Pharmacy Benefits Management-Medical Advisory Panel

E_z-Minutes

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Inside this issue:

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Rofecoxib Removed from Market

On September 30th, the manufacturer of rofecoxib (Vioxx®) issued a press release announcing the immediate voluntary withdrawal of their product from worldwide markets based upon data from a three-year, randomized, prospective, placebo-controlled clinical trial called APPROVe (Adenomatous Polyp Prevention on VIOXX). In the APPROVe trial, 2,600 patients with a history of colorectal adenomas were enrolled and randomized to rofecoxib 25 mg or placebo for 3 years. Although the exact rate or number of cardiovascular events (e.g. heart attack and stroke) has not been made available, patients randomized to rofecoxib are reported to have experienced an increased relative risk for cardiovascular events compared to those on placebo. The increased rate of these types of events was observed after 18 months of treatment with rofecoxib. As a result, effective immediately, VA will discontinue all prescribing and dispensing of VIOXX.

PBM-MAP has written several documents related to this topic including information for VA providers on other treatment options, titled "Rofecoxib Guidance." In addition, documents titled "FAQ Physicians", "Dear Healthcare Professional", "Physician Notification Letter", and "Pharmacist Notification" are available at the following web site: *http://vaww.pbm.med.va.gov/pbm/vioxx.htm*. Be sure to check out the patient letter template for use by the VISN and/or facility level clinical staff. It can be modified to communicate to patients the need to contact their provider. Sites are requested to send each patient a letter and include a phone number for patients to contact the Pharmacy Service with questions. Please be sure to advise patients to return any portion(s) of the unused medication to the VA Pharmacy Service the next time they visit the VA.

It is unclear if, and to what degree, other Cox-2 inhibitors will have similar problems. Recent information about valdecoxib raises concerns that there may be a class effect, though this remains uncertain at this time. Further information is expected as these agents undergo scrutiny by the medical and pharmaceutical community. The PBM is actively investigating their databases to deterimine if a risk for cardiovascular events exists for the other available COX-2 agents. So, stay tuned!

Recent National PBM Reviews Postings on Web Site

Criteria for Use
http://www.vapbm.org/PBM/criteria.htm
Linezolid, quinupristin-dalfopristin and daptomycin
Biologics in Psoriasis
Fondaparinux
High dose vitamin supplementation for AMD
Gabapentin

Criteria for Nonformulary Use
http://www.vapbm.org/PBM/criteria.htm

Treatment Guidelines
http://www.vapbm.org/PBM/treatment.htm

Drug Class Reviews
http://www.vapbm.org/PBM/reviews.htm
Angiotensin II Receptor Antagonists

Drug Monographs
http://www.vapbm.org/PBM/drugmonograph.htm
Miglustat (Zavesca®)
Fondaparinux (Arixtra®) Addendum
Eplereonone (Inspra™)
Olanzapine IM (Zyprexa IM®)

Frequently Asked Questions
http://www.vapbm.org/PBM/faq.htm
Reversal and Prove-It Trials

Safety Reports—NEW!
http://www.vapbm.org/PBM/safety.htm
Statin-fibrate

Therapeutic Interchange Guidance
(Formerly Patient and/or Provider Information Letters)
http://www.vapbm.org/PBM/tig.htm

Apomorphine (Apokyn®) Distribution

Apomorphine is a direct-acting dopamine agonist with strong D_1 and D_2 dopamine receptor stimulating properties. Apomorphine is approved for the treatment of acute, intermittent hypomobility, "off" episodes (end-of-dose wearing off and unpredictable "on/off" episodes) associated with advanced Parkinson's Disease. Because of the unique nature of this agent and its place in therapy, a procedure for distribution has been developed and soon will be posted on the PBM web page. Please click on the following address to locate the document and learn more details. http://www.vapbm.org/PBM/menu.asp

New Molecular Entities Review

- **Miglustat (Zavesca®)**-Not added to VA National Formulary (VANF) or VISN Formularies
- **Oxaliplatin® Update**-Added to VANF and VISN Formularies
- **Bevacizumab (Avastin®)**-Not added to VANF and VISN Formularies
- **Eplerenone (Inspra™)-**Not added to VANF or VISN Formularies
- **Fondaparinux (Arixtra®) -**Not added to VANF but allow VISNs to add.
- **Apomorpine (Apokyn ®)-**Added to VANF restricted to Neurology Services
- **Cincalet (Sensipar®) -**Not added to VANF or VISN Formularies
- **Olanzapine IM (Zyprexa IM®)-**Added to the VANF, restricted to criteria

QUESTION FROM THE FIELD: *"How are the PBM-MAP, VA-DoD criteria for use and treatment guidelines disseminated to front-line physician providers? Are they sent to the Chief Medical Officers in each VISN and then they are responsible for distribution through Chiefs of Staff?"*

ANSWER: **Criteria for use developed by the VA PBM-MAP are disseminated to the field in the following manner: Notification is sent to the VA Medical Advisory Panel, VISN Formulary Leaders, and VA Clinical Pharmacists that the final document has been posted on the PBM intERnet and intRAnet Web sites (www.vapbm.org and http://vaww.pbm.med.va.gov). A request is made that the notification be forwarded to interested individuals. Please note, documents will usually be posted 2 weeks post meeting in order to finalize the minutes. The opportunity to comment on draft documents occur when they are forwarded to the field through the VISN Formulary Leaders, Pharmacy Chiefs, CMOP Directors, and Chief Medical Officers.**

The VA/DoD Clinical Practice Guidelines (CPGs) are disseminated through the Office of Quality and Performance with notification to the Chief Medical Officers and Quality Medical Officers in the VISN and to Nursing. Facility Directors, Chiefs of Staff, and VISN Directors are notified of completion of the CPGs through the Publications Office. At the culmination of the concurrence process, there is a letter that is signed by the USH which announces the guidelines and directs people to the Office of Quality and Performance Web site www.oqp.med.va.gov where the documents are posted.

Thanks for your question Christine!

PBM Projects in Progress:
Combination therapy for prostatism
COX-2 and CV Risks

Criteria for Use:
clopidrogrel/ASA in CABG/PVD
cinacalcet

Drug Class Review:
Sedative Hypnotics

Drug Monographs:
cilostazol
duloxetine

Nefazodone and Hepatotoxicity

On June 14, 2004, Bristol-Meyers-Squibb ceased distribution of nefazodone (Serzone).[1] Nefazodone was removed from the market in the United Kingdom and Canada in 2003 due to its association with severe hepatoxicity. Public Citizen filed suit against the FDA to force the withdrawal of nefazodone in the U.S. in March 2004. Nefazodone is still available from generic manufacturers.

The PBM-Medical Advisory Panel (MAP) addressed the question of whether nefazodone should remain on the VA National Formulary. Since 2000, the number of patients in the VA taking nefazodone has decreased 71% and the number of patients started on nefazodone has declined 94%. Below is a summary of the data:

First, nefazodone's labeling requires inclusion of a black box warning with the following information.[2]

- **The reported rate of hepatic failure in the U.S. is ~1 case resulting in death or transplant per 250,000 – 300,000 patient-years of treatment. This is ~3 – 4 times the estimated background rate of liver failure.**
- **There is no evidence that the use of nefazodone by patients with pre-existing liver disease increases their probability of developing liver failure, although it does complicate monitoring.**
- **The time to liver injury for the reported cases resulting in death or transplant ranged from 2 weeks to 6 months after nefazodone initiation.**
- **Periodic liver function tests (LFTs) have not been proven to prevent serious injury, although baseline transaminases are recommended.**
- **Patients presenting with clinical signs or symptoms of liver dysfunction should have their liver transaminases measured. Patients whose ALT or AST values are increased 3 times the upper limit of normal should have nefazodone stopped and considered to be at increased risk for liver injury should it be restarted.**

Second, data from the Spanish Pharmacovigilance System found the estimated incidence of hepatotoxicity to be 29 cases compared to 1.3 – 2.6 cases per 100,000 patient-years associated with nefazodone and serotonin reuptake inhibitors respectively.[3]

Thirdly, the WHO's analysis of its spontaneous case reports of suspected adverse reactions found that hepatic injury, attributed to nefazodone, occurred in a statistically significant unexpected number of reports; the only antidepressant to do so.[4] The other antidepressants included were citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine.

Lastly, a review of the case reports appearing in the literature suggests the following:

- **There is no clear dose-hepatotoxic relationship as the dose of nefazodone ranged from 100 mg to 600 mg per day.**
- **Women may be at greater risk since 31 of the 41 cases (76%) were in women; including 68.8% of 32 cases reported in one series from Canada.[5] However, these crude numbers are not adjusted for exposure by gender.**
- **Patients of all ages are vulnerable since cases have ranged in age from 16 to 73 years of age.**
- **The time frame from the start of nefazodone to the onset of symptoms ranged from 10 days to 2 years. The Canadian series found that 88% of 32 cases occurred within 6 months.**
- **Universal initial patient symptoms included fatigue and jaundice.[5] Nausea and/or vomiting, abdominal tenderness, decreased appetite, arthralgias, pruritis, dark urine, and clay-like stools were reported in some cases.**
- **Liver enzymes, including alkaline phosphatase, were routinely elevated.**

Summary:

There are no set guidelines as to when or how frequently to monitor LFTs in patients taking nefazodone. It is recommended that baseline LFTs tests be performed and that they be repeated regularly in the first 6 months of treatment and then every 6 months thereafter.[6] Patients should also be educated and reminded regularly of the signs and symptoms of hepatotoxicity such as fatigue, nausea, vomiting, and jaundice. Nefazodone should be discontinued if there is any suspicion of hepatotoxicity.

Conclusion:

Concerned that patients who are refractory to other antidepressants would not have nefazodone as an option, the low incidence of hepatotoxicity, and the already declining use (particularly new patients), the MAP voted to keep nefazodone on the VA National Formulary.

Submitted by Todd Semla, MS, PharmD, BCPS, FCCP

1. The Pink Sheet. May 24, 2004.
2. Serzone (nefazodone) package insert, 2004.
3. Garcia-Pando AC, de Ipozo JG, Sanchez AS, et al. Hepatotoxicity associated wit the new antidepressants. J Clin Psychiatry 2002; 63:135-7.
4. Spigset O, Hagg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug effects. Int Clin Psychopharmacology 2003; 18:157-161.
5. Stewart DE. Hepatic adverse reactions associated with nefazodone. Can J Psychiatry 2002; 47:375-377.
6. Lucena MI, Carvajal A, Andrade RJ, et al. Antidepressant-induced hepatotoxicity. Expert Opin Drug Safety 2003; 2(3): 249-62.

National Drug File (NDF) Guidelines for Drug-Drug Interaction Entry:

Please refer to a previous issue of the EZ-Minutes http://www.vapbm.org/ezminutes/Ez-MinutesVol2Iss1Jan-March04.pdf for a more detailed article describing the NDF guidelines. Below is a list of the current interactions that have been added to the NDF since 8-1-04. Interactions to be discussed in the near future include erythromycin, cinacalcet, and apomorphine. To learn more about the NDF drug-drug interactions, be sure to click on the following link: http://vapbm.org/natform/National%20Drug%20File%20Support%20Group.pdf

INGREDIENT 1	INGREDIENT 2	SEVERITY
aspirin	methotrexate	critical
amiodarone	indinavir	critical
amiodarone	atazanavir	critical
amiodarone	ritonavir	critical
amiodarone	saquinavir	critical
cranberry juice	warfarin	critical
alatrofloxacin	mesoridazine	critical
atazanavir	rifapentine	critical
atazanavir	tenofovir	critical
digitalis	rabeprazole	critical
eplerenone	erythromycin	critical
eplerenone	nelfinavir	critical
eplerenone	saquinavir	critical
eplerenone	verapamil	critical
ergotamine	fosamprenavir	critical
oxandrolone	warfarin	critical

INGREDIENT 1	INGREDIENT	SEVERITY
almotriptan	ketoconazole	significant
almotriptan	itraconazole	significant
eletriptan	ketoconazole	significant
eletriptan	itraconazole	significant
ethinyl estradiol	secobarbital	significant
butabarbital	ethinyl estradiol	significant
ethinyl estradiol	primidone	significant
ethinyl estradiol	mephobarbital	significant
amobarbital	ethinyl estradiol	significant
estradiol	phenobarbital	significant
estradiol	secobarbital	significant
butabarbital	estradiol	significant
estradiol	primidone	significant
estradiol	mephobarbital	significant
amobarbital	estradiol	significant
cimetidine	quinidine	significant
doxazosin	sildenafil	significant
fluvastatin	nelfinavir	significant
fluvoxamine	warfarin	significant
irinotecan	phenytoin	significant
phenelzine	tryptophan	significant
prazosin	sildenafil	significant
propoxyphene	ritonavir	significant
sildenafil	tamsulosin	significant
sildenafil	terazosin	significant
sulfamethoxazole	warfarin	significant
terazosin	vardenafil	significant
tranylcypromine	tryptophan	significant

"Treatment of Dyslipidemia in the High Risk Patient"

Many thanks to Cathy Kelley, Pharm. D, C. Bernie Good, MD, MPH, FACP and Rick Downs, MD, FACP for their outstanding job as the presenting faculty. The remaining rebroadcast dates of the program (all ET and on VAKN Channel 1) are Oct. 14th, 3PM; and Oct. 18th, 12 noon. Continuing education credit for ACCME, ANCC and ACPE is available for viewing the initial broadcast, rebroadcast programs or a tape of the broadcast until November 18, 2004. As a reminder, a post-test is required to receive pharmacy continuing education. Ask your respective site teleconference coordinator (see web site) http://vaww.lrn.va.gov/satcoord/default.asp for the sign-in sheet, course form evaluation and post-test. If any problems or have further questions, please contact Rick Lussier at Richard.Lussier@lrn.va.gov.

VAMedSAFE

The following programs are still available for your immediate viewing. Check it out!

- **"How to Enter an Allergy or Adverse Drug Event (ADE)."**
  http://www.vapbm.org/vamedsafe/How%20To%20Enter%20an%20Allergy%20or%20Adverse%20Drug%20.ppt.
- **"ADR Frequently Asked Questions"**
  http://vapbm.org/vamedsafe/Adverse%20Drug%20Reaction.pdf
- **VHA's Adverse Drug Event Reporting Program**
  http://vapbm.org/Reporting%20Program.pdf

Evaluation and Validation of Look Alike and Sound Alike Medication Error within the VA System Using Computerized Prescription Data: A Pilot Project

By: Marie Sales, Pharm.D.

PURPOSE: A pilot project was conducted based on concerns expressed from the field regarding medication errors that have occurred in ordering prescriptions for certain agents with similar drug names. The data represented in this pilot project are based on prescription data only. This does not confirm administration or patient receipt of the drug(s).

OBJECTIVES: The objectives of this pilot project were:

1. To evaluate and compare the number and percent of look alike (LA) and sound alike (SA) medication errors using the following pairs of agents with orthographic and phonetic similarities in names:
   A) Oxycontin and Oxybutynin
   B) Quinine and Quinidine
   C) Hydralazine and Hydroxyzine
   D) Hydrochlorothiazide (HCTZ) and HCTZ/ Triamterene
   E) Simvastatin and Simethicone
2. To compare LA and SA medication errors in regards to switching patterns to determine:
   - "Potential" error
   - "Real" error
3. To examine diagnosis codes in patients receiving the selected LA and SA drug pairs using automated ICD-9 codes and perform limited medical chart review at sites to validate/verify true indication for receiving these agents.

METHODS: A retrospective national database review was conducted using the Pharmacy Benefits Management version 3.0 prescription database (PBMv3.0) to examine drug utilization. Veterans receiving oxycontin, oxybutynin, quinidine, quinine, hydralazine, hydroxyzine, HCTZ, HCTZ/triamterene, simvastatin, and simethicone were included. The following were evaluated: new prescriptions of the aforementioned agents (index dates October 1, 2001 – September 30, 2003); drug switching patterns from one agent to its respective LA and SA pair after the start of the new prescription; number and percent correct versus incorrect users (medication errors); and number and percent "potential" error compared to "real" error based on switching patterns.

Data for patients in the "potential error" group and the "real error" group for each drug pair determined using the above methods were used in merging with ICD-9 codes from the Austin Automation Center (AAC) to assess actual incorrect use, correct use, and unconfirmed error. As limitations occur in using automated diagnoses codes (i.e., lack of problem list and medical history information), a limited medical chart review at selected sites was carried out to confirm true incorrect use compared to correct use as ascertained by merging of the databases.

RESULTS: Preliminary results from the pilot database review show correct use ranging from 91.8%-99.9% for the aforementioned LA/SA drug pairs. Out of the small percentage of incorrect use, potential error occurred within a range of .1%-5.5% among the drug pairs; and real error occurred within a range of .03%-.97% among the drug pairs. Using the "potential" error and "real" error results from the initial database review, a validation was performed by merging with automated ICD-9 codes. These results identified that the most incorrect use occurred with the Simvastatin/Simethicone pari (approx 70-80%) and the least incorrect use occurred with Quinidine/Quinine pair (approx 0%-37.5%). See Figures 1-4 on page 6. The limited chart review occurred at 2 sites and used a small sample of patients. This uncovered actual correct use in patients categorized in the "potential" error and "real" error groups. Full chart review of all patients identified at the sites continues in order to complete the validation.

SUMMARY: Results from this project will provide insight into the extent of LA/SA medication errors within the VA system. The project will assist in the development of a tool that can evaluate system-wide medication errors of LA/SA origin. Information from this project may possibly assist in meeting the JCAHO requirements for patient safety with respect to evaluating the percentage of medication errors.

Figures 1-4. (SEE PAGE 6) Percent Incorrect vs. Percent Correct Use Confirmed in Real Error and Potential Error Groups Detected from Pilot Database Review*.

Preliminary results from the pilot database review showed incorrect use ranging from 0.1% - 8.2% among the drug pairs. This incorrect use was further broken down into "Real Error" and "Potential Error". "Real Error" is defined by a drug switching pattern of ABA and "Potential Error" is defined by an AB switching pattern without reverting to A. "A" represents the intended or correct drug and "B" represents the LA/SA counterpart possibly prescribed in error for "A". Patient data from the "potential error" and "real error" groups determined from the pilot database review were merged with automated ICD-9 codes to validate error rate. Validation consisted of identifying use as "Incorrect Use" (error confirmed by diagnosis code), "Unconfirmed Error" (absence of a diagnosis code related to use of drug A or B), and "Correct Use" (presence of diagnosis code that correlates with use of agent A or B). N=number of patients in each error group detected by pilot database review. Full chart review of all patients continues in order to complete the validation as limitations occur with using computerized ICD-9 codes (i.e., lack of problem list or medical history information).

**THESE DATA REPRESENT PRESCRIPTION DATA ONLY. THIS DOES NOT CONFIRM ADMINISTRATION OR PATIENT RECEIPT OF DRUG.*

Figure 1.

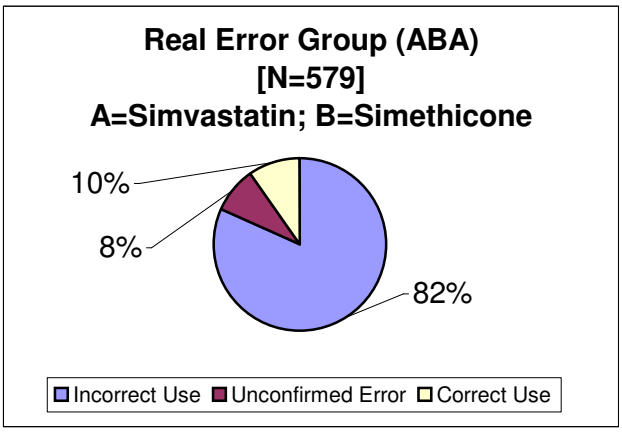


Figure 2.

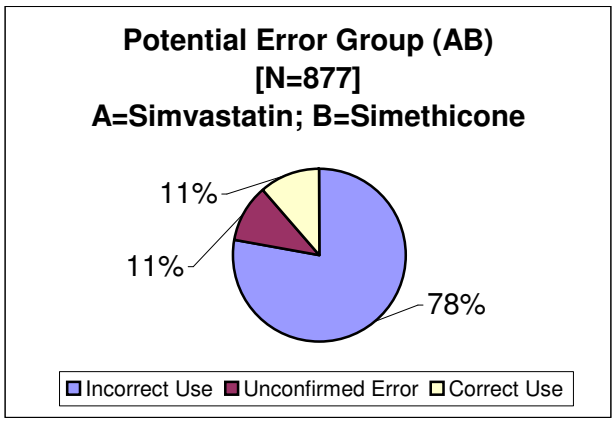


Figure 3.

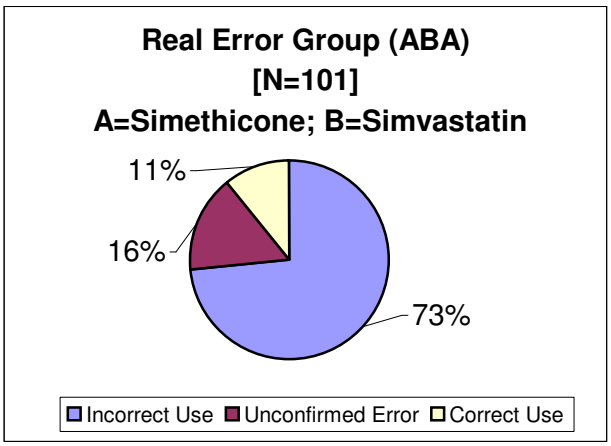
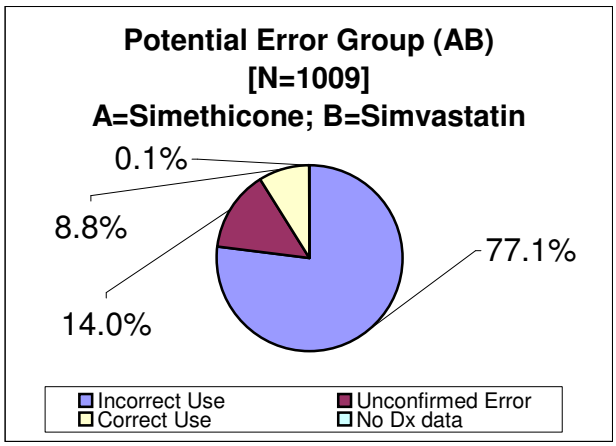


Figure 4.



The results of the PBM-MAP on-line Education Survey are in! READ ON!

Even though the Olympics were recently finished in Greece, that same spirit of competition was still fresh in everyone's mind and very much alive at the recent PBM-MAP joint meeting held in Chicago during October 16th - 18th. Olympic medals (minus the laurels) were awarded at the meeting to the 3 top VISNs completing the most survey. Congratulations to VISN 6 for completing the most survey. Present at the meeting was Steve Coombs, RPh to accept the gold medal. A close second was VISN 12 with Ken Siehr, RPH, MPA accepting the silver medal. The bronze medal was awarded to VISN 7 with Joette S. Lowe, Pharm.D. present to accept the medal. Congratulations Winners! Of the topics available to choose from, the highest percentage of votes were for the following topics: various anemias (62%), DM (55%), CHF (49%) and COPD (42%). Of the topics that were written in, the top 3 choices were hepatitis C, PTSD, and HRT. Other topics included multiple times were drug-drug interaction, PVD, Alzheimers/dementia, and osteoporosis.

Thanks to all VISNs for their participation and input!

Do you have any additional questions, comments or want to submit an article to the next PBM-MAP E_z - Minutes? Please e-mail: Editor: Janet Dailey, PharmD at vhapbh Dailey, JH OR Co-Editor: Pete Glassman, at peter.glassman@med.va.gov.