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New FDA Warning for Simvastatin and Amiodarone by Huong Le

Simvastatin (brand name Zocor) is an HMG-CoA reductase inhibitor “statin” drug indicated for various types of dyslipidemias and reduction in risks of cardiovascular events and coronary heart disease mortality. The dosing range is from 5 to 80mg daily with the recommended usual starting dose of 20 to 40mg per day.¹

Amiodarone (brand name Cordarone) is an antiarrhythmic medication indicated for life-threatening ventricular arrhythmias. Due to its toxicity profile, amiodarone should only be administered by experienced professionals.²

Both amiodarone and simvastatin are metabolized by Cytochrome P450 isoform 3A4 (CYP3A4), and amiodarone is also an inhibitor of CYP3A4. This may cause major drug-drug interactions when given together and healthcare professionals are strongly advised to carefully weigh the risks and benefits prior to starting patients on those two medications concomitantly. Two serious side effects of statin drugs, including simvastatin, are myopathy and rhabdomyolysis. When patients are taking both simvastatin and amiodarone, the augmented side effects of rhabdomyolysis could be life-threatening. Prescribers should also be aware of combination medications that contains simvastatin including Vytorin (ezetimibe/simvastatin) and Simcor (niacin extended-release/simvastatin).³

Additionally, the prescribing information for simvastatin was revised in 2002 to include the warning of increased risk of rhabdomyolysis for patients also on amiodarone. However, the U.S. Food and Drug Administration continued to receive serious reports of rhabdomyolysis involving these two medications taken together. On August 8, 2008, the FDA released a reinforced notice of the increased risks of using amiodarone with simvastatin doses higher than 20mg daily. Patients who are taking amiodarone and more than 20mg daily of simvastatin are at a greater risk for rhabdomyolysis, which may lead to kidney failure and death. However, no deaths due to this drug-drug interaction have been reported for simvastatin. Like other statins, the risk of rhabdomyolysis is dose related. Signs and symptoms of myopathy and rhabdomyolysis such as unexplained muscle pain, spasm or weakness, should be monitored for patients on simvastatin. For patients taking amiodarone, healthcare professionals are encouraged to use other statin alternatives due to less marked effects of rhabdomyolysis.³

In summary, prescribers should take into consideration the high risk for myopathy and rhabdomyolysis before starting amiodarone patients on simvastatin doses higher than 20mg.

References:

1. Zocor Website. Available at www.zocor.com. Accessed August 11, 2008.
2. Wyeth Pharmaceuticals Website. <http://www.wyeth.com/content/showlabeling.asp?id=93>. Accessed August 12, 2008.
3. U.S. Food and Drug Administration Website. Simvastatin, Ezetimibe/Simvastatin, Niacin extended-release/Simvastatin used with Amiodarone. Written August 8, 2008. Available at http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm. Accessed August 11, 2008.

Inside This Issue:

Recent Controversies with Chantix (varenicline)	Page 2
PhRMA Updates Code on Interactions with Healthcare Professionals	Page 3
ACE Consensus Statement on the Management of Pre-Diabetes	Page 4
New Guidelines for PSA Testing	Page 5
Fatal Drug Errors Involving Alcohol and/or Street Drugs	Page 6

Recent controversies with Chantix® (varenicline) by Bridget Follmer

Chantix® (varenicline) has been approved by the FDA as a prescription drug since May 2006 for use as an adjunct to the management of smoking cessation in patients with nicotine withdrawal.¹ Chantix® works as a partial nicotine agonist that both stimulates and blocks the alpha-4-beta-2 nicotinic acetylcholine receptors. By stimulating the alpha-4-beta-2 nicotinic acetylcholine receptor, a modest amount of mesolimbic dopamine is produced, diminishing nicotine cravings and withdrawal symptoms. Chantix® also acts by occupying, and therefore blocking the receptor.¹

Recently the FDA has issued warnings concerning side effects that are associated with Chantix® therapy. The subject was first addressed by the FDA in November 2007, when the public was informed that serious neuropsychiatric symptoms could result from Chantix® therapy. In February 2008, the FDA released a public health advisory stating that new safety information was added to the patient information sheet for Chantix®.² Post marketing evaluations have shown that Chantix® use can lead to bizarre behavior, suicidal ideation, and suicide. The FDA has started a review of adverse event data for Chantix®, and as of February 2008, there have been 491 reports of suicidal thoughts; and 39 completed suicides in patients currently taking Chantix®.³



In May 2008, an article published by the Institute for Safe Medical Practices (ISMP), stated that Chantix® therapy had been associated with serious accidents and falls, potential lethal cardiac rhythm disturbances, severe skin reactions, acute myocardial infarction, seizures, diabetes, psychosis, aggression, suicide, dizziness, loss of consciousness, and abnormal spasms and movements.^{3,4} Investigations are still being done to determine whether Chantix® is causing these adverse effects or if nicotine withdrawal or nicotine use could be the reason. Smoking has been shown to increase the risk of heart disease, stroke, and diabetes while nicotine withdrawal can lead to depression, insomnia, irritability, anxiety, difficulty concentrating, restlessness, and an exacerbation of underlying psychiatric disorders.³

These recent reports have caused safety concerns for people who operate aircraft, trains, buses and other vehicles, or in any settings where a lapse in alertness or motor control could lead to massive, serious injury.⁴ The Federal Aviation Administration has banned the use of Chantix® for persons working in these areas of employment. Because of these new reports, the Federal Motor Carrier Safety Administration (FMSCA) also prohibits it's operators to use of any prescription drugs (including Chantix®) that can potentially alter the safe operation of a commercial motor vehicle.³ The ISMP recommends that doctors use caution when Chantix® therapy is prescribed to consider other adjuncts to smoking cessation. Healthcare providers should speak to their patients about all alternative therapies.

Any adverse effects related to Chantix® should be reported to the FDA. In the U.S., call the FDA MedWatch program at 1-800-FDA-1088. The MedWatch form is also available online at www.fda.gov/medwatch/getforms.htm.

References:

1. Clinical Pharmacology web site. Available at: <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed August 13, 2008.
 2. Drugs and suicidality. Pharmacist's Letter/Prescriber's Letter 2008; 24(3): 240313.
 3. Smoking cessation drug therapy: an update. Pharmacist's Letter/Prescriber's Letter 2008; 24(7): 240706.
- Moore TJ, Cohen MR, Furberg CD. Strong safety signal seen for new varenicline risks. The Institute for Safe Medication Practices. Available at <http://www.ismp.org/docs/vareniclinestudy.asp>. Accessed on August 8, 2008.

PhRMA Updates its Code on Interactions with Healthcare Professionals

By Tina Jennings



On June 10, 2008, the Pharmaceutical Research and Manufacturers of America (PhRMA) released its updated version of Code on Interactions with Healthcare Professionals. The PhRMA represents researched-based pharmaceutical and biotechnology companies in the United States. This voluntary code sets forth new recommendations about how pharmaceutical and biotechnology companies should interact with healthcare professionals with respect to marketing their products.

PhRMA states, "In interacting with the medical community, we are committed to following the highest ethical standards as well as all legal requirements. We are also concerned that our interactions with healthcare professionals not be perceived as inappropriate by patients or the public at large. This Code is to reinforce our intention that our interactions with healthcare professionals are professional exchanges designed to benefit patients and to enhance the practice of medicine. The Code is based on the principle that a healthcare professional's care of patients should be based, and should be perceived as being based, solely on each patient's medical needs and the healthcare professional's medical knowledge and experience."

Major points made in the Code include:

1. **Informational Presentations by Pharmaceutical Company Representatives and Accompanying Meals:** Meals offered in connection with informational presentations made by field representatives should only be offered to in-office or in-hospital settings. Meals should be modest, not part of recreation or entertainment, and are provided in a manner conducive to informational communication.
 2. **Prohibition on Entertainment and Recreation:** Companies should never offer tickets to events, vacations, or give away sporting equipment to any healthcare professional who is not a salaried employee of the company, regardless of value of the item or whether the healthcare professional is a speaker or consultant.
 3. **Prohibition of Non-educational and Practice Related Items:** Non-educational items (pens, highlighters, mugs, note pads, and other "reminder" items), even if handed out with patient or physician education materials, are no longer acceptable. Also, items such as flower arrangements, artwork, CDs, gift certificates or tickets should also not be offered. It is appropriate, however, to provide product samples.
 4. **Educational Items:** These items are deemed appropriate if they offer educational value to the patient or healthcare professional and their value is less than \$100. Educational items include things such as anatomical models, posters, or DVDs.
 5. **Pharmaceutical Company Support for Continuing Medical Education (CME) or Third-Party Educational or Professional Meetings:** It is appropriate for companies to sponsor or support CMEs/training programs/conferences as long as the following is done: financial support should not be given directly to any one healthcare professional to cover registration, but the financial support can be used to reduce the overall fee for all attendees. Industries are not allowed to compensate for travel related expenses, provide meals, entertainment, compensate wages, etc.
 6. **Healthcare Professionals Who are Members of Committees that Set Formularies or Develop Clinical Practice Guidelines:** Companies should require healthcare providers who are members of committees that set formularies or develop practice guidelines to disclose to the committee the existence and nature of his or her relationship to the company. This disclosure should extend at least 2 years beyond the date of termination of any speaking or consulting arrangement. It would be advisable to the healthcare professional to recuse themselves from decisions relating to the medicine that they were speaking for.
- Scholarships and Educational Funds:** It is appropriate for companies to provide financial assistance to medical students, residents, fellows, and other healthcare professionals in training to attend selected educational conferences as long as the individual who will receive the funds is selected by the academic or training institution.

More detailed information and clarifications concerning the updated Code on Interactions with Healthcare Professionals can be found at www.phrma.org.

Reference:

PhRMA Web site. Available at http://www.phrma.org/code_on_interactions_with_healthcare_professionals/. Accessed August 12, 2008.

New Guidelines for PSA Testing by Bridget McCullough

Prostate cancer is the leading cancer and the second most common cause of cancer deaths in men in the United States. One in every six men will be diagnosed with prostate cancer at some point in their lifetime. From 2000 through 2004, the average age of death from prostate cancer was 80 years. The incidence rate for African American men is significantly higher than white men, leading to a mortality rate which is twice as high. Prostate cancer is also more common in older men and those with a family history of prostate cancer.

Two types of screening tests for prostate cancer include the digital rectal examination (DRE), and measurement of prostate specific antigen (PSA), which is the more sensitive of the two. Currently, a PSA level of 4.0 µg/L is considered the screening cut-off. Cases of early cancer may be missed with this cut-point, but by lowering the level there would be a significant increase in false positives.

According to the U.S. Preventive Services Task Force (USPSTF) PSA screening for prostate cancer every 4 years may be just as beneficial as screening yearly, given that PSA screening would reduce mortality. When taking into account the harms and benefits of PSA screening, USPSTF suggests that evidence is inadequate to determine improvement in health outcomes from screening in men less than 75 years of age. As a result, USPSTF gives no recommendation on PSA screening in this population; however physicians should still discuss the potential harms and benefits of PSA screening. For men 75 years of age and older or those with a life expectancy less than 10 years, the benefit of screening and treating prostate cancer is little to none. Therefore, USPSTF recommends no PSA screening in this population.

Detecting prostate cancer by screening may potentially cause more harm. It is questionable whether or not screening is appropriate when there are such uncertainties in the benefit of treatment. Treatment can cause complications that may not have arisen from the cancer if left alone, including erectile dysfunction, urinary incontinence, bowel dysfunction and death. The screening process alone may potentially cause difficulties such as pain and discomfort as well as psychological effects if given a false-positive result.

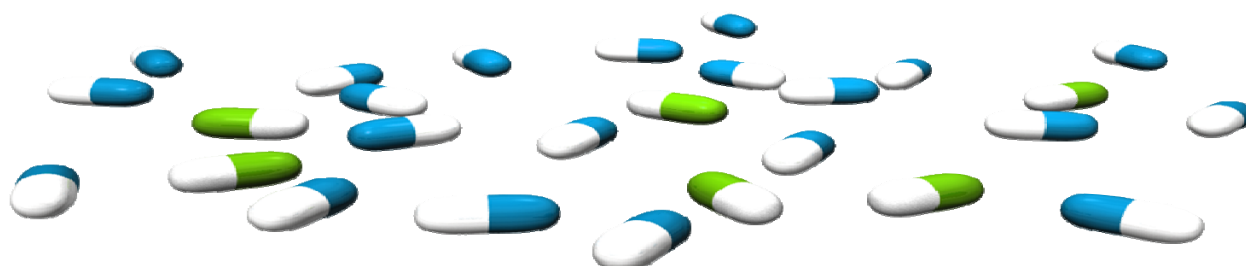
In summary, the USPSTF concludes that there is insufficient evidence to make a recommendation for PSA screening in men less than 75 years of age. The USPSTF recommends not screening for prostate cancer in those age 75 and older.

Reference:

1. U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*. 2008;149:185-191

Look for information on the following current topics in upcoming issues of *Health Matters*

- Links between ezitimibe and cancer?
- Effects of DTCA on Canadian prescribing
- 20 drugs hit FDA's side-effect probe





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Fatal Drug Errors Involving Alcohol and/or Street Drugs By Stephanie Morgan

With the untimely death of actor Heath Ledger, the dangers of combining prescription medications with illicit drugs and alcohol have made front page news. A study published in the Archives of Internal Medicine reviewed death certificates and found that fatal medication errors (FMEs) at home involving alcohol and/or street drugs are rapidly increasing.¹ In fact, more years of potential life are lost from fatal medication errors than from every other major accident type aside from motor vehicle traffic accidents.¹ The authors were not able to identify any one cause for this steep increase in deaths, but many factors may contribute.

The authors examined death certificates from 1983 through 2004 and included death certificates that listed a fatal medication error anywhere on the death certificate. The fatal medication error deaths were divided into four categories based on whether the death occurred at home and whether or not alcohol and/or street drugs were involved in the deaths. FMEs did not include deaths that resulted after the proper administration and dosage of a medication, suicides or homicides by poisoning.

The largest increase in FMEs over the past 20 years has occurred with individuals in their homes. This indicates a need for better management of patients' home medications and represents an opportunity for healthcare professionals to be involved in teaching patients about safety and proper use of medications, including instructions about what to do in case of a missed dose.²

There was noted to be a very large increase in FMEs in the home in the past 20 years when alcohol and/or drugs were also consumed. This is clear evidence of the need to screen patients for alcohol and/or drug use prior to recommending, prescribing or dispensing medications with known dangerous interactions.

Further studies addressing the specific medications contributing to fatal medication errors, as well as the specific substances of abuse that are causing the most fatalities, would be very beneficial in directing patient counseling and therapy management.

1. Phillips DP, Barker GE, Eguchi MM. A steep increase in domestic fatal medication errors with use of alcohol and/or street drugs. [Arch Intern Med.](#) 2008 Jul 28;168(14):1561-6.

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To serve the health care professional community by providing evidence-based, timely and unbiased information in an effort to contribute to comprehensive patient-based care. We also strive to provide excellent training and foundational skills to prepare our students to competently meet the challenges of providing such information throughout their careers.

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