

MEDICATION SAFETY IN SECONDS

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

Helping to achieve safe medication use

STUDY SHOWS CHANGES IN PILL APPEARANCE LEAD TO DRUG DISCONTINUATION IN MYOCARDIAL INFARCTION (MI) PATIENTS

Changes in the appearance (between brand and generic counterparts as well as among available generics on the market for the same active ingredient of a given medication) may contribute to patient confusion and drug discontinuation according to a recent study. Kesselheim and colleagues looked at patients initiating treatment with cardiovascular (CV) medications after hospital discharge for myocardial infarction (MI) and followed their refill habits for 1 year to measure the effect of a change in pill appearance (color and shape unrelated to variations in strength) on patients' persistence (time from initiation to discontinuation of therapy) to prescribed regimens. Results showed that approximately 30% (3286/11513) of patients who initiated treatment with a generic prescription of CV drugs of interest (beta [β]-blockers, angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs], and statins) had a change in pill

appearance unrelated to a change in dose for these drugs in the first year post-hospitalization. Changes in pill color and shape occurred most frequently with statins and least frequently with β-blockers, and significantly preceded cases of nonpersistence. The odds of non-persistence increased by 34% after a change in color (adjusted odds ratio [OR] 1.34 [CI, 1.12 to 1.59]) and 66% after a change in shape (adjusted OR, 1.66 [CI, 1.43 to 1.94]). Study limitations include that only 3 classes of CV medications were evaluated (decreasing generalizability) and that assessments did not link discontinuations to clinical outcomes.

Ensuring patient education regarding changes in the appearance of their medications can reduce morbidity, mortality, and costs associated with preventable complications, medication errors, and/or disease recurrence. Authors recommend that: "Cardiologists and

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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

- Digoxin in Patients with Atrial Fibrillation: Potential Harms – 09/30/2014 - [National PBM Bulletin](#)
- UPDATE: Niacin Study Results and Implications – 08/29/2014 - [National PBM Bulletin](#) ***UPDATE from 08/08/2014 to clarify trial findings and recommendations regarding niacin.***

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from the fda

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RESPIRATORY

[FDA approves label changes for asthma drug Xolair \(omalizumab\), including describing slightly higher risk of heart and brain adverse events](#)

09-26-2014 ***UPDATE FROM 07-16-2009***

FDA has added information about the findings of a slightly elevated risk of cardiovascular and cerebrovascular serious adverse events in patients treated with omalizumab to the Adverse Reactions section of the drug label. FDA has also added information about uncertain findings regarding a potential risk of cancer to the Warnings and Precautions section of the product insert. These changes were prompted by the FDA's review of the manufacturer's postmarketing commitment study entitled *An Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS)*, which assessed the safety of Xolair over a 5-year period. Results showed:

- a higher incidence rate per 1,000 patient-years of overall cardiovascular and cerebrovascular serious adverse events observed in Xolair-treated patients compared to non-Xolair-treated patients, as well as for myocardial infarction, unstable angina, transient ischemic attack, pulmonary embolism/venous thrombosis, and pulmonary hypertension. No increases in the rates of ischemic stroke or cardiovascular death occurred in patients treated with Xolair compared to non-Xolair-treated patients. To further investigate these findings, FDA conducted a review of a pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration completed by December 31, 2010, which showed no notable differences in the rates of specific cardiovascular events (including cardiovascular death, myocardial infarction, arrhythmias, heart failure, stroke, transient ischemic attack, pulmonary hypertension, pulmonary embolism, and unstable angina) between Xolair-treated patients and placebo patients.
- similar incidence rates of primary malignancies per 1,000 patient-years among Xolair-treated and non-Xolair-treated patients.

Although weaknesses in study design and conduct of the above analyses make it difficult to definitively confirm or determine the exact increased level of these risks with omalizumab, label revisions now warn about these safety signals.

Getting the most from our safety surveillance

MINERALOCORTICOID RECEPTOR ANTAGONISTS IN HEART FAILURE SAFETY SURVEILLANCE: FOCUS ON APPROPRIATE INITIAL FOLLOW-UP OF POTASSIUM AND KIDNEY FUNCTION

Contributed by Elaine Furmaga, Pharm.D. and Cedric Salone, Pharm.D.

Treatment with a mineralocorticoid receptor antagonist (MRA), in addition to standard therapy in patients with heart failure (HF) with reduced ejection fraction (HFrEF), has been shown to decrease all-cause and cardiovascular mortality, and reduce HF hospitalizations.^{1,2} Current clinical practice guidelines recommend treatment with a MRA in patients with New York Heart Association (NYHA) class II-IV HF and a left ventricular ejection fraction $\leq 35\%$.^{3,4} However, careful monitoring is recommended as there is the potential for adverse outcomes related to hyperkalemia with a MRA, and lack of appropriate follow-up.⁵⁻⁷

The VA Pharmacy Benefits Management Services (PBM), Medical Advisory Panel (MAP), and VISN Pharmacist Executives (VPEs), in collaboration with members of the Chronic Heart Failure (CHF) Quality Enhancement Research Initiative (QUERI), developed clinical recommendations for the use of the MRAs in patients with HFrEF, to emphasize appropriate selec-

tion of patients as well as the need for close monitoring and follow-up. Per the clinical recommendations, patients initially prescribed a MRA should have an evaluation of their potassium (and serum creatinine for spironolactone) prior to receiving a new prescription for either spironolactone or eplerenone, then again at or within 1 week. Thereafter, for spironolactone, it is recommended that continued monitoring should be every 4 weeks for the first 3 months, every 3 months for 1 year, then every 6 months (for eplerenone, continued monitoring should be at 4 weeks, then periodically) [refer to [Mineralocorticoid Receptor Antagonists \(Eplerenone, Spironolactone\) in Heart Failure, Recommendations for Use](#)].

In collaboration with the CHF QUERI, the PBM and the VA Center for Medication Safety (VA MedSAFE) conducted a safety evaluation to:

- Determine the extent of potassium monitoring as per

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Getting the most from our safety surveillance

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recommendations after initial prescription of a MRA.

- Identify potential reasons for nonadherence to recommendations where monitoring is deficient.
- Compare potassium in patients with follow-up within the recommended timeframe vs. those outside the recommendations.
- Explore whether implementation of a sustainable method for improving follow-up is feasible from a national level.

Eight sites agreed to participate in the evaluation and included: Ann Arbor, Bay Pines, Black Hills/Ft. Meade, Cincinnati, Detroit, Kansas City, Memphis, Puget Sound/Seattle. The evaluation was conducted in patients with a history of HF \neq EF and a new prescription for a MRA between September 1, 2012 and February 28, 2013. Patients were divided into those who received laboratory follow-up of their potassium within 1 week of the new prescription (or within 2 weeks if the prescription was mailed), and those who did not have laboratory follow-up within this timeframe. The sites were asked to complete a questionnaire on those patients who did not receive laboratory follow-up within the recommended timeframe as described above.

Based on laboratory and prescription data obtained from the national database, and responses from the site questionnaire, the following observations were made:

- Approximately 42% of patients being evaluated with HF \neq EF and an initial prescription for a MRA, received follow-up laboratory monitoring according to the recommendations of within 1 week (or within 2 weeks for patients who had their prescription mailed).
- Of the patients who exceeded the recommended timeframe for follow-up, approximately 78% had laboratory follow-up within 3 months of the initial MRA prescription.
- It appeared that the most frequent reason for the patient not having follow-up labs within the recommended timeframe was either that the lab was ordered for > 2 weeks (46%; 28% had lab ordered for \leq 2 weeks) or that a lab was not ordered (13%).
- Patient understanding of the prescription or lab instructions did not appear to be a major reason for patients not having lab follow-up.
- When comparing potassium in patients with follow-up within the recommended timeframe vs. those outside the recommendations (but within 3 months of the initial prescription):
 - An elevated potassium (> 5.5 mEq/L) after the initial MRA prescription occurred in 0.96% of patients with follow-up within 1 week (within 2 weeks if prescription was mailed) compared to 1.6% who had lab follow-up within 3 months.

- A similar number of patients in each group who had potassium levels > 5.0 mEq/L upon follow-up, had risk factors for developing hyperkalemia (e.g., baseline potassium > 5.0 mEq/L or serum creatinine \geq 2.5 mg/dl; prescribed potassium supplements).
- There were no reports of potassium \geq 6.0 mEq/L in either follow-up group.
- Due to the lag time of obtaining and reporting laboratory results to the sites, national level follow-up using the method described in this project would not be feasible; however, implementation via a National Medication Use Evaluation Tracker (MUET) or VISN Dashboard may be suitable for patient follow-up and intervention.

Conclusions and Recommendations

Laboratory evaluation of potassium as recommended within 1 week after initial prescription of a MRA in patients with HF \neq EF is suboptimal. Provider education should emphasize the recommended timeframe for follow-up (i.e., prior to receiving a new prescription for a MRA, then again at or within 1 week; then, for spironolactone, every 4 weeks for the first 3 months, every 3 months for 1 year, then every 6 months), and the potential factors that may increase the risk for hyperkalemia during treatment with a MRA (e.g., baseline elevated potassium and/or serum creatinine; concomitant medications that may contribute to increased potassium levels, noting the recommendation that potassium supplements or potassium-sparing diuretics should be discontinued when therapy with a MRA is initiated). Methods for implementing appropriate follow-up with a MRA (e.g., MUET, Dashboard) should be explored.

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other prescribers of cardiovascular medications should proactively warn patients about the potential for these changes and their lack of clinical import, especially in light of the growing prevalence of use of generic drugs." In addition, Pharmacy may consider:

- Maintaining a consistency with the use/choice of manufacturers;
- Educating patients with verbal or written information when a change in the physical appearance of a medication may occur, such as with utilizing a new/different manufacturer or

new strength of the same product;

- Affixing warning labels/stickers to affected prescriptions to communicate to patients any changes in pill appearance.

Further details regarding this study may be found at: <http://annals.org/article.aspx?articleid=1887026> .

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