U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking

Safety Announcement

[3-9-2015] The U.S. Food and Drug Administration (FDA) is warning that the prescription smoking cessation medicine Chantix (varenicline) can change the way people react to alcohol. In addition, rare accounts of seizures in patients treated with Chantix have been reported. We have approved changes to the Chantix label to warn about these risks. Until patients know how Chantix affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients who have a seizure while taking Chantix should stop the medicine and seek medical attention immediately.

Millions of Americans have serious health problems caused by smoking, which can be reduced by quitting. Chantix is a prescription medicine that is FDA-approved to help adults quit smoking. In clinical trials, Chantix increased the likelihood of quitting smoking and "staying quit" for as long as 1 year compared to treatment with a placebo, an inactive treatment.

We reviewed the case series submitted by Pfizer, the manufacturer of Chantix, as well as the cases in the FDA Adverse Event Reporting System (FAERS) database describing patients who drank alcohol during treatment with Chantix and experienced adverse reactions. Some patients experienced decreased tolerance to alcohol, including increased drunkenness, unusual or aggressive behavior, or they had no memory of things that happened (see Data Summary).

We also reviewed FAERS and the medical literature[1] for cases of seizures with Chantix and identified cases in which the patients who had seizures while taking Chantix either had no history of seizures or had a seizure disorder that had been well-controlled. In most of these cases, the seizures occurred within the first month of starting Chantix. Information about these risks has been added to the *Warnings and Precautions* section of the drug label and to the patient Medication Guide.

We also updated the *Warnings and Precautions* section of the label to include information about several studies that investigated the risk of neuropsychiatric side effects on mood, behavior, or thinking occurring with Chantix. These included observational studies,[2-5] as well as analyses that Pfizer conducted of randomized controlled clinical trial data.[6] These studies did not show an increased risk of

neuropsychiatric side effects with Chantix; however, they did not examine all types of neuropsychiatric side effects, and they had limitations that prevented us from drawing reliable conclusions.

We previously communicated about possible serious neuropsychiatric side effects with Chantix in 2009 and 2011, and these recent studies were discussed at an FDA Advisory Committee meeting in October 2014. Pfizer is conducting a large clinical safety trial of Chantix to investigate this risk and results from this study are expected in late 2015. We will update the public as appropriate when this new information becomes available.

We urge health care professionals and patients to report side effects involving Chantix to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Chantix (varenicline)

- Chantix is a prescription medicine that is used to help adults quit smoking.
- Clinical trials show that Chantix increases the likelihood of abstinence from smoking for as long as 1 year compared to treatment with placebo, an inactive treatment.
- In 2013, approximately 1.2 million patients received a dispensed prescription for Chantix from U.S. outpatient retail pharmacies.[7]

Additional Information for Patients

- Chantix (varenicline) may change the way people react to alcohol.
- Decrease the amount of alcoholic beverages you drink during treatment with Chantix until you know how it affects your ability to tolerate alcohol.
- Seizures have been reported in patients treated with Chantix.
- Before you take Chantix, tell your health care professional if you drink alcohol, have a history of seizures, or have ever had depression or other mental health problems.
- If you have a seizure during treatment with Chantix, stop taking the medicine and seek medical attention immediately.
- If you develop nervousness or agitation, hostility, aggressive behavior, depression, thoughts of suicide, or have other changes in your behavior or thinking that are not typical for you, stop taking Chantix and contact your health care professional right away.
- Read the patient Medication Guide you get along with your Chantix prescription. It explains the risks associated with the use of Chantix.
- Talk to your health care professional if you have questions or concerns about Chantix or would like information about quitting smoking.
- More information about quitting smoking can be found on the National Cancer Institute's website.
- Report side effects from Chantix to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Interactions between alcohol and Chantix (varenicline) have resulted in some patients experiencing increased intoxicating effects of alcohol, sometimes associated with aggressive behavior and/or amnesia.
- Advise patients to reduce the amount of alcohol they consume while taking Chantix until they know whether the drug affects their tolerance for alcohol.
- Seizures have been reported in patients treated with Chantix.
- Weigh the potential risk of seizures against the potential benefits before prescribing Chantix in patients with a history of seizures or other factors that can lower the seizure threshold.
- Advise patients to discontinue Chantix and seek medical attention immediately if they experience a seizure while on treatment.
- Advise patients to immediately stop taking Chantix if they develop agitation, hostility, aggressive behavior, depressed mood, or changes in behavior or thinking that are not typical for them, or if they develop suicidal ideation or behavior.
- Encourage patients to read the patient Medication Guide they receive with their Chantix prescription.
- Report adverse events involving Chantix to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

Alcohol interaction

FDA searched the FDA Adverse Event Reporting System (FAERS) database and identified, since the approval of Chantix (varenicline) in 2006, 48 cases of adverse events involving decreased tolerance to alcohol (n=11) or aggressive behavior (n=37) in patients taking Chantix and who also consumed alcohol. None of the cases of decreased alcohol tolerance reported that the amount of alcohol consumed was excessive for the individuals involved; before initiating Chantix, the same amount of alcohol had been consumed without the patients experiencing these adverse effects. The outcomes included one case of decreased alcohol tolerance resulting in a motor vehicle accident with police arrest; in another case, the patient experienced a significant facial injury. For the 37 cases involving aggressive behavior, the amount of alcohol consumed while taking Chantix was insufficient to explain the event. In more than half of these cases, the patients described their behavior as a significant change from their behavior prior to Chantix treatment. Twenty-two cases reported harm to a person or property.

Amnesia was also reported following alcohol ingestion in patients taking Chantix. In most of the FAERS cases of decreased alcohol tolerance, as well as several submitted by Pfizer that were not identified in the FAERS search, patients described poor memory of their experience. In addition, in 16 of the 37 aggression cases (43%), patients reported no memory or impaired memory of their experience, and most of these 16 cases reported physical harm to a person and/or property.

Seizures

We searched FAERS and the medical literature[1] and identified 64 cases of seizures in patients using Chantix. The median time to onset of seizure following starting Chantix was 2-3 weeks (time to seizure onset information provided in 60 percent of cases). In 37 cases, the patients had no history of seizure. Ten of these 37 cases had no contributing factors to the seizures other than Chantix. In the remaining 27 cases, other factors may have contributed to the seizures, including concomitant medications that can lower the seizure threshold, such as psychiatric medications. Of the 64 cases, 27 patients had a history of controlled seizures.

Neuropsychiatric adverse events

Pfizer-conducted analyses of randomized controlled trial data

A meta-analysis of five randomized, double-blind, placebo-controlled trials that included a total of 1,907 patients (1,130 Chantix, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (n=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (n=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with Chantix compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval (CI): 0.46-1.36). Fifty-five patients reported suicidal ideation or behavior, 48 of which (24 Chantix, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (four Chantix, three placebo).

A pooled analysis of 18 randomized, double-blind, placebo-controlled clinical trials that included the five trials described above was conducted to assess the psychiatric safety of Chantix. This pooled analysis included 8,521 patients (5,072 Chantix, 3,449 placebo), some of whom had psychiatric conditions at baseline. The results showed a similar incidence of common psychiatric events in patients treated with Chantix compared to patients treated with placebo.

Observational studies

Four observational studies, each including 10,000 to 30,000 Chantix users in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and nonfatal self-harm) between users of Chantix and users of prescription nicotine replacement therapy (NRT) or bupropion.[2-5] All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between Chantix users and nicotine patch users (Hazard Ratio (HR)=1.14; 95% CI: 0.56-2.34 in the first study, and HR=0.76; 95% CI: 0.40-1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between Chantix

users and bupropion users (HR=0.85; 95% CI: 0.55-1.30). Bupropion has also been associated with neuropsychiatric adverse events; therefore, this finding cannot be used to rule out an increased risk with Chantix compared with other smoking cessation treatments, including nicotine and nonpharmacologic approaches.

A fourth study examined the risk of fatal and nonfatal self-harm in users of Chantix compared to users of NRT. Although the occurrence of detected suicide was rare during the 3 months after patients initiated any drug treatment (2 cases in 31,260 Chantix users and 6 cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following public awareness of reports of neuropsychiatric adverse events in Chantix users. Physicians may have started prescribing Chantix to patients without risk factors for neuropsychiatric illness, which would then have made it appear that Chantix was not associated with neuropsychiatric adverse events. Chantix users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed Chantix. This kind of bias, along with other possible residual confounding, may have distorted the comparison. Another important limitation of the observational studies is that they did not cover the full range of the neuropsychiatric adverse events that have been seen in postmarketing spontaneous adverse events reports associated with Chantix.

Although the findings of the observational studies appear reassuring, they do not completely evaluate the effect of Chantix on neuropsychiatric adverse events and cannot be interpreted to mean that there is no risk of neuropsychiatric events with Chantix. The limitations in these studies may underestimate the actual incidence of neuropsychiatric adverse events and restrict our ability to predict the direction of the relative risk associated with Chantix. The required postmarketing clinical trial that Pfizer is conducting was designed to include a more complete neuropsychiatric risk ascertainment, and therefore may provide a better understanding of these risks. The results of the trial are expected in late 2015.

All the neuropsychiatric studies were discussed at the October 16, 2014, Joint Meeting of FDA's Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee (for complete safety reviews, background information, and minutes of this meeting, click here).

References

1. Serafini A, Crespel A, Velizara R, Gelisse P. Varenicline-induced grand mal seizure. Epileptic Disord 2010;12:338.

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