VA Center for Medication Safety

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Medication safety in seconds

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

Helping to achieve safe medication use

POTENTIAL DOSE-RELATED RISK OF OPIOID DEATHS IN VETERANS

A recent VHA case-cohort study evaluated the association of maximum prescribed daily opioid dose with risk of opioid overdose death among veterans in various diagnostic subgroups. Data were obtained from 154,684 patients who used VHA medical services in 2004 or 2005 and received opioid therapy for pain during the 5-year study period (2004–2008) and 750 unintentional prescription opioid overdose decedents. The results showed that maximum prescribed doses of opioids of 100 mg/d or more morphine equivalents were associated with greater than a 4- to 11-fold increased risk of opioid overdose-related deaths depending on the diagnostic subgroup (substance use disorder, chronic pain, acute pain, and cancer) (Table 1).

Overall, fatal overdose was rare, being identified in about 0.04% of individuals treated with opioids during the 5-year study period. The approximate absolute risk increases in opioid deaths were also small among the diagnostic subgroups, ranging from 0.14% to 0.45%.

The study also evaluated the association between opioid dose and dosing schedule. The combination of regularly scheduled and as-needed opioid doses was not shown to be associated with increased overdose risk after adjustment for demographic and clinical factors.

This study is significant because it was the first to evaluate potential factors associated with opioid-related deaths in VHA's patient population. Further studies are needed to verify the results.

TABLE 1. Risk of Opioid Overdose-Related Deaths

DIAGNOSTIC SUBGROUP	HAZARD RATIO †	95% CI	ARDA
Substance Use Disorders	4.54	2.46-8.37	0.14%
Chronic Pain	7.18	4.85-10.65	0.25%
Acute Pain	6.64	3.31-13.31	0.23%
Cancer	11.99	4.42-32.56	0.45%

ARDA, Absolute risk difference approximation
† Adjusted hazard ratio associated with maximum prescribed daily opioid dose in morphine equivalents of 100mg/d or more relative to the dose category of 1 mg/d to less than 20mg/d

RECOMMENDATIONS TO CONSIDER:

- As recommended by the VHA/DoD Clinical Practice Guideline on the Management of Opioid Therapy in Chronic Pain, assess the safety and utility of opioid therapy prior to initiation of opioids, at regular intervals during the course of opioid therapy, and as indicated by changes in the patient's clinical status.
- Document a comprehensive assessment of benefits, side effects, and risk for misuse/abuse associated with opioid therapy, followed by

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NEWS YOU CAN USE

FROM THE VA NATIONAL PBM: BULLETINS, COMMUNICATIONS, & RECALLS

- Citalopram Hydrobromide (Celexa®) and Dose-Dependent QT Interval Prolongation ***UPDATE*** - National PBM Bulletin - 09-29-2011
- Citalopram Hydrobromide (Celexa®) and Dose-Dependent QT Interval Prolongation - National PBM Bulletin - 08-31-2011
- Erythropoiesis-Stimulating Agents (ESAs) in Chronic Kidney Disease (CKD) and New Dosing Recommendations - National PBM Communication - 08-09-2011

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NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Celexa (citalopram hydrobromide)- Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide)
8/24/2011
Citalopram causes dose-dependent QT interval prolongation and FDA no longer recommends using doses above 40 mg per day.

- Post-marketing reports submitted to FDA document cases of QT interval prolongation and Torsade de Pointes associated with branded and generic citalopram.
- FDA evaluated a randomized, multi-center, double-blind, placebo-controlled, crossover study, assessing the effects of 20-mg and 60-mg doses of Citalopram versus placebo on the QT interval in adults. Results showed maximum mean QT interval prolongations of 8.5, 12.6, and 18.5 milliseconds (ms) for 20 mg, 40 mg, and 60 mg citalopram, respectively.
- Other studies revealed no improvement in symptoms of depression at doses greater than 40 mg citalopram per day, although previous product labeling permitted use of 60 mg per day in certain patients. Typically, higher doses of selective serotonin reuptake inhibitors (SSRIs) are most commonly used for anxiety disorders where there is dose-response.

Actos(pioglitazone) - Updated drug labels for pioglitazone-containing medicines
8/4/2011 **(***UPDATE FROM 06/15/2011***)**
Product labeling for the pioglitazone-containing medicines now includes safety information stating that the use of pioglitazone for more than one year may result in an increased risk of bladder cancer. The updated drug labels recommend that healthcare professionals should:

- Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer.
- Educate patients to contact their healthcare providers if experiencing new or worsening urinary pain or urgency as well as hematuria.

*(NOTE: Current VA Thiazolidinediones Criteria for Nonformulary Use will be updated to include **active or prior history of bladder cancer** as an exclusion criteria for pioglitazone therapy within the VA system.)*

Somatropin - Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death
8/4/2011 **(***UPDATE FROM 12/22/2010***)**
In December 2010, FDA could not conclusively link recombinant human growth hormone use with increased risk of death after reviewing a French study (the Santé Adulte GH Enfant [SAGhE] study) as well as other available data. Further evaluation of the medical literature as well as reports from the FDA's Adverse Event Reporting System (AERS) did not support the association of increased risk of death with recombinant human growth hormone use. FDA anticipates more data from the SAGhE study in Spring 2012 and recommends the continued prescription and use of recombinant human growth hormone according to the labeled recommendations.

Diflucan - Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants
08/03/2011
The pregnancy category for the antifungal drug fluconazole (Diflucan) for indications other than vaginal candidiasis changed from C to D, suggesting evidence of human fetal risk based on human data. Published case reports document birth defects with chronic high doses (400-800 mg/day) of fluconazole in the first trimester of pregnancy. Teratogenic effects resemble the autosomal recessive genetic disorder known as Antley-Bixler syndrome, and include short, broad head; abnormal looking face; abnormal development of the skullcap; oral cleft lip or palate; bowing of the thigh bones; thin ribs and long bones; muscle weakness and joint deformities; or congenital heart disease. Available human data do not associate this risk to a single, low dose of fluconazole 150 mg to treat vaginal candidiasis, leaving the pregnancy category for this indication at C. Healthcare providers should discuss potential risks to fetus if prescribing chronic, high dose fluconazole during pregnancy, or if a patient becomes pregnant during chronic, high dose fluconazole use.

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development and enactment of a plan for patient education, continued close monitoring and implementation of a risk management plan when opioid-related risk is specifically identified. The use of written opioid treatment agreements, informed consents, patient education materials, and opioid monitoring templates may aid in such documentation.

- Start opioids at the lowest dose and titrate the dose slowly based on adequacy of treatment response.
- Consider the potential risks versus benefits of opioid therapy before increasing doses to 100 mg/d or more morphine equivalents.
- As dosing is increased, particularly above 100 mg/day of oral morphine equivalents, monitor for any signs of overmedication (e.g., confusion, forgetfulness, excessive sleepiness or drowsiness, periods of unconsciousness, increased snoring, periods of apnea during sleep, word slurring, altered mental status).
- Educate patients taking opioid doses 100 mg/d or more morphine equivalents and/or their caregivers about the potential for increased risk and what to do if the patient develops signs of possible overdose.
- Instruct patients to avoid increasing opioid doses on their own.
- Avoid interacting drugs, if possible, that may increase the risk for opioid overdose or opioid-related death when used concurrently with opioids. A few notable examples are concomitant use of benzodiazepine and other CNS depressants with any opioid, CYP3A4 inhibitors with fentanyl, and QTc-prolonging drugs with methadone.
- Use caution if long- and short-acting opioids (for rescue or breakthrough pain) are used concomitantly to manage severe, chronic pain. Note that the VHA/DoD Clinical Practice Guideline on the Management of Opioid Therapy in Chronic Pain supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed (p.r.n.) opioids for pain exacerbations.
- Use extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients who have a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. Use caution when using opioids in elderly patients and in patients with renal or liver dysfunction (of note, morphine may cause neurotoxicity in patients with renal impairment). Consult specific product information for contraindications, warnings, and dosage adjustments.

REFERENCES:
1. Bohnert ASB, Valenstein M, Bair MJ, et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. JAMA. 2011;305(13)1315–1321.
2. VA/DoD Clinical Practice Guideline on Management of Opioid Therapy in Chronic Pain, May 2010. Available at: http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp . Accessed 2011 08 16.

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Getting the most from our safety surveillance

DRONEDARONE SAFETY CONCERNS

Due to potential safety concerns identified during the VA national drug review of dronedarone, the VA Center for Medication Safety (VAMedSAFE) was asked to conduct an ongoing safety surveillance of patients prescribed dronedarone. Results of these database evaluations are reported on a quarterly basis to the VA Pharmacy Benefits Management Services (PBM) Medical Advisory Panel (MAP) and VISN Pharmacist Executives (VPEs).
Parameters of the evaluation of patients on dronedarone focus on:

- New onset heart failure (HF)
- HF exacerbations
- Potential contraindication to therapy due to decompensated HF
- Drug interaction with warfarin and potential for bleeding
- Thyroid-related adverse events
- Pulmonary toxicity
- Hepatotoxicity

Per data from 08/01/2009-06/30/2011 of patients with a new prescription for dronedarone:

Patients without a previous diagnosis of HF (N=1109):

- 1 (0.09%) hospitalized for HF within 30 days of dronedarone prescription
- 3* (0.27%) within 90 days
- 7* (0.63%) within 180 days

**cumulative within timeframe*

Patients with a previous diagnosis of HF (N=293):

- 6 (2%) hospitalized for HF within 30 days of dronedarone prescription
- 15* (5%) within 90 days
- 24* (8%) within 180 days

**cumulative within timeframe*
These percentages were slightly less than the amiodarone comparator group.

Patients with recent decompensated HF* (HF hospitalization within 30 days prior to prescription):

- 14 of 1481 new users of dronedarone (0.95%)
- 1 of these patients was rehospitalized for HF within 30 days of dronedarone prescription.

**Dronedarone is contraindicated in patients with New York Heart Association (NYHA) Class IV HF or Class II-III HF with a recent decompensation requiring hospitalization or referral to a HF clinic (Boxed Warning).*

Sites were asked to conduct data validation on 12 patients identified from 08/01/2009–03/31/2011 as having recent HF decompensation (2 additional patients through 6/30/2011 pending evaluation):

- Of the 12 patients, 6 were confirmed to have a HF hospitalization within 30 days prior to initial dronedarone prescription.

Reported rationale for prescribing dronedarone despite the warning for contraindication included:

- Previous intolerance or inefficacy with amiodarone (3)
- Concern for potential toxicity with amiodarone (2)
- Prescribed by nonVA provider with patient informed of risk vs. benefit (1)

Due to early reports of a probable drug interaction with concomitant dronedarone and warfarin in the VA Adverse Drug Event Reporting System (VA ADERS), bleeding in patients prescribed dronedarone and warfarin were included in the VAMedSAFE safety surveillance.* Per the VAMedSAFE report from (08/01/2009-06/30/2011):

- 37 of 685 (5.4%) patients prescribed dronedarone and warfarin had new onset major hemorrhage after starting concomitant therapy.
- Incidence compares to patients prescribed concomitant amiodarone and warfarin, a known drug interaction.

** Revision to dronedarone product information on 03/2011 describes a potential drug interaction with warfarin.*

In addition, VAMedSAFE has been tracking adverse events with dronedarone reported to VA ADERS. Data submitted to VA ADERS from Q1FY10 through Q3FY11 for dronedarone include 57 events (29 mild, 15 moderate, 13 severe) reported in 31 patients:

- HF related symptoms (27 events, occurring in 14 patients)
- Bleeding/increased INR (4 events)
- Gastrointestinal symptoms (8 events)
- Rash (2 events)
- Hypotension (2 events)
- Dizziness/vertigo/syncope (5 events)
- Fatigue (1 event)
- Increased liver function tests (2 events)
- Angioedema (1 event)
- Palpitations (1 event)
- Myalgia (1 event)
- Unexpected therapeutic effect (1 event)
- Drug interaction (1 event)
- Contraindication (1 event)

VAMedSAFE and VA ADERS data will continue to be reviewed and reported to the MAP and VPEs on a regular basis. Data on thyroid, pulmonary and hepatic adverse events, as well as drug interaction data with warfarin and other antiarrhythmic agents for comparison, will be discussed when available. With the recent discontinuation of a clinical trial with dronedarone in patients with permanent atrial fibrillation (non-FDA approved indication; refer to PBM Safety Communication dated 07/28/2011 below) due to an increased risk of death and cardiovascular events, it has been suggested that the rate of death in VA patients on dronedarone also be evaluated.

Recently, several National PBM Safety Communications have been disseminated by VAMedSAFE and the PBM-MAP including:

- Dronedarone (Multaq) and Increased Risk of Death and Serious Cardiovascular Events in Patients with Permanent Atrial Fibrillation, 07/28/2011
- Dronedarone and Liver Injury, 01/21/2011
- ISMP Medication Safety Alert: Dronedarone (Multaq) Adverse Event Signal, 11/15/2010

In addition, several updates to the dronedarone criteria for use have been made as a result of safety alerts and changes to the product labeling.

Contributed by: Elaine Furmaga, Pharm.D.

PROVIDER RECOMMENDATIONS:

- Refer to the VA PBM-MAP-VPE Dronedarone, Criteria for Use for recommendations on the appropriate patient population, place in therapy, and monitoring and safety considerations for prescribing dronedarone.
- Refer to VHA Directive National Dual Care Policy for considerations in the management of veteran patients also receiving care from non-VA providers.
- Continue to report any adverse reactions with the use of dronedarone 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).