

MEDICATION

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

SAFETY IN SECONDS

Helping to achieve safe medication use

VARENICLINE (CHANTIX®): POTENTIAL ALCOHOL INTERACTION, RARE RISK OF SEIZURES, AND OTHER NEUROPSYCHIATRIC EVENTS

The Food and Drug Administration (FDA) warns that use of varenicline (Chantix®) may be associated with decreased alcohol tolerance and rare accounts of seizures and updates product label accordingly. Data from the manufacturer, cases submitted to the FDA Adverse Event Reporting System (FAERS), and reports in the medical literature show:

- 48 cases of alcohol-related adverse events since the drug's approval in 2006.
 - 11/48 involved decreased tolerance to alcohol without an increase in the amount of alcohol consumed or consumption of excessive amounts of alcohol compared to before varenicline (Chantix®) initiation.
 - 1/11 resulted in a motor vehicle accident with police arrest.
 - 1/11 experienced a significant facial injury.
 - 37/48 involved aggressive behavior in patients who consumed alcohol while taking varenicline (Chantix®).
 - The amount of alcohol consumed could not justify the extent of the events.
 - More than half of the patients described a significant change

in behavior from prior to starting varenicline (Chantix®) treatment.

- 22/37 reported harm to a person or property.
- 16/37 reported no memory or impaired memory of their experience and most of these 16 cases reported physical harm to a person and/or property.
- 64 cases of seizures.
 - Median time to onset after initiation of varenicline (Chantix®) therapy was approximately 2-3 weeks.
 - 37/64 had no history of seizure.
 - 10/37 had no contributing factors other than varenicline.
 - 27/37 had possible risk factors for seizures, such as psychiatric medications that can lower the seizure threshold.

Additionally, the manufacturer continues to further assess neuropsychiatric risks via a required post-marketing clinical trial whose results are expected later this year. Although FDA held an Advisory Committee meeting last October 2014 to discuss four retrospective cohort studies of up to 30,000 varenicline (Chantix®) users, findings did not

(continued on page 3)

IN THIS ISSUE:

- ▶ VARENICLINE (CHANTIX®): POTENTIAL ALCOHOL INTERACTION, RARE RISK OF SEIZURES, AND OTHER NEUROPSYCHIATRIC EVENTS...1,3
- ▶ MEDICATION SAFETY NEWS FROM THE VA NATIONAL PHARMACY BENEFITS MANAGEMENT SERVICES [PBM] AND THE FOOD AND DRUG ADMINISTRATION [FDA].....2
- ▶ UPDATE: TESTOSTERONE PRODUCTS AND SAFETY CONCERNS.....2-3



VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

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from the fda

ENDOCRINOLOGY

[FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients](#)

02/25/15

FDA continues to warn against the sharing among patients of pen devices for insulins and other diabetes drugs, regardless of the use of a fresh needle with each administration because blood may get caught in the pen after injection. This can increase the risk for transmission of bloodborne pathogens (such as the human immunodeficiency virus [HIV] and the hepatitis viruses). Inadequate or inconsistent training regarding risks associated with pen sharing, proper use of these devices, and the difference between multi-dose vials and multi-dose insulin pens may lead to this type of error. As such, FDA now requires new wording in the product labels prohibiting sharing of these injectable devices. Labels that display “For single patient use only” warnings will now appear on the pens and on the pen cartons. Additional warnings against sharing pens will also be added to the prescribing information and to the patient Medication Guides, Patient Package Inserts, and Instructions for Use. To further promote safe use, FDA recommends that health care practitioners should:

- Label pens clearly with each patient’s name or other identifying information in a way that does not obstruct the dosing window or other product information such as the product name, strength, and the warning that states, “For single patient use only.”
- Verify the pen with the name of the patient and other patient identifiers to ensure the correct device is used on the correct patient.
- Review policies and educate staff regarding the safe use of diabetes pens.
- Counsel patients to never share their diabetes pens with another person.

Getting the most from our safety surveillance

UPDATE: TESTOSTERONE PRODUCTS AND CARDIOVASCULAR SAFETY

FDA continues to caution that testosterone replacement therapy is approved for use only in men with primary or secondary hypogonadism resulting from certain medical conditions. The safety and efficacy of testosterone replacement therapy for age-related hypogonadism have not been established. Uses for “low T syndrome”, anti-aging purposes, or for physical enhancement are not FDA-approved indications.

Published literature and meta-analyses to date show conflicting results regarding cardiovascular harm with the use of testosterone therapy. Please see this month’s [National PBM Bulletin](#) for more details. Based on FDA’s review of these findings as well as further discussion at an Advisory Committee meeting last September 2014, FDA determined a possible, although weak, association of cardiovascular risk with testosterone use and came to the consensus that only a prospective, well-controlled clinical trial could more clearly define cardiovascular safety in relation to testosterone replacement therapy.

In the meantime, FDA recommends that providers:

- *Ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing before initiating testosterone replacement therapy.*

- *Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range.*
- *Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.*
- *Weigh the potential increased risk of major adverse cardiovascular outcomes and other risks of testosterone replacement therapy against the potential benefits of treating hypogonadism for each patient.*
- *Inform patients of the potential increased cardiovascular risk associated with testosterone replacement therapy.*

The VA system has seen a decrease in testosterone prescriptions in the last year since the PBM originally announced this issue via a [National PBM Bulletin](#) in February 2014 as well as in the [Issue 3, Volume 4; March 2014](#) edition of this safety newsletter. Utilization data shows that use of testosterone products within the VA system has trended downwards; and a query of the VA Adverse Drug Event Reporting System (VA ADERS) shows adverse events reported with testosterone use within that same time frame have remained consistent until the first quarter of fis-

(continued on page 3)

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(continued from page 1)

show an increased risk of selected serious neuropsychiatric adverse events (neuropsychiatric hospitalizations, fatal and nonfatal self-harm) in patients on varenicline (Chantix®) compared to users of nicotine replacement therapy (NRT) or bupropion. However, limitations of these observational studies prevent any reliable conclusions from being drawn and not all types of neuropsychiatric side effects were evaluated.

REFERENCES:

FDA Drug Safety Communication: 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. <http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm>. (Accessed 03/09/2015).

Getting the most from our safety surveillance

UPDATE: TESTOSTERONE PRODUCTS AND CARDIOVASCULAR SAFETY

(continued from page 2)

cal year 2015 when overall ADE reports/symptoms decreased. Providers should continue to report any adverse reactions with the use of testosterone products by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

REFERENCE

1. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>. (Accessed 03/03/15)
2. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310:1829-36.

3. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;9:e85805.
4. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97:2050-8.
5. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169:725-33.
6. Baillargeon J, Urban RJ, Kuo YF et al. Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother* 2014.
7. Xu L, Freeman G, Cowling BJ, Schooling CM (2013). Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*, 11, 108.
8. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E et al. (2014). Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*, 13, 1327-1351.