

MEDICATION SAFETY IN SECONDS

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

Helping to achieve safe medication use

THE THERAPY-RELATED RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Growing evidence suggests an increased risk of cardiovascular (CV) events from use of inhaled long-acting beta-2 agonists (LABAs) or long-acting antimuscarinic antagonists (LAMAs) for the treatment of chronic obstructive pulmonary disease (COPD). Past studies have shown a variable association, concluding no increased risk¹⁻⁶ to an almost 5-fold increased risk⁷⁻¹⁰. The studies that have observed an increased risk of cardiovascular disease (CVD) from the use of LABAs and LAMAs looked at elderly patients with COPD⁷, observed few CVD events^{10,11}, or included prevalent users of these medications⁷⁻¹². None have examined acute therapy-related risk of CVD in patients with COPD within 30 days after initiation of LABAs and LAMAs.

Wang and colleagues¹³ conducted a nested case-control study to investigate the risk for

developing CVD associated with new use and recent initiation of LABAs or LAMAs for COPD. Over 284,000 COPD patients in Taiwan were followed from 2007 through 2011. The primary endpoint was an inpatient or emergency department (ER) visit with a primary diagnosis of coronary heart disease, cardiac arrhythmia, heart failure, or ischemic stroke. Each case was matched to 4 randomly selected controls. LABA or LAMA use was evaluated within the year before the event or index date, and stratified by time to event from treatment initiation, new and prevalent use, concomitant therapy with other COPD medications, and individual agents. Nonusers of LABAs or LAMAs and new theophylline users served as comparator groups. Authors used conditional logistic regressions to report the odds ratio (OR) of CVD with LABA or LAMA use; and expressed the absolute risk of

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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

- Edaravone (Radicava™) and Potential for Leaking at Valve Site – 01/10/2018 - [National PBM Bulletin](#)

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from the fda (continued from page 1)

GASTROENTEROLOGY

[FDA limits packaging for anti-diarrhea medicine Loperamide \(Imodium\) to encourage safe use](#)

1/30/2018

FDA continues to receive reports of serious heart problems and deaths with higher than recommended doses of loperamide, mostly due to intentional misuse or abuse, despite addition of a warning to the medicine label and a previous safety alert. Loperamide is FDA-approved to help control symptoms of diarrhea, with a maximum approved daily dose for adults of 8 mg per day for OTC use and 16 mg per day for prescription use. Loperamide works at the level of the opioid receptors in the gut to decrease intestinal activity and frequency of bowel movements. Using doses greater than recommended, either intentionally or unintentionally, can lead to serious cardiac adverse events, such as QT interval prolongation, Torsades de Pointes, other ventricular arrhythmias, syncope, and cardiac arrest. If loperamide toxicity is suspected, promptly discontinue the drug and start necessary therapy. FDA is working with manufacturers to limit the number of doses in a package via blister packs or other single dose packaging.

PULMONOLOGY

[FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older](#)

1/11/2018

FDA requires safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because risks of respiratory depression, misuse, abuse, addiction, overdose, and death with these medicines outweigh their benefits in patients younger than 18. FDA will also require the addition of safety information about these risks to the *Boxed Warning* in product labeling. Codeine and hydrocodone are available in combination with other medicines, such as antihistamines and decongestants, in prescription medicines to treat coughs and other symptoms associated with allergies or the common cold (Tables 1 and 2).

Table 1. List of Prescription Cough and Cold Medicines Containing Codeine Active Ingredient(s)	Brand Name(s)
codeine, chlorpheniramine	Tuxarin ER, Tuzistra XR
codeine, phenylephrine, promethazine	Only generics available
codeine, promethazine	Only generics available
codeine, pseudoephedrine, tripolidine	Triacin C

Table 2. List of Prescription Cough and Cold Medicines Containing Hydrocodone Active Ingredient(s)	Brand Name(s)
hydrocodone, guaifenesin	FlowTuss, Obredon
hydrocodone, pseudoephedrine, guaifenesin	Hycofenix, Rezira
hydrocodone, chlorpheniramine	Tussionex Pennkinetic, Vituz
hydrocodone, chlorpheniramine, pseudoephedrine	Zutripro
hydrocodone, homatropine	Only generics available

FDA recommends further measures to safeguard children under 18 years of age from risks from exposure to prescription cough and cold medicines containing codeine or hydrocodone:

- Notify your child's provider if your child is currently prescribed a cough and cold medicine containing codeine or hydrocodone to discuss alternatives.
- Breastfeeding is not recommended during treatment with opioid cough and cold medicines, because the medicine passes through breast milk and can harm the baby.
- Always lock up medicines and dispose of them properly when no longer needed to keep them from being taken accidentally by children or teenagers or falling into the wrong hands.

Getting the most from our safety surveillance

COMPOUNDING PHARMACY SCAM TARGETS VA PATIENTS AND PROVIDERS FOR UNSOLICITED PRESCRIPTION MEDICATIONS

Contributed by: *Alicia Sutterfield, Pharm.D., PGY2 Ambulatory Care Resident*

Recent investigations of alleged fraud by compounding pharmacies highlight the need for increased scrutiny. VA patients and providers have been targeted by these schemes, which involve phishing for patient and physician information for unsolicited medical prescriptions in the attempt to make a profit from private and public insurers using unscrupulous billing practices. Reports have been received from multiple sites about compounding pharmacies soliciting topical creams to VA patients and faxing a prescription to VA medical centers needing VA physician signature to be filled outside of VA and billed to Medicare.

Case Report

A VA physician received a fax from a compounding pharmacy requesting a signature to approve a prescription “pain cream.” The faxed prescription was pre-filled with all the necessary information, including the Veteran’s personal identifiers. The compounding pharmacy was based out-of-state, so the physician called the Veteran to inquire about the prescription. The Veteran reported he was contacted by the compounding pharmacy and asked for the name of his medical provider in order to receive the “pain cream,” to be billed to Medicare at no cost to him. The Veteran stated he did not know how the caller obtained his personal information, and did not request nor want the “pain cream.” Additionally, the Veteran informed the caller he did not have any pain. The caller was persistent, and the Veteran stated he reluctantly complied with the caller’s request. Next, the physician called the compounding pharmacy for further details, including the dollar amount of the claim to be submitted to Medicare, and the safety and efficacy of the “pain cream.” The compounding pharmacy was unwilling to provide this information and referred the physician to their company website. The prescription for the compounded cream was not signed by the physician and a formal complaint was filed with the appropriate State Board of Pharmacy.

At a different site, pharmacy leadership was notified of concerns from a local VA Privacy/FOIA officer, who reported that one of their local CBOCs had been receiving faxed prescription requests from an outside pharmacy, pre-prepared with a Veteran’s personal identifying information, seeking the medical provider’s signature. When the VA patient was called, the patient reported not knowing anything about it. Pharmacy leadership responded by filing a formal complaint with the local State Board of Pharmacy to initiate an investigation.

A separate instance involved a Telecare Pharmacist who re-

ceived a call from an outside pharmacy. The outside pharmacy asked for physician information for a prescription for a topical pain medication that they would then fax to the doctor for signature on behalf of the patient. The pharmacist refused and reported the incident to management.

Another VA physician reported receiving a similar faxed prescription request. In this case, the physician could never make contact with the requesting pharmacy. These scenarios are not unique to the VA, as similar reports of scams involving compounded creams have surfaced nationwide in recent years.

The Compounded Pain Cream Scam

Reports of scams to submit inflated claims for medically unnecessary compounded creams have increased in the last two years. Since 2015, over a dozen cases nationwide have been reported totaling more than \$100 million in fraudulent reimbursements. Reported cases have involved improper relationships between marketing companies, compounding pharmacies, and willing providers to defraud insurance plans, including TRICARE, Medicare, and Medicaid.

The prescribed “pain cream” formula used was calculated to result in the highest reimbursement rate, reported to be as much as \$21,000 for a one-month supply, most of which was all profit. Pharmacies often used bulk powder ingredients for compounding and submitted false claims that crushed tablets had been used. Some pharmacies even billed for ingredients they did not actually possess. To further maximize profits, “pain cream” prescriptions were often refilled automatically, whether the patient requested it or not. The pharmacy then shared a percentage of its profits with the marketing company and prescribing physicians.

Marketers were tasked with generating more prescriptions in return for monthly commissions. Their tactics included obtaining prescriptions for themselves and family members. In some cases, marketers would volunteer at clinics to obtain patient information, which was then copied to pre-printed prescription forms and signed by the corroborating physician. Patients were often never examined by the prescribing physician or only interviewed briefly over the phone. Marketers would also directly solicit health insurance beneficiaries with cash, food, or entertainment in return for their insurance information and agreement to obtain the compounded “pain cream.” The most egregious case recruited TRICARE beneficiaries to participate in a

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Getting the most from our safety surveillance

COMPOUNDING PHARMACY SCAM TARGETS VA PATIENTS AND PROVIDERS FOR UNSOLICITED PRESCRIPTION MEDICATIONS

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fictitious medical study to determine the efficacy and safety of the compounded creams. Beneficiaries were paid for their participation from a tax-exempt charity developed to conceal the scam's profits.

Recommendations

In order to protect against potential fraud and identity theft within the VA health care system in a consistent manner, the following actions are recommended:

- Providers should use caution if contacted to authorize a prescription for a compounded topical medication by a compounding pharmacy or representative.
 - For each patient for whom a physician signature is requested by a compounding pharmacy or representative for a prescription for a compounded medication to be obtained outside of the VA, verify with the patient that an appropriate indication/need exists and whether the patient initiated the pharmacy's request.
 - Contact compounding pharmacy to verify prescription details.
 - Confirm validity of compounding pharmacy and licensure with the appropriate State Board of Pharmacy.
 - If fraud is suspected, document a detailed description of the acts in question (i.e., who contacted the Veteran, whether contact was solicited or unsolicited, and whether the Veteran was offered any form of compensation in return), as well as the contact information of the compounding pharmacy involved and report the incident to:
 - Local Information Security Officer (ISO) and Privacy Officer (PO)
 - Local Chief of Pharmacy Service
 - Submit an Issue Brief to the appropriate VISN, including statement that report has been forwarded to local ISO
 - File a formal complaint with appropriate State Board of Pharmacy
 - File a report with the Office of the Inspector General (OIG), which is involved in a growing number of cases related to compounded drugs. The OIG Hotline accepts tips and complaints from all sources about potential fraud, waste, abuse, and mismanagement of Department of Health and Human Services' programs. Call the Office of the Inspector General at 1-800-HHS-TIPS (1-800-447-

8477). TTY: 1-800-377-4950 or visit <https://oig.hhs.gov/fraud/report-fraud/>.

- Inform impacted patients to:
 - Be wary of unsolicited attempts by any entity, either by phone or in person, to obtain personal health information and personal identifying information so for the purpose of allegedly providing prescribed topical medications (i.e., pain creams).
 - Safeguard personal health information and personal identifying information from any unsolicited requests by a person or group.
 - Refuse delivery of unsolicited medications if received in the mail and from an unrecognized pharmacy service.

Be Vigilant

Knowledge of clinical phishing scams will help protect providers from perpetuating prescription fraud and contributing to the accompanying losses that strain an already fragile health care system, impacting both health care providers and payers. Within the VA health care system, Veterans may request to have prescriptions filled at a non-VA pharmacy. Per VHA Handbook 1108.05, VA providers are permitted to write prescriptions for Veterans to be filled in private sector pharmacies, upon request by the Veteran in certain circumstances. This mechanism of necessity may facilitate the schemes used by dishonest compounding pharmacies looking to take advantage of the system. Recognizing the common elements involved in the typical compounding prescription scam can help to prevent additional cases of clinical phishing that prey on the information of Veterans and their providers.

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Helping to achieve safe medication use

THErapy-RELATED RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CVD arising from LABA and LAMA treatment as the number needed to harm (NNTH).

Results show that new initiation of LABA treatment was associated with a 1.50-fold (95% CI, 1.35-1.67; $P < .001$) increased cardiovascular risk; and new LAMA treatment was associated with a 1.52-fold (95% CI, 1.28-1.80; $P < .001$) increased cardiovascular risk. On the other hand, prevalent LABA or LAMA use yielded a 9% to 12% reduction in risk. There was no difference in the risk of CVD between new LABA use and new LAMA use ($P = .93$). The CV risks peaked approximately 30 days after new initiation of LABA or LAMA therapy and trended downwards thereafter, dropping below the baseline risk around 71 to 240 days after starting therapy. The increased risk of CVD with either new LABA or LAMA use persisted in the case-crossover analysis and in comparison with new use of theophylline. The risk of CVD remained significant regardless of patients' CV history and COPD exacerbations. One severe CVD event requiring hospitalization or ER care occurred for every 406 (95%CI, 303-580) new LABA users and 391 (95%CI, 254-725) new LAMA users during the first 30 days of therapy.¹³

As cardiac abnormalities may contribute to the morbidity associated with COPD, better understanding of their potential for development during the initiation of LABA and LAMA treatment can help management strategies and prevent any harmful events. LABA and LAMA use may cause CV events because beta agonists directly stimulate beta receptors while anticholinergics inhibit vagal tone. These effects cause increased sympathetic stimulation on the heart and blood vessels leading to vasoconstriction and ischemia. Similar mechanisms influence the development of tachyarrhythmia. Hypokalemia induced by beta agonists may potentiate arrhythmias, and the accompanying increased heart rate may lend to heart failure.¹⁴⁻¹⁵

Although the study concludes that new use of inhaled LABAs or LAMAs for COPD management is associated with a 1.5-fold increase in the risk for CVD within 30 days of initiating therapy (regardless of past CVD and history of COPD exacerbations), the authors recognize that the study has limitations¹³. Additional considerations that call for caution when interpreting the results of this study include:

- As a retrospective database study, only association and not causation can be inferred from the results of this nested-case control study. The observed association between the prescribed LABAs and LAMAs and the occurrence of CVD may have been due to other factors, although the authors

performed multiple analyses to adjust for confounding. It may not be possible to control for all variables that may influence the development of CVD through statistical analysis. In addition, since existing health records were used, not all pertinent risk factors may have been recorded. In this case, smoking was not available, which could affect findings.

- The authors did not account for smoking in the study because the information was not available. Smoking is an important determinant of COPD and CVD. Recurring toxic effects associated with cigarette smoke can lead to abnormal cell repair, oxidative stress, tissue destruction, impaired gas exchange, vascular remodeling, and systemic inflammation, which may have direct effects on cardiopulmonary interactions and cardiac function.
- COPD and CVD commonly coexist due to shared causal factors (i.e., cigarette smoking and sedentary lifestyle) as well as similar pathogenic mechanisms, such as impaired gas exchange and systemic inflammation. The symptoms of dyspnea and chest tightness are common to both COPD and CVD. Uncontrolled dyspnea and chest tightness could occur as a result of worsening COPD or an underlying CV event. It may be possible that cardiac manifestations of an undiagnosed CV issue (i.e., dyspnea) prompted patients with COPD to seek care, but their complaint of shortness of breath was treated as COPD exacerbation instead. Inappropriate diagnosis of these inextricably intertwined conditions may allow CV symptoms to surface, recur, or persist if not addressed regardless of LABA or LAMA exposure.

Clinicians may wish to consider the following based on the study findings¹³:

- As clinically appropriate, assess and address CV risks or CV disease symptoms before initiating LABAs or LAMAs.
- Advise and/or monitor patients for new CV symptoms, particularly after initiation, in those prescribed LABAs or LAMAs.

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