

▶ PRADAXA—LEARN WHAT IS NEW ABOUT THIS MEDICATION JUST APPROVED IN OCTOBER, 2010 1

▶ TAKE A LOOK AT THE LATEST VITAMIN D RECOMMENDATIONS..... 2

▶ SAFETY SIGNALS IN HEALTH CARE - A LOOK AT THE AERS DATABASE 3

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LECOM *Point*

WELCOME TO LECOM POINT, ISSUE 1 VOLUME 1. A DRUG INFORMATION SOURCE THAT IS DIRECT AND TO THE POINT

Welcome to LECOM CDIR!

The LECOM Center for Drug Information and Research has great plans for the future. The Center was established with a mission to provide students, faculty, preceptors, and the public with timely, independent, best-evidence analysis and commentary on pharmaceuticals and healthcare policy as it relates to pharmaceuticals. Our aim is to take advan-

tage of our virtual world and develop an online drug resource accessible to anyone via the Internet.

On a more personal note, the CDIR will also act as a direct resource for our medical, pharmacy and dental providers, faculty and preceptors who need answers to specific drug information questions.

The CDIR [website](#) is being up-

dated with new content added frequently. Users can sign up for our Twitter updates and RSS feeds. As we work to develop our virtual presence, the CDIR team will provide this quarterly newsletter as a service to the entire LECOM family.

Feel free to contact us with questions or comments at cdir@lecom.edu.

PRADAXA[®] – WHAT'S NEW

Pradaxa[®] (dabigatran) is an anticoagulant approved by the FDA on October 19, 2010. It is indicated to reduce stroke and clot risk in patients with non-valvular atrial fibrillation.

Dabigatran is the first oral direct thrombin inhibitor. Inhibiting thrombin prevents conversion of fibrinogen to fibrin in the clotting cascade, thus preventing thrombus formation. Unlike warfarin, the INR is not used to monitor dabigatran.¹

This new anticoagulant was approved based on the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.² This noninferiority trial showed that dabigatran was “not unacceptably worse” than warfarin. A new drug can be approved on noninferiority trials and is NOT required to show superiority to drugs already on the market.³

The RE-LY trial did conclude that in patients with nonvalvular atrial fibrillation, dabigatran 150mg twice daily, compared to warfarin, was associated with lower rates of stroke, and systemic embolism but similar rates of major hemorrhage.



Continued from Page 1—Pradaxa

The number needed to treat (NNT) gives a measure of outcome effectiveness to help compare dabigatran and warfarin. In the RE-LY trial, 83 patients would need to be treated with dabigatran in order to prevent a stroke or systemic embolism within a 2 year period in one patient.² This is a reasonable NNT for preventing serious outcomes like these, but the time period and cost may be disproportionate to the benefit. The monthly drug cost for a patient on dabigatran would be approximately \$270 vs \$21 for warfarin. Even including weekly INR draws, the total monthly cost for warfarin is about \$110.⁴ Over two years, that's almost \$6500 vs just over \$2600 for warfarin.

The RE-LY trial had some limitations, including the amount of time patients

spent within therapeutic INR range (64%) and dropout rates. Patients taking dabigatran had a higher dropout rate as compared to patients taking warfarin, most likely due to the increased dyspepsia in the dabigatran group.⁵ It was estimated that in order to have a stroke rate as low as those receiving dabigatran within the trial, warfarin patients would have to be in therapeutic range 79% of the time.⁵ This was not achieved within the RE-LY study.

Dabigatran has a favorable adverse effect profile, with most discontinuations due to dyspepsia (21%). The NNT in order to prevent any one bleeding event is 33 patients within a year's time.

Dabigatran is subject to a Risk Evaluation Mitigation Strategy (REMS) to inform patients about risks associated with dabigatran while ensuring proper

use of this new medication. A Medication Guide will be dispensed with every new dabigatran prescription and Boehringer Ingelheim Pharmaceuticals Inc. will submit REMS Assessments to the FDA at 18 months, 3 years and 7 years from the date of approval.

Dabigatran was recently recommended as an alternative to warfarin for afib management in an update to the joint guideline from the American Heart Association and American College of Cardiovascular Foundation.⁶ However, tight control of INR with warfarin may be sufficient to produce similar efficacy to dabigatran at a lower cost with less incidence of GI side effects.

References:

1. Pradaxa (dabigatran) Professional Product Label. At: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf. Accessed: November 2, 2010.
2. Connolly SJ, Ezekowitz MB, Phil D, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009. 361(12):1139-51.
3. Fleming TR, Powers JH. Issues in noninferiority trials: the evidence in community-acquired pneumonia. *Clin Infect Dis*. 2008. 47(3):108-20.
4. Cost data for INR lab draws via Sarasota Memorial Hospital, Sarasota, FL. Accessed by phone February 21, 2011.
5. Gage BF. Can we rely on RE-LY? *N Engl J Med*. 2009. 361(12):1200-01.
6. Wann et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran): American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. <http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1>. Accessed Feb 22, 2011.

NEW RECOMMENDATIONS FOR VITAMIN D

Vitamin D has been receiving much attention with many adults discovering they are deficient in this critical, fat-soluble vitamin. This is of main concern due to the pivotal role vitamin D plays in bone growth and development.^{1,2} Additionally, vitamin D has been evaluated for use in cancer, diabetes, hypertension, immunity, and muscle strength.³⁻⁶ These studies are interesting, but don't yet provide adequate evidence for the use of vitamin D beyond bone growth and development.

The Institute of Medicine recently established new recommendations for increased vitamin D intake. The new recommended dietary allowance (RDA) for adults <70 years old is 600 IU/day. For

adults over 70, the RDA is now 800 IU/day.⁷ These recommendations are established only for the prevention of rickets and osteomalacia.⁷

Many healthcare providers are recommending vitamin D doses up to 2000 IU/day. This can confuse patients since these doses are much higher than the RDA. Concrete dosing recommendations are difficult to establish because the recommendations given by the Institute of Medicine are for average daily intake sufficient to meet nutrient requirements and prevent deficiency.⁷ Doses greater than the RDA are often necessary to raise vitamin D in those with low levels.

What recommendations can you safely make as a

healthcare provider?

There are several methods to increase vitamin D levels such as dietary modification or increased sunlight exposure, but the most reliable method remains through supplementation. Vitamin D is available in the United States in two forms, D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 is approximately one-third as effective as D3 in raising blood concentrations of vitamin D.⁸ In general, dosage recommendations up to 2000 IU/day in adults are considered safe and do not require monitoring of blood levels.⁷ When choosing a dose, keep in mind that 100 IU/day will raise levels by approximately 1ng/mL over the span of a few months.⁷ Routine moni-

toring is not necessary if using doses below 2000 IU/day, but is a good idea when prescribing higher doses.⁷

For patients taking daily doses greater than 2000 IU/day or with concern regarding deficiency or possible toxicity, monitoring is important. Vitamin D levels between 30 and 50 ng/mL are generally considered to be appropriate, though there is potential for adverse effects at levels above 50 ng/mL.⁷ Toxicity is rare at doses below 10,000 IU/day, but the Institute of Medicine has determined that prolonged levels over 50 ng/mL should be avoided as they may be linked to complications.⁷

Continued on Page 3

Continued from Page 2

Despite being rare at normal doses, it is important to monitor for signs and symptoms of toxicity. Common signs of vitamin D toxicity include hypercalcemia, impaired renal function, and calcification of the soft tissues.⁹ Advise patients to contact you with any health changes after starting vitamin D.

References:

1. Wagner CL, Greer FR, Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008; 122(5): 1142-1152.
2. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporos Int* 2007 Jun;18(6):811-8.
3. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007 Jun;85(6):1586-91.
4. Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007 Jun;92(6):2017-29.
5. Zhu K, Austin N, Devine A, Bruce D, Prince RL. A randomized controlled trial of the effects of vitamin D on muscle strength and weakness in older women with vitamin d deficiency. *J Am Geriatr Soc* 2010;58(11):2063-8.
6. Hewison M. Vitamin d and the immune system: new perspective on an old theme. *Endocrinol Metab Clin North Am* 2010;39(2):365-79.
7. Dietary Reference Intakes for Calcium and Vitamin D. Institute of Medicine. November 30, 2010. <http://www.iom.edu/~media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf>. Accessed February 4, 2011.
8. O'Connell Mary B, Vondracek Sheryl F, "Chapter 93. Osteoporosis and Other Metabolic Bone Diseases" (Chapter). Joseph T. DiPiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey: *Pharmacotherapy: A Pathophysiologic Approach*, 7e: <http://0www.accesspharmacy.com.polar.onu.edu/content.aspx?aID=3210726>.

INTRODUCTION TO THE AERS DATABASE

CDIR will highlight important safety signals released from the Food and Drug Administration (FDA) and the Institute for Safe Medication Practices (ISMP). Both the FDA and ISMP monitor the Adverse Event Reporting System (AERS) Database quarterly for potential safety signals.

What is the AERS database?

The AERS database is designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products.¹ The FDA and ISMP use the AERS database to monitor for new adverse events and medication errors that occur with marketed products. The AERS database is dependent on voluntary case reporting by healthcare providers and consumers, and mandatory reporting from drug companies.

What is a "safety signal"?

The term "safety signal" commonly

means there is sufficient evidence to justify an alert to the public and scientific community, and to warrant additional investigation to assess a causal relationship and calculate an incidence. For example, ISMP screens domestic case reports of adverse events that are classified as "serious", or events that resulted in death, permanent disability, a birth defect, required hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences.² Also, ISMP uses statistical techniques for signal detection such as the Proportional Reporting Ratio (PRR). The PRR evaluates the possibility that an adverse event might have been reported by chance, and adjusts for the likelihood that a drug that accrued more reports would have greater exposure to chance events.^{2,3} Many of the safety signals identified by the FDA have resulted in labeling changes, from drug interactions to black box warnings.

With regard to reporting, the last evaluated quarter from ISMP² noted the following:

"With more than 800,000 active physicians in the United States and more than 900 million prescriptions dispensed in the second quarter, a total of 425 direct reports to the FDA suggest that physicians are essentially not participating... Meanwhile, the nation's 270,000 pharmacists reported 1,382 serious adverse events directly to the FDA in the second quarter and another 952 cases that became expedited reports from drug manufacturers. Despite fewer numbers and less direct patient exposure than physicians, pharmacists were much more likely to report adverse events directly to the FDA."

CDIR will be reporting important safety signals released from the FDA and ISMP. We encourage all healthcare providers and students to continue to submit adverse event reports to the FDA. Online voluntary reporting forms can be located on the FDA's [MedWatch](#) website.

References:

1. Food and Drug Administration. Adverse Event Reporting System. August 20, 2009. (Accessed February 2, 2011 at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.)
2. Moore TJ, Cohen MR, and Furberg CD. Institute for Safe Medication Practices. Quarter Watch: 2010 Quarter 2. January 27, 2011. (Accessed February 2, 2011 at <http://freepdfhosting.com/3bdc3adea1.pdf>.)
3. Evans SJ, Waller PC, and Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* 2001 Oct-Nov;10(6):483-6.

Overtime....

Two New Drugs

The FDA has recently approved two new drugs, roflumilast (Daliresp), a PDE-4 inhibitor for COPD, and belimumab (Benlysta), the first new drug for lupus in over 50 years. Read more about them on our website!

Unapproved Cough, Cold, Allergy Products: FDA Prompts Removal From Market

The FDA is removing unapproved prescription cough, cold, and allergy drug products from the U.S. market. These unapproved medications have not been evaluated by the FDA for safety, effectiveness, and quality. Patients may be at greater risk for adverse events or side effects when using these products than when using FDA-approved prescription drugs or drugs that are appropriately marketed over-the-counter (OTC).

Many health care providers are unaware of the unapproved

status of these drugs and have continued to unknowingly prescribe them because the drugs' labels do not disclose that they lack FDA approval.

Cough, cold, and allergy drug products are used to relieve symptoms associated with the common cold or upper respiratory allergies. These symptoms may include coughing, chest congestion, nasal congestion, itchy eyes, and sneezing. Some cough, cold, and allergy products may be purchased OTC, while others require a prescription. A [list](#) of unapproved prescription cough, cold, and allergy drug products FDA intends to remove from the market is available on their website.

Patients who believe they are taking an unapproved prescription product should contact their health care provider immediately to discuss alternatives. Healthcare professionals and patients are encouraged to report adverse events, side effects, or product quality problems related to the use of these products to the FDA's MedWatch Program.



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Lake Erie College of Osteopathic Medicine School of Pharmacy includes campuses in Erie, Pa and Bradenton, Fl. Consistent with LECOM's core value of creating student-centered education, two distinct learning pathways are offered for the Pharm.D. degree providing students the option of choosing a pathway most suited to their learning needs. In Erie, Pa, an accelerated three-year pathway is offered enabling students to complete the Pharm.D degree in three calendar years; in Bradenton, Fla, a traditional four-year pathway is offered. Both curricula offer the same spectrum of didactic courses, credit hours, and experiential education and experiences. The full array of supporting services exists at both campuses. Physical facilities, at each campus, are state-of-the art and of sufficient volume to meet all educational and administrative functions.

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