



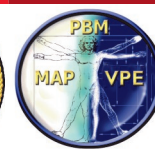
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VA Center for Medication Safety

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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

AVOID USING OPIOID ANALGESICS FOR ACUTE PAIN IN PATIENTS TAKING SUBLINGUAL BUPRENORPHINE

Sublingual buprenorphine/naloxone (Suboxone[®]) or buprenorphine (Subutex[®]) is recommended for the treatment of opioid addiction. However, use of sublingual buprenorphine concomitantly with opioid analgesics may result in complications including:

- **Inadequate pain relief** due to buprenorphine blocking opioid receptors from mu-receptor agonists.
- **Opioid withdrawal symptoms** if the buprenorphine-maintained patient stops buprenorphine to take an opioid analgesic and then restarts buprenorphine.
- **Relapse of opioid addiction or opioid overdose** since typical doses of full mu-receptor agonists may not relieve severe pain, leading to additional and/or illicit opioids for pain control.

RECOMMENDATIONS:

1. Acute pain management (dentistry, surgery, and emergency medicine):

- Check for current buprenorphine use.
- Avoid concomitant opioid use in patients taking buprenorphine.
- Consider other analgesics and discuss with buprenorphine prescriber.

2. Anticipated Pain (e.g., elective surgery, tooth extraction):

Mild pain

- Inform the buprenorphine prescriber prior to surgery.
- Do not prescribe additional opioids.
- Consider nonopioid analgesics such as acetaminophen or NSAIDs.
- Continue the buprenorphine at the same dosing regimen.

Moderate to severe pain

- Refer patient to their buprenorphine prescriber for:
 - Discontinuation of buprenorphine prior to surgery;

- Prescription of short-acting opioids for up to 5 or more days pre-surgery;
- Postoperative tapering of opioids and reinitiation of buprenorphine.

3. Unanticipated Pain (e.g., emergency surgery, major trauma, renal colic, bone fracture):

Mild pain

- Same approach as for anticipated pain; OR
- Consult the buprenorphine prescriber about administration of an equal or higher buprenorphine daily dose divided every 6 to 8 hours for improved analgesic effects.

Moderate to severe pain

- Discontinue buprenorphine.
- Start patient-controlled analgesia (i.e., fentanyl, as high receptor affinity and short duration).
- Avoid high-dose continuous opioid infusions.
- Monitor closely (i.e., ICU).
- Consider regional anesthesia.
- Optimize non-opioid, adjunctive analgesia.
- Consult anesthesiologists or pain specialists.

4. Concomitant Opioid Use:

- Do not give buprenorphine concomitantly with opioids. Severe opioid withdrawal may precipitate.

5. If the patient has been off of buprenorphine for 5 or more days:

- Usual postoperative opioid agents may be used; however, opioid tolerance may necessitate higher doses.
- Refer patient to their buprenorphine prescriber after surgery to taper opioids and restart buprenorphine.



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NEWS YOU CAN USE

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

- Dronedarone (Multaq®) and Risk of Death and Serious CV Events in Patients with Permanent AF - [National PBM Communication](#) - 07/28/2011
- Colistimethate for Injection and Dosing Confusion - [National PBM Bulletin](#) – 07/08/2011
- Recall of Butalbital, APAP, and Caffeine Tablets and Hydrocodone Bitartrate and APAP Tablets – Mislabeling - [National PBM Communication](#) - 06/30/2011
- Churchill Medical Skin-Prep Wipes Recall Due to Bacterial Contamination - [National PBM Communication](#) – 06/17/2011
- SimplyThick Thickening Gel Products Recall and Possible Presence of Bacteria - [National PBM Communication](#) – 06/10/2011
- Simvastatin: Updated Restrictions, Contraindications and Dose Limitations - [National PBM Bulletin](#) – 06/09/2011

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

[Linezolid \(Zyvox®\) - Serious CNS reactions possible when linezolid \(Zyvox®\) is given to patients taking certain psychiatric medications](#)

7/26/2011

Accounts of serotonin syndrome and fatalities due to the concomitant administration of linezolid and a serotonergic psychiatric medication appear in the FDA Adverse Event Reporting System (AERS) database as well as in the literature. This reaction can also develop after discontinuing serotonergic psychiatric medications with long half-lives. Linezolid may inhibit monoamine oxidase A from breaking down serotonin in the brain, leading to toxicity. As a result, healthcare professionals should not prescribe linezolid to patients receiving serotonergic drugs unless benefits outweigh risks, such as in life-threatening cases of vancomycin-resistant *Enterococcus faecium* (VRE) infections or nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

[Methylene Blue - Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications](#)

7/26/2011

FDA concluded that concomitant use of a serotonergic psychiatric medication with methylene blue can cause serotonin syndrome based on reports to the FDA Adverse Event Reporting System (AERS) database as well as in the literature. This reaction can also develop after discontinuing serotonergic psychiatric medications with long half-lives. Methylene blue may inhibit monoamine oxidase A from breaking down serotonin in the brain, thus leading to toxicity. Documented adverse events include: lethargy, confusion, delirium, agitation, aggression, obtundation, coma, myoclonus, expressive aphasia, hypertonia, seizures, and autonomic symptoms, such as pyrexia and elevated blood pressure. Providers should avoid methylene blue use with serotoergic agents unless benefits outweigh risks (i.e., life-threatening cases of methemoglobinemia, ifosfamide-induced encephalopathy, or cyanide poisoning).

[CardioGen-82 - FDA alerts healthcare professionals to stop performing heart scans with CardioGen-82 due to potential for increased radiation exposure in patients](#)

7/26/2011 (**UPDATE FROM 07/15/2011**)

FDA has recommended ceasing use of CardioGen-82 for cardiac positron emission tomography (PET) scans. The manufacturer, Bracco Diagnostics, Inc. has decided to voluntarily recall CardioGen-82 due to:

- Insufficient manufacturing procedures to ensure reliable performance of the generator used to produce the Rb-82 chloride injection and help prevent strontium breakthrough; and
- FDA's ongoing investigation of the procedures used to test for strontium breakthrough at the clinical sites that use CardioGen-82.

Healthcare professionals should consider alternatives to the CardioGen-82 generator when planning nuclear medicine cardiac scans.

[Chantix \(varenicline\) drug label now contains updated efficacy and safety information](#)

7/22/2011 (**UPDATE FROM 06/16/2011**)

The *Dosage and Administration*, *Warnings and Precautions*, *Clinical Studies*, and *Patient Counseling Information* sections of the Chantix product labelling now includes information from three additional clinical trials:

- [Use of Chantix in patients with stable cardiovascular \(CV\) disease](#) - A randomized clinical trial of 700 smokers with CV disease receiving either Chantix 1 mg twice daily or placebo for 12 weeks with follow-up for an additional 40 weeks showed that Chantix helped patients with CV disease quit smoking, and remain abstinent from smoking for up to one year compared to placebo. This trial also demonstrated the association of Chantix with a small, increased risk of certain CV adverse events in this patient population.
- [Information on the use of Chantix in patients with COPD](#) - A randomized clinical trial of Chantix safety and efficacy in 460 patients at least 35 years of age with mild-to-moderate COPD receiving either Chantix 1 mg twice daily or placebo for 12 weeks with follow-up for an additional 40 weeks indicated that Chantix helped COPD patients stop smoking and abstain from smoking for up to one year compared to placebo.
- [Alternative directions for patients to select a quit smoking date after they have already started taking Chantix](#) - A randomized clinical trial in a healthy population of smokers given either Chantix 1 mg twice daily or placebo for 12 weeks with follow-up for an additional 12 weeks and instructed to select a target quit date between Day 8 and Day 35 after starting Chantix treatment demonstrated smoking cessation and abstinence from smoking for as long as 24 weeks compared to placebo. Revised labeling states that patients should start taking Chantix 7 days before their quit date or alternatively, begin Chantix dosing and then quit smoking between Days 8 and 35 of treatment.

[Multaq \(dronedarone\) and increased risk of death and serious cardiovascular adverse events](#)

7/21/2011

Sanofi Aventis conducted "A randomized, double blind, placebo controlled, parallel group trial for assessing the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors" (PALLAS) to evaluate major cardiovascular (CV) events (stroke, systemic arterial embolism, myocardial infarction or CV death); or unplanned CV hospitalization or death from any cause. However, a significant excess of CV events in the Multaq group for both co-primary endpoints, lead to the cessation of the study. Due to preliminary data

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

(continued from page 2)

and ongoing review, FDA has not concluded whether the results of the PALLAS study apply to patients taking Multaq for paroxysmal or persistent atrial fibrillation or atrial flutter, but does not recommend use of Multaq in patients with permanent atrial fibrillation.

[Bisphosphonates - Ongoing safety review of oral osteoporosis drugs \(bisphosphonates\) and potential increased risk of esophageal cancer](#)

7/21/2011

FDA has not concluded that oral bisphosphonate drugs increase the risk of esophageal cancer due to conflicting data. A case series from January 2009 described reports to the FDA of esophageal cancer in patients taking oral bisphosphonates. Other published epidemiological studies evaluated the association between oral bisphosphonates and esophageal cancer with discrepant findings. The two largest published studies used data from the U.K.'s General Practice Research Database (GPRD). FDA continues to review available data regarding oral bisphosphonate drug use and esophageal cancer risk.

[CardioGen-82 - Increased radiation exposure due to undetected strontium breakthrough when using CardioGen-82 for cardiac positron emission tomography \(PET\) scans](#)

7/15/2011

Two patients received more radiation than expected while undergoing cardiac positron emission tomography (PET) scans with rubidium (Rb)-82 chloride injection from CardioGen-82 (manufactured by Bracco Diagnostics, Inc.) according to reports submitted to FDA. The excess radiation originated from strontium isotopes which may have been inadvertently injected into the patients due to a "strontium breakthrough" problem with CardioGen-82 and persisted in the patients' bodies months after their PET scans. FDA assured minimal harm from this exposure but maintains that any unnecessary exposure to radiation remains undesirable. Healthcare professionals should follow the prescribing information to determine rubidium and strontium contents using an ionization chamber-type dose calibrator prior to the administration of Rb-82 chloride injection to any patients.

[Tamiflu - Important safety changes to the influenza drug Tamiflu \(oseltamivir phosphate\) for oral suspension](#)

7/11/2011

FDA and Genentech instituted product safety changes to the influenza drug Tamiflu (oseltamivir phosphate) for oral suspension in order to reduce medication errors resulting from prescribing and dosing confusion. Changes to Tamiflu oral suspension and the product label include:

- New concentration = 6 mg/mL (change from former concentration of 12 mg/mL).
- New oral dosing device measurement units of volume (milliliters – mL) instead of weight (milligrams - mg).
- Revisions in the dosing table to accommodate the new 6 mg/mL concentration.
- Updated container labels and carton packaging.
- Modified compounding instructions for preparation of a 6 mg/mL oral suspension from Tamiflu capsules in the event that the commercially manufactured oral suspension becomes unavailable.

The 12 mg/mL product has no quality issues and remains usable through its expiration date, but will no longer be marketed after current supplies run out. Genentech established a voluntary Take Back Program for wholesale buyers, distributors and pharmacies to remove the 12 mg/mL product from the marketplace in order to reduce the potential for error while both strengths remain in circulation.

[Valproate - Children born to mothers who took Valproate products while pregnant may have impaired cognitive development](#)

6/30/2011

Published epidemiological studies show that exposure to the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) in utero results in lower cognitive test scores in children when compared to exposure to another antiepileptic drug or to no antiepileptic drugs during pregnancy. Factors that remain unknown include the long-term effect on cognitive development and the effect on cognitive development when fetal exposure is less than the full duration of pregnancy. Valproate products belong to Pregnancy Category D due to increased risk of major malformations, including neural tube defects, when used during pregnancy. Healthcare professionals should weigh the benefits and risks of valproate when prescribing this drug to women of childbearing age and should consider alternative medications with a lower risk of adverse birth outcomes.

[ESAs - New dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents \(ESAs\) in chronic kidney disease](#)

6/24/2011

FDA has made new recommendations for **more conservative dosing** of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) due to controlled trials indicating increased risks of cardiovascular events, stroke and death in this patient population when administered ESAs to target a hemoglobin level above 11 g/dL. Revisions to the *Boxed Warning*, *Warnings and Precautions*, and *Dosage and Administration* sections of the labels for the ESAs include this new information:

For patients with CKD not on dialysis:

- Consider initiating ESA treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
 - The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion; and
 - Reducing the risk of alloimmunization and/or other red blood cell transfusion-related risks is a goal.
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.

For patients with CKD on dialysis:

- Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.

Current labeling has removed the previous recommendation that ESAs dosing should achieve and maintain hemoglobin levels within 10 to 12 g/dL in CKD patients.

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

(continued from page 3)

[Chantix - Chantix \(varenicline\) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease](#)

6/16/2011

FDA reviewed a randomized, double-blind, placebo-controlled clinical trial designed to assess the efficacy and safety of Chantix for smoking cessation in 700 patients aged 35 to 75 years with stable, documented cardiovascular (CV) disease. Certain CV adverse events (angina pectoris, nonfatal myocardial infarction, need for coronary revascularization, and new diagnosis of peripheral vascular disease or admission for a procedure for the treatment of peripheral vascular disease) occurred in more patients treated with Chantix than patients treated with placebo, although smoking represents an independent and major risk factor for CV disease. The trial was not designed to have statistical power to detect differences between the arms on the safety endpoints. FDA continues to evaluate the CV safety of Chantix and requires that the manufacturer conduct a large, combined analysis (meta-analysis) of randomized, placebo-controlled trials. New product labeling will address this updated risk information in the *Warnings and Precautions* section as well as the patient Medication Guide.

[Actos - Update to ongoing safety review of Actos \(pioglitazone\) and increased risk of bladder cancer](#)

6/15/2011

Results from a five-year analysis showed no greater risk of bladder cancer with pioglitazone use overall, but the risk of bladder cancer increased in patients with the longest exposure to pioglitazone and in those exposed to the highest cumulative dose of pioglitazone. Another epidemiologic study conducted in France indicated a higher risk of bladder cancer with pioglitazone use, and because of this data, France suspended the use of pioglitazone while Germany proposed not starting pioglitazone in new patients. Based on this information, FDA recommends 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. The benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence.*

FDA will continue to evaluate data from an ongoing ten-year epidemiological study conducted by the drug manufacturer (Takeda) in patients with diabetes who belong to Kaiser Permanente Northern California (KPNC) health plan.

[Risperdal and Requip - Medication errors resulting from confusion between risperidone \(Risperdal\) and ropinirole \(Requip\)](#)

6/13/2011

Look-Alike/Sound-Alike confusion between risperidone (Risperdal) and ropinirole (Requip) and vice versa lead to 226 actual errors in administration of the wrong medication resulting in 5 patient hospitalizations. One of the cases from outside the United States reported a patient death due to administration of Risperdal instead of Requip for one month before a healthcare worker noticed the error and restarted Requip without titration. Factors contributing to the confusion between the two products include:

- Brand and generic nomenclature similarity,
- Labels and carton packaging resemblance (i.e., similar font size and type, layout, and color),
- Illegible handwriting on prescriptions, and
- Likeness in product characteristics (drug strengths, dosage forms, and dosing intervals).

[5-ARIs - 5-alpha reductase inhibitors \(5-ARIs\) may increase the risk of a more serious form of prostate cancer](#)

6/9/2011

FDA reviewed two large, randomized controlled trials that evaluated the reduction in the risk of prostate cancer in men at least 50 years of age—the Prostate Cancer Prevention Trial (PCPT) which evaluated daily use of finasteride 5 mg versus placebo for 7 years and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial which evaluated daily use of dutasteride 0.5 mg versus placebo for 4 years. Results from both trials depicted:

- a decreased incidence of lower risk forms of prostate cancer leading to an overall reduction in prostate cancer diagnoses.
- an increased incidence of high-grade prostate cancer with finasteride and dutasteride treatment.

Revisions to the *Warnings and Precautions* section of the labels for the 5-ARI class of drugs address the increased risk of high-grade prostate cancer.

[Simvastatin - New restrictions, contraindications, and dose limitations for Zocor \(simvastatin\) to reduce the risk of muscle injury](#)

6/8/2011

FDA's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial and other data lead to new recommendations limiting the use of simvastatin 80 mg due to an increased risk of muscle damage. Higher risk for myopathy and rhabdomyolysis with simvastatin 80 mg were associated with:

- Older age;
- Female gender;
- Genetic variations in regulating simvastatin uptake into the liver that may increase plasma concentration of simvastatin and the risk of myopathy;
- Concomitant use of a calcium channel blocker (risk of myopathy doubled); and
- Initial 12 months of simvastatin 80 mg treatment.

Recommendations state that providers should:

- Use simvastatin 80 mg only in patients maintained on this dose for 12 months or more without evidence of muscle toxicity.
- Not initiate simvastatin 80 mg in new patients, including patients already taking lower doses of simvastatin without optimal benefit.
- Be aware of drug interactions between simvastatin 80 mg and certain medications that may increase the risk of muscle injury; dosage limitations, adjustments, and/or use of an alternative agent may be necessary.

[Angiotensin Receptor Blockers - No increase in risk of cancer with certain blood pressure drugs](#)

6/2/2011

FDA conducted a trial-level meta-analysis of 31 clinical trials randomizing approximately 156,000 patients to an angiotensin receptor blocker (ARB) treatment or a non-ARB treatment. This meta-analysis did not show an increased risk of cancer in patients using an ARB. The results from three additional published studies also do not associate any increased risk of cancer to ARB use.

Getting the most from our safety surveillance

TROPICAMIDE OPHTHALMIC SOLUTION USP 1% AND ATROPINE SULFATE OPHTHALMIC SOLUTION USP 1%: POTENTIAL LOOK-ALIKE CONFUSION

One facility reported an actual look-alike medication error due to similar packaging of ophthalmic agents which resulted in a patient receiving Atropine Sulfate Ophthalmic Solution USP 1% instead of Tropicamide Ophthalmic Solution USP 1%. Atropine and tropicamide are antimuscarinic ophthalmic agents that produce mydriasis and cycloplegia during procedures of the eye (examinations and/or surgery). Atropine has a longer half-life than tropicamide, resulting in prolonged dilation and blurry vision when compared to the shorter-acting tropicamide. Both ophthalmic agents do not appear as pairs of confusion on any look-alike/sound-alike (LA/SA) medication lists.

Atropine Sulfate Ophthalmic Solution USP 1% does not usually reside in clinic floor stock. Reports state that an eye surgeon transported

the Atropine Sulfate Ophthalmic Solution USP 1% to the eye clinic to “save money and reuse”. The bottle became mixed with other medications that technicians store and secure in the evenings. A label displaying the date of the medication obstructed the name of the agent. This, along with the uniform color coding of ophthalmic products (anti-infectives use tan caps and labeling, mydriatics and cycloplegics use red caps and labeling, miotics use green, etc.) potentiated the look-alike error because of similar logos, fonts, package shapes/sizes, and color combinations (See Figure 1). No harm to the patient was documented. Staff reported this error to the Pharmacy Chief.

REFERENCES

1. Field Information Report.
2. USP Quality Review: Use Caution, Avoid Confusion. Rockville, MD: USP Center for the Advancement of Patient Safety. 79; 2004 April.

PROVIDER RECOMMENDATIONS:



Figure 1. Potential Look-Alike Confusion Due to Similar Product Packaging - Tropicamide Ophthalmic Solution USP 1% and Atropine Sulfate Ophthalmic Solution USP 1%

- Providers should be aware of the potential for look-alike confusion between Tropicamide Ophthalmic Solution USP 1% and Atropine Sulfate Ophthalmic Solution USP 1% due to similar packaging and label color.
- Providers should carefully check the name on the vial when either Tropicamide Ophthalmic Solution USP 1% and Atropine Sulfate Ophthalmic Solution USP 1% is ordered and/or administered.
- Pharmacy should ensure that a method is in place to return unused stock of Tropicamide Ophthalmic Solution USP 1% and Atropine Sulfate Ophthalmic Solution USP 1% to designated pharmacy area(s) when not ordered for a particular patient.
- Pharmacy should review their stock for Tropicamide Ophthalmic Solution USP 1% and Atropine Sulfate Ophthalmic Solution USP 1% and ensure that a method is in place to distinguish between the two agents in order to avoid future look-alike confusion (i.e., warning stickers/labels).

MUES & MUETS

New link to VAMedSAFE Portal for launching MUET:
https://medora.va.gov/vaadrs/medsafe_portal/index.asp

CURRENT MUET INITIATIVES

- ESAs (ongoing discussion on revisions needed based on recent FDA guidance on dosing and elimination of target Hgb 10 – 12 g/dL)
- Glyburide
- Pseudoephedrine

FUTURE PLANNED MUET INITIATIVES

- Dabigatran

CURRENT MUE INITIATIVES

- Amiodarone
- Fracture/Osteoporosis Initiative (FrOstI)