

# MEDICATION SAFETY IN SECONDS

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

## Helping to achieve safe medication use

### UPDATE: HIGH-DOSE VITAMIN E

Free radical-mediated reactions and inflammatory responses influence atherogenesis, carcinogenesis, and neuronal damage. Theoretical and empirical findings propose that vitamin E can interrupt harmful oxidative processes by scavenging toxic free-radicals that damage biological membranes and propagate pathology. However, evidence in recent years casts doubt on the benefit of vitamin E in cardiovascular disease and implicates vitamin E as potentially causing serious side-effects as well as increased mortality.

Concerns with the use of high-dose vitamin E ( $\geq 400$  IU daily) have been previously addressed in a [VAMedSAFE Bulletin](#) from December 2004, with recommendations that high-dose vitamin E not be used for the purpose of cardiovascular disease prevention and that VA clinicians consider the evidence

for benefit versus risk when using high-dose vitamin E for other chronic disease indications. These recommendations were based on data suggesting that supplementation with vitamin E has no apparent benefit in preventing or reducing cardiovascular events as well as a meta-analysis suggesting an increased risk in all-cause mortality with the use of high-dose vitamin E.<sup>1</sup> This meta-analysis has been heavily criticized in the form of numerous letters to the editor citing issues including, but not limited to, methodologic concerns, diverse study populations, publication or selection bias, different forms of vitamin E evaluated, combinations of vitamin E with other antioxidants, and lack of assessment of adherence to supplementation regimens. Despite these concerns, the authors of this meta-analysis stand by their conclusions that high-dosage vitamin E supplementation

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### 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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NEWSWORTHY...

## from the pbm

- UPDATE: Testosterone Products and Cardiovascular Safety – 03/26/15 - [National PBM Bulletin](#)
- Amiodarone Use with Ledipasvir/Sofosbuvir (Harvoni) or Sofosbuvir (Sovaldi) Combined with Another Direct-Acting Antiviral and Bradycardia – 03/31/15 - [National PBM Bulletin](#)

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# from the fda

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## HEMATOLOGY

### FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol)

3/30/2015

FDA updated the prescribing instructions and other label information for ferumoxytol (Feraheme), adding a *Boxed Warning* that describes serious and fatal risk of anaphylaxis during and following administration. FDA recommends that health care professionals should:

- Only administer IV iron products to patients who require IV iron therapy.
- Do not administer ferumoxytol (Feraheme) to patients with a history of allergic reaction this agent or other IV iron products.
- Only administer diluted ferumoxytol (Feraheme) as an IV infusion in 50-200 mL of 0.9% sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution. Do not administer ferumoxytol (Feraheme) by undiluted IV injection.
- Closely monitor patients for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during ferumoxytol (Feraheme) administration and for at least 30 minutes following each infusion.
- Carefully consider the potential risks and benefits of ferumoxytol (Feraheme) administration in elderly patients with multiple or serious medical conditions, as these patients may experience more severe reactions.
- Carefully consider the potential risks and benefits of ferumoxytol (Feraheme) administration in patients with a history of multiple drug allergies. Patients with multiple drug allergies may also be at higher risk.
- Advise patients to seek immediate medical attention if these signs and symptoms occur during and following ferumoxytol (Feraheme) administration: respiratory distress, hypotension, dizziness or lightheadedness, edema, rash, or itching.
- Allow at least 30 minutes between administration of ferumoxytol (Feraheme) and administration of other medications that could potentially cause serious hypersensitivity reactions or hypotension or both, such as chemotherapeutic agents or monoclonal antibodies.

For more information, please see the recent [National PBM Bulletin](#) or click on the link above.

## INFECTIOUS DISEASE

### FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug

3/24/2015

FDA warns of serious symptomatic bradycardia when amiodarone is taken with ledipasvir/sofosbuvir (Harvoni) or with sofosbuvir (Sovaldi) plus another direct acting antiviral for hepatitis C (e.g., simeprevir). According to the FDA :

- Use of ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (Sovaldi) combined with another direct-acting antiviral drug in patients already taking amiodarone is not recommended.
- For patients taking amiodarone who have no other alternative treatment options and who will be co-administered either Harvoni or Sovaldi in combination with another direct-acting antiviral:
  - Counsel patients about the risk of serious symptomatic bradycardia which may present as syncope, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.
  - Cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment, as bradycardia can occur for up to two weeks following combined use of these agents.
- Patients taking ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (Sovaldi) in combination with another direct-acting antiviral, who need to start amiodarone therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.

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# from the fda

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- *Patients who will stop treatment with amiodarone due to initiation of ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (Sovaldi) combined with another direct-acting antiviral drug should undergo similar cardiac monitoring as outlined above since amiodarone has a long half-life and important drug interactions may occur for some time after discontinuation.*

Additional information can be found in a recent [National PBM Bulletin](#) as well as by clicking on the link above.

## MENTAL HEALTH

[FDA review of study sheds light on two deaths associated with the injectable schizophrenia drug Zyprexa Relprevv \(olanzapine pamoate\)](#)

3/23/2015

Two unexplained deaths occurring several days after receiving injectable olanzapine pamoate (Zyprexa Relprevv) prompted the FDA to study possible causes, but results were inconclusive. Although the patients received appropriate doses, elevated levels of olanzapine were found in both patients, who died 3-4 days after intramuscular (IM) administration of the drug. Animal studies conducted by the manufacturer at the request of the FDA showed that post-mortem redistribution of olanzapine can take place following IM administration of the drug and that various tissues could act as reservoirs contributing to an increase in olanzapine concentrations after death. As an alternative explanation, olanzapine pamoate (Zyprexa Relprevv) does hold a boxed warning for causing post-injection delirium sedation (PDSS), whose signs and symptoms are consistent with overdose. However, in clinical trials, PDSS occurred approximately 3 hours post-injection and no deaths were reported. Based on this information, FDA does not recommend any changes to the prescribing or use of olanzapine pamoate (Zyprexa Relprevv).

## CENTRAL NERVOUS SYSTEM

[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](#)

3/9/2015

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. Additionally, the manufacturer continues to further assess neuropsychiatric risks via a required post-marketing clinical trial whose results are expected later this year. Details can be found in the [Issue 3; Volume 5; March 2015](#) issue of the newsletter and are also available by clicking on the link above.

## UROLOGY

[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](#)

3/3/2015

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. Age-related hypogonadism is not an FDA-approved indication for testosterone replacement therapy, and safety and efficacy for this use has not been established. FDA recommends that providers:

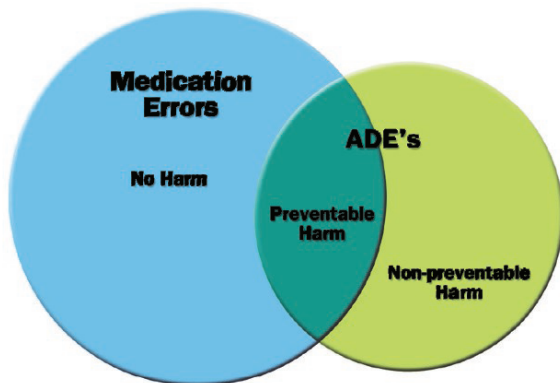
- *Ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing before initiating testosterone replacement therapy.*
- *Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range.*
- *Avoid measuring 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 cardiovascular risk associated with testosterone replacement therapy.*

Further details are available in the [Issue 3; Volume 5; March 2015](#) issue of the newsletter, a recent [National PBM Bulletin](#), and also by clicking on the link above.

# Getting the most from our safety surveillance

## MEDICATION-RELATED HARM: A NEW PARADIGM

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) issued a new paradigm to help health care professionals distinguish among Adverse Drug Events (ADEs), Adverse Drug Reactions (ADRs), and Medication Errors (Figure 1). This includes new terminology to explain relationships among the terms as well as a new algorithm to encourage consistency in adoption of these current views and assessment of medication safety issues across the health care community. These new tools are available on the NCC-MERP website at: [http://www.nccmerp.org/sites/default/files/nccmerp\\_fact\\_sheet\\_2015-02-v91.pdf](http://www.nccmerp.org/sites/default/files/nccmerp_fact_sheet_2015-02-v91.pdf).



**Figure 1. Relationship between medication errors and ADEs.** According to NCC MERP, “preventable ADE” pertains to “harm caused by the use of a drug as the result of an error” (i.e., a drug given to a patient with a known contraindication), while “non-preventable ADE” refers to “drug-induced harm occurring with appropriate use of medication” (i.e., an allergic reaction to a drug in a patient with no documented sensitivity).

The VA uses two separate spontaneous adverse drug event (ADE) reporting systems to manage provider- and patient-reported ADEs associated with drugs, vaccines, and biologics:

- the Allergy/Adverse Reaction Tracking System (ARTS), which resides within the VA electronic medical record and houses all allergies as well as adverse drug reactions (ADR) entered into the Computerized Patient Record Sys-

- tem (CPRS) by providers for use in direct patient care; and
- the VA Adverse Drug Event Reporting System (VA ADERS), a web-based spontaneous ADE reporting system that allows for system-wide tracking/monitoring of ADEs on an aggregate or individual level, and from which Med-Watch reports can be generated from provider entries for electronic submission to the FDA. VA ADERS can be accessed at: [https://vaww.cmop.med.va.gov/MedSafe\\_Portal/index.asp](https://vaww.cmop.med.va.gov/MedSafe_Portal/index.asp). Select VA ADERS – Launch to login and report events.

Both systems have been previously discussed in detail in a prior issue ([Issue 7; Volume 2; July/August 2012](#)) and help to strengthen VA’s capacity for capturing adverse events on a national level. Information below shows examples of ADE data available through the VA ADERS application for system-wide identification and trending of adverse drug events.

VA ADERS Reports - potentially preventable*	Oct 2014	Nov 2014	Dec 2014	Jan 2015	Feb 2015	Mar 2015
HISTORY OF ALLERGY	54	36	53	42	28	58
NOT PREVENTABLE	4,634	4,198	4,494	3,889	3,695	3,983

\*Based on reporter evaluation and answer to the question: ‘Was there a history of allergy or previous reactions to the drug or drug class that was severe or would indicate the drug should not be used again?’

In general, medication errors are not submitted or reported to VA ADERS, but some ADEs are evaluated and determined to be potentially preventable. These VA ADERS reports allow the reporter to identify potential steps to prevent future reactions of similar nature from occurring.

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## Helping to achieve safe medication use

### UPDATE: HIGH-DOSE VITAMIN E

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may increase mortality.<sup>2-12</sup>

Aside from cardiovascular disease prevention, use of high doses of vitamin E has been studied in patients with moderately severe Alzheimer’s disease (AD). Sano and colleagues found that in

AD of moderate severity, there were significant delays to the primary outcome (time to occurrence of death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia) in patients receiving vitamin E 2000 IU daily (670 days; P=0.001), selegiline 10 mg daily (655 days;

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P=0.012), or the combination (585 days; P=0.049) compared to placebo (440 days) when followed for two years. The estimated increase in survival over placebo with vitamin E, selegiline, or the combination was 230 days, 215 days, and 145 days, respectively, which was not statistically significant. A significant increase occurred in each treatment group versus placebo with respect to three areas of adverse events: dental events (P = 0.023); falls (P = 0.005); and syncopal episodes (P = 0.031). Mortality rates were not significantly different among groups and reached approximately 10% with selegiline, 12% with vitamin E, 7% with the combination and 12% with placebo.<sup>13</sup>

Recent evidence suggests that vitamin E protects function in mild to moderate AD. The Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD) was conducted at 14 Veterans Affairs medical centers and assessed the effectiveness as well as safety of vitamin E 2000 IU daily, memantine 20mg daily, or the combination versus placebo for the treatment of functional decline in patients with mild to moderate AD who were taking a background acetylcholinesterase inhibitor (AChEI). Over the average follow-up time of 2.3 years, participants receiving vitamin E had a slower decline than those receiving placebo according to the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) inventory, which measures functional abilities to perform activities of daily living in Alzheimer patients with a broad range of dementia severity. Results show a delay in progression of 19% per year in the vitamin E group which translates into a clinically meaningful delay in progression of 6.2 months compared to the placebo group. In addition, caregiver time was reduced by about 2 hours per day in the vitamin E group. However, these improved functional outcomes are tempered by the lack of benefit observed on any cognitive tests. Neither memantine nor the combination of vitamin E and memantine showed clinical benefit with respect to delaying clinical progression in the ability to perform activities of daily living in this trial.<sup>14</sup> Mortality was not significantly different among groups, with rates of 7.3% for the vitamin E group (hazard ratio [HR] 0.87; 95% confidence interval [CI], 0.67-1.13), 11.3% for the memantine group (HR 1.06; 95% CI, 0.91-1.24), and 9.0% for vitamin E plus memantine (HR 0.94; 95% CI, 0.57-1.54) versus 9.4% for placebo. These findings contrast with those of the meta-analysis which showed that high-dose vitamin E (400 IU daily or greater) may increase the risk for all-cause mortality.<sup>2, 14</sup>

While these results are encouraging for the use of vitamin E supplementation in improving function in the management of mild to moderately severe AD, caution remains because studies have

shown that high doses of vitamin E may increase risk of death, particularly in those with cardiovascular disease. Studies have linked high doses of vitamin E with other significant side effects as well. Vitamin E has a tendency to cause bleeding and can exacerbate the platelet-inhibiting effects of aspirin.<sup>15, 16</sup> A meta-analysis found that vitamin E supplementation increased the risk of hemorrhagic stroke by 22% (although risk of ischemic stroke decreased by 10%).<sup>17</sup> The Heart Outcomes Prevention Evaluation (HOPE) trial suggests that long-term exposure of vitamin E taken in moderately high doses may increase the risk of heart failure (relative risk [RR], 1.13; 95% CI 1.01-1.26; P=0.03) and hospitalizations for heart failure (RR, 1.21; 95% CI, 1.00-1.47; P=0.045) in patients aged  $\geq 55$  years old with diabetes and vascular disease.<sup>18</sup> Results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) trial showed that vitamin E supplementation at a dose of 400 IU daily was associated with an increased risk of prostate cancer [HR, 1.17; 99% CI, 1.004-1.36; P=0.008].<sup>19</sup> A meta-analysis of 19 clinical trials assessing vitamin E alone or in combination with other supplements reported a significant dose-dependent relationship between vitamin E intake and all-cause mortality.<sup>2</sup> Additionally, a Cochrane review including 78 randomized trials with 296,707 participants also showed that in trials of low risk bias, vitamin E (compared to placebo or no intervention) significantly increased mortality (11,689 deaths/97,523 [12.0%] versus 7561 deaths/73,721 [10.3%]; 46 trials with low risk of bias; RR, 1.03; 95% CI, 1.00 to 1.05).<sup>20</sup> Alternatively, another meta-analysis, that did not stratify trials by dose of vitamin E, found no significant effect of supplementation on all-cause mortality.<sup>21</sup>

While there is some evidence that higher doses of vitamin E are associated with various types of adverse events, possibly including an increased risk of mortality, other data indicates it is helpful in slowing functional decline in patients with mild to moderate AD, at least over the course of approximately two years. Therefore, when considering use of high dose vitamin E for managing mild to moderate AD, we recommend that the potential benefits and risks be discussed with the patient and/or caregiver, and the decision to utilize high dose vitamin E be based on shared decision making. Further clinical guidance and evidence summaries regarding the pharmacotherapeutic management of AD can be found on the PBM website, available at this link: <http://www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse.asp>

Providers should continue to report any adverse reactions with the use of vitamin E supplements by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local

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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).

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