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DEPARTMENT OF VETERANS AFFAIRS - VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND
CENTER FOR MEDICATION SAFETY PSCI (VA MEDSAFE),
AND PUBLIC HEALTH STRATEGIC HEALTHCARE GROUP

ADDENDUM: RECENT SAFETY ISSUES REGARDING VARENICLINE (CHANTIX™)

I. ISSUE

Varenicline is a partial agonist at the $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor approved by the Food and Drug Administration (FDA) in May 2006 as an aid to smoking cessation treatment. The $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor releases dopamine in the central nervous system, and activation is thought to mediate dependence, including reinforcement, tolerance, and sensitization of the receptor. As a partial agonist, varenicline binds to the receptor and produces low to moderate levels of dopamine release that reduces craving and withdrawal symptoms. At the same time, varenicline acts as an antagonist, blocking the binding and positive reinforcement effects of smoked nicotine.

Reports of neuropsychiatric events (i.e., changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and/or completed suicide) among treated smokers led to several safety warnings regarding the use of varenicline.^{1, 2, 3} On May 22, 2008, the Federal Aviation Administration (FAA) banned the use of varenicline in airline pilots and air traffic controllers due to reports to the FDA of loss of consciousness, seizures, muscle spasms, vision disturbances, hallucinations, paranoia and psychosis.

II. BACKGROUND

In November 2007, the FDA released an early communication about an ongoing safety review of varenicline regarding reports of suicidal thoughts and aggressive and erratic behavior in patients who have taken the medication. FDA also reviewed postmarketing cases submitted by Pfizer, Inc., varenicline's manufacturer, describing suicidal ideation and suicidal behavior. FDA's preliminary assessment indicated that many cases presented with new-onset depressed mood, suicidal ideation, and behavior and emotional changes within days to weeks of starting varenicline. Not all cases had a pre-existing psychiatric illness or had stopped smoking. The causality of varenicline to these behavioral changes is uncertain.¹

In February 2008, the FDA issued a Public Health Advisory on varenicline to alert health professionals and patients about new warnings related to changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. Following a review of post-marketing adverse events, FDA requested that Pfizer elevate the prominence of this safety information to the warnings and precautions section of the prescribing information of the labeling.²

Since March 2007, the VA Center for Medication Safety (VAMedSAFE) has monitored varenicline via national pharmacovigilance efforts such as collecting and analyzing spontaneous reports of adverse events. Between September 2006 and April 30, 2008, there were a total of 147,718 prescriptions for varenicline (69,765 unique patients) within VA. As of May 26, 2008, VA practitioners submitted 417 reports on possible adverse drug

events (ADEs) associated with varenicline. The reports include (number of events in parentheses): vomiting (95), nightmares/abnormal dreams (82), depression (68), as well as agitation (33), suicidal ideation (31) homicidal ideation (2), hallucinations (25), anxiety (12), and suicide (1). Other reported ADEs include angioedema (2), rash (8), eosinophilia (1), visual disturbance (1), and hyperglycemia (1).

III. VA MEDSAFE RECOMMENDATIONS remain the same and appear below:

- Varenicline is not first-line pharmacotherapy for smoking cessation. It should be reserved for veterans who have not been successful with smoking cessation despite repeated attempts using nicotine replacement therapy and/or bupropion. These attempts should involve an adequate trial of nicotine replacement therapy (NRT) alone and/or bupropion alone, and if monotherapy is unsuccessful, NRT and bupropion together (unless bupropion is contraindicated). Another alternative is using combination NRT (e.g., patch and gum) as the Public Health Service Clinical Practice Guidelines Update notes that combination NRT has a higher odds ratio compared to varenicline.⁴
- Varenicline should not be used in combination with other smoking cessation products.
- Health care providers should be aware that patients taking varenicline may experience changes in behavior and/or mood and should educate and warn patients and/or caregivers accordingly. Patients using varenicline should be instructed to report any changes of behavior or mood to their provider(s) immediately. They should seek care emergently if they experience suicidal or homicidal ideation or other potentially serious or health-threatening events (e.g., psychosis/paranoia, loss of consciousness)
- Patients should also be warned of other potential adverse effects such as drowsiness, sudden loss of consciousness, seizures, muscle spasms, visual disturbances, hallucinations, paranoia and psychosis while taking varenicline. Patients should use caution when driving or operating machinery when starting varenicline and/or until they are sure that varenicline will not affect these activities adversely.
- Providers should document/report all possible adverse events related to varenicline as per the usual protocols used at their VA.
- For further guidance on varenicline, please refer to the PBM-MAP Criteria for Use for Varenicline that will soon be posted on the PBM website (<http://www.pbm.va.gov/default.aspx>).

IV. REFERENCES

1. U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Early communication about an ongoing safety review: Varenicline (marketed as Chantix). November 20, 2007, updated February 1, 2008. Available at: http://www.fda.gov/cder/drug/early_comm/varenicline.htm. Accessed May 2008.
2. U.S. Food and Drug Administration. FDA News: FDA issues Public Health Advisory on Chantix - Agency requests that manufacturer add new safety warnings for smoking cessation drug. February 1, 2008. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01788.html>. Accessed May 2008.
3. U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Public Health Advisory: Important information on Chantix (varenicline). May 16, 2008. Available at: <http://www.fda.gov/cder/drug/advisory/varenicline.htm>. Accessed May 2008.
4. Public Health Service Clinical Practice Guideline. Treating tobacco use and dependence: 2008 update. Washington, D.C.: U.S. Department of Health and Human Services May 2008. Available at: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf. Accessed May 2008.