularly concerning given the limited efficacy of the drug over the long-term, he added.

“The adverse effects tend to outweigh the benefits, particularly in patients with mental health problems,” he said.

He noted that in light of this risk-benefit profile, the VA has developed a policy that the drug should be used only after other cessation therapies have failed, and that when it is used, the patient’s mental status should be closely monitored.

“That is the least you can do,” he said. “Ideally, it should come off the market.”