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Studies Linking Smoking-Cessation Drug With Suicide Risk Spark Concerns

Bridget M. Kuehn

EMERGING EVIDENCE SUGGESTS THE smoking-cessation drug varenicline is among a growing list of medications that might cause serious psychiatric adverse events.

A new analysis by the US Food and Drug Administration (FDA) adds to evidence that varenicline might be associated with an increased risk of suicidal thoughts and behavior, including among patients with no psychiatric history. The results, which were published in January, follow warnings from the agency that such a link is likely, as well as label changes noting a possible risk.

The latest findings emphasize the importance of physicians monitoring patients taking varenicline for such adverse events. They also raise questions about how well new drugs are being screened for unwanted psychiatric effects. Continued reports of crashes and other serious adverse events among patients taking this drug also have raised concerns about other possible risks.

RISKS PROBED

An analysis of adverse event reports submitted to the FDA between May 2006 (when varenicline was approved) and November 2007 found 116 cases of suicidal ideation and 37 cases of suicidal behavior, more than half resulting in death (http://www.fda.gov/cder/dsn/2009_v2_no1/DSN_Vol2Num1.pdf).

Half of the patients reporting either suicide ideation or suicidal behavior had a history of psychiatric problems, 26% had no such history, and 24% had an unknown psychiatric history.

In one case described in the analysis, a 45-year-old nurse taking varenicline reported that after taking the drug for 10 weeks, she noticed suicidal thoughts, aggression, erratic behavior, uncontrolled emotions, and less clarity in her thinking. Within a week of stopping the drug, she reported most of the symptoms subsided, although she experienced some residual effects.

The agency staff also reviewed adverse event reports for other smoking-cessation products. Bupropion, an antidepressant also used as a cessation aid, already carries a black box warning noting an increased risk of suicide among patients taking antidepressants. Be-

tween bupropion's approval as a cessation drug in 1997 and November 2007, the agency received 46 reports of suicide ideation in patients taking the drug and 29 reports of suicidal behavior, roughly one-third resulting in death—about half the number of reports of suicidality among patients taking varenicline, which has been on the market only 17 months vs bupropion's decade of availability for cessation. The agency found no link between transdermal nicotine products and suicidality.

Suicidality resolved in about one-third of patients taking either varenicline or bupropion after they stopped taking the drug.

Outcomes noted in the FDA's Adverse Event Reporting System of suicidal ideation (SI) and suicidal behavior (SB) with varenicline and bupropion						
Outcomes ^a	No.					
	Varenicline			Bupropion		
	SI	SB	Total	SI	SB	Total
Serious	110	37	147	30	29	59
Death	0	19	19	0	10	10
Hospitalization	12	7	19	9	12	21
Life-threatening	26	5	31	10	6	16
Disability	6	3	9	3	2	5
Required intervention	6	0	6	1	1	2
Other	92	20	112	11	7	18
Nonserious	6	0	6	16	0	16

^aThe outcomes listed are not mutually exclusive.
Source: US Food and Drug Administration (FDA). Drug Safety Newsletter. http://www.fda.gov/cder/dsn/2009_v2_no1/DSN_Vol2Num1.pdf

A Food and Drug Administration analysis of adverse event reports suggests that cessation drugs varenicline and bupropion are associated with an increased risk of suicidality.



Although such analyses cannot confirm a cause-and-effect relationship or suggest a mechanism, there is a biologically plausible mechanism by which both drugs might contribute to mood disturbances. Thomas J. Moore, senior scientist at the Institute for Safe Medication Practices, noted in an interview that both bupropion and varenicline have effects on the dopamine system, which modulates behavior, mood, and cognition.

The label for varenicline has been updated to include a warning about serious psychiatric events and to advise patients who experience such events to stop taking the product immediately and contact a clinician.

"Going forward, more specific attention will be given to assessing for psychiatric side effects in clinical trials for smoking cessation products," according to an e-mailed statement from the FDA.

OTHER RISKS?

Varenicline has continued to generate a large number of adverse event reports throughout the first half of 2008, the majority involving psychiatric problems, according to analyses by the Institute for Safe Medication Practices. The institute is a watchdog organization that has been actively monitoring FDA adverse event reports for signals of drug safety problems.

The institute identified 988 reports of serious injuries linked to varenicline in the fourth quarter of 2007, more reports to the FDA's adverse report system than for any other drug. In the first quarter of 2008, varenicline accounted for more reports of serious injury than the top 10 best-selling drugs combined (1001 compared with 837). In the second quarter of 2008, varenicline was the second most-reported drug (after digoxin), with 910 new reports of serious injury. Most of the reports for varenicline have involved psychiatric problems, but motor vehicle crashes, skin reactions, cardiac problems, and diabetes-related symptoms also were frequently reported.

Postmarketing reports of serious psychiatric adverse events in patients taking

varenicline and several other drugs raise questions about how well such products are being screened before they reach the market, Moore said. "What I think this tells us is that our premarketing testing is not doing a good job of detecting psychiatric adverse events," he added. He explained that premarketing clinical trials may be too small to detect such problems or they may not be actively screening participants for the development of psychiatric symptoms. For example, if a patient is asked about any change in his or her medical condition, he or she may not report things like unusual dreams, agitation, or sleeplessness, he said.

Closer examination of adverse events other than psychiatric problems that have been reported in patients taking varenicline also may be warranted.

Moore said he and his colleagues do not have access to enough data on the reported cardiac adverse events to probe them further, and they hope that the FDA and the manufacturers are examining those events.

Additionally, reports of crashes among individuals taking varenicline have spurred the Federal Aviation Administration, the Department of Defense, and the Department of Transportation to ban use of the drugs by individuals such as pilots and truck drivers. The patient information section of the varenicline label urges individuals to use caution when driving or operating machinery while taking the drug, although Moore said he would like to see a stronger warning. □

Promising Marker Found for Deadly Prostate Cancer

Bridget M. Kuehn

A MULTI-INSTITUTIONAL TEAM OF SCIENTISTS has identified a biological marker of prostate cancer progression that may be useful for urine-based screening. The discovery also suggests potential new targets for treatment.

Using a combination of liquid and gas chromatography along with mass spectrometry, the scientists examined levels of various metabolites in 262 samples. These included 42 tissue samples and 110 matched specimens of plasma and urine from 59 patients who had a biopsy positive for prostate cancer, as well as 51 controls (Sreekumar A et al. *Nature*. 2009; 457[7231]:910-914). Based on these results and findings from previous studies suggesting that amino acid metabolism and methylation are enhanced during cancer progression, the researchers identified sarcosine as a promising metabolite. Further interrogations revealed that levels of sarcosine, a product of the methylation of the amino acid glycine, increase as prostate cancer progresses.

According to the authors, sarcosine, which can be detected noninvasively in

urine, may be most useful as a biomarker to identify which patients with a modestly increased level of prostate-specific antigen are likely to have a positive biopsy result. It might also be helpful in ascertaining how far such cancer has progressed.

Other testing by the scientists suggested that sarcosine and other components of its pathway may play a role in the progression of prostate cancer. For example, they found that sarcosine levels in prostate cancer cell lines are elevated compared with benign cells from tissues surrounding the prostate gland. In addition, adding sarcosine to benign prostate epithelial cells caused the cells to take on an invasive phenotype, while reducing sarcosine levels in cancer cells by manipulating genes and other chemicals that regulate sarcosine levels attenuated invasive behavior.

Such findings, the researchers said, suggest that therapies that reduce sarcosine levels may be useful in the treatment of prostate cancer.

These results are preliminary and will need to be validated in other studies prior to being applicable clinically. □