



## **Family Medicine Clinical Pharmacy Forum Vol. 3, Issue 3 (May/June 2007)**

*Family Medicine Clinical Pharmacy Forum is a brief bi-monthly publication from the Family Medicine clinical pharmacists distributed to faculty and residents of the Department of Family Medicine. Our intent is to provide timely information on broad-based issues of pharmacotherapy, as well as regulatory and practiced-based issues affecting you as a prescriber. If you have suggestions for things you would like to see, please contact us.*

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### **Rimonabant**

Rimonabant (Acomplia) is a selective endocannabinoid receptor antagonist under investigation for the treatment of obesity. It works by blocking endogenous cannabinoid binding to neuronal CB1 receptors. Activation of these receptors by endogenous cannabinoids increases appetite. Rimonabant 20 mg/d was associated with significant mean weight loss (-6.7 kg), reduction in waist circumference (-5.8 cm), increase in HDL (+10.0%), and reduction in triglycerides (-13.0%) in a 12-month study of 1036 obese patients published in the New England Journal of Medicine (NEJM 2005;353:2121-34).

Rimonabant has been available in Europe since the middle of 2006. The company submitted it for approval to the FDA in April 2005, but at this point has only received an “approvable letter” from the FDA, meaning that the agency believes it *can* be approved pending results of further study. One concern may be an increased incidence of depression (2.9% vs 0.6%) observed in trials with the drug; also, the long-term effects of interfering with the endocannabinoid system which regulates pleasure, relaxation, and pain tolerance, are unknown. A summer 2007 decision appears likely.

### **New Drug Warnings**

#### **Antidepressants**

On May 2, the FDA notified healthcare professionals that the makers of ALL antidepressant medications need to update the existing black box warning on the

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prescribing information to include warnings about the increased risks of suicidal thinking and behavior in young adults aged 18 to 24 years during the first one to two months of treatment. This change follows similar labeling changes made in 2005 that warned of a suicidality risk in children and adolescents. The new labeling changes stem from further post-marketing surveillance studies that have revealed a slight, but consistent, increase in suicidality for young adult patients taking antidepressants. Available data were not sufficient to exclude any single medication from the increased risk. The risk did not appear to increase in adults older than 24, and those aged 65 and older actually had a decreased risk.

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html>

### Ketek

FDA and Sanofi-Aventis notified healthcare professionals of revisions to the prescribing information, including a BOXED WARNING and a new Patient Medication Guide, for the antibiotic Ketek. Two of the three previously approved indications, acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis, were removed from the prescribing information because the balance of benefits and risks no longer support approval of the drug for these indications. Ketek will remain on the market for the treatment of community acquired pneumonia of mild to moderate severity. In addition, warnings were strengthened for hepatotoxicity (liver injury), loss of consciousness, and visual disturbances.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#Ketek>

### Erythropoiesis-stimulating Agents

FDA notified healthcare professionals of new safety information for erythropoiesis-stimulating agents (ESAs) Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa). Four new studies in patients with cancer found a higher chance of serious and life-threatening side effects or death with the use of ESAs. These research studies were evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA. FDA believes these new concerns apply to all ESAs and is re-evaluating how to safely use this product class. FDA and Amgen, the manufacturer of Aranesp, Epogen and Procrit, have changed the full prescribing information for these drugs to include a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#ESA>

## **Drug Withdrawals**

### Zelnorm

FDA notified healthcare professionals and patients that Novartis has agreed to discontinue marketing Zelnorm, a drug used for the short-term treatment of women with

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irritable bowel syndrome with constipation and for patients younger than 65 years of age with chronic constipation. FDA analysis of safety data pooled from 29 clinical trials involving over 18,000 patients showed an excess number of serious cardiovascular adverse events, including angina, heart attacks, and stroke, in patients taking Zelnorm compared to patients given placebo.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#Zelnorm>

### Pergolide

FDA notified healthcare professionals and patients that companies that manufacture and distribute pergolide have agreed to withdraw the drug from the market. Pergolide is a dopamine agonist (DA) used with levodopa and carbidopa to manage the signs and symptoms of Parkinson's disease. Results of two new studies showed that some patients with Parkinson's disease treated with pergolide had serious damage to their heart valves when compared to patients who did not receive the drug. These two studies confirm earlier studies that also describe this problem.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#Pergolide>

### **Bisphosphonates and Increased Risk of A-fib?**

A once-**yearly** infusion of intravenous zoledronic acid (Zometa) was recently studied for the treatment of osteoporosis in 3889 patients in a double-blind, randomized, placebo-controlled trial. The primary end point was new vertebral fracture and hip fracture. After 36 months, zoledronic acid was found to significantly reduce the risk of vertebral fracture by 70% (absolute event rate: 3.3% in zoledronic acid group vs 10.9% in placebo group) and by 41% for hip fracture (absolute event rate: 1.4% in zoledronic acid group vs 2.5% in placebo group). Interestingly, new onset arrhythmia occurred more often in the zoledronic acid group (6.9% vs 5.3%;  $P=0.003$ ). The majority of the excess risk came from new onset atrial fibrillation (1.3% zoledronic acid vs 0.5% placebo;  $P<0.001$ ). The majority of these events occurred more than 30 days after the infusion and could not be attributed to early, transient hypocalcemia. Fortunately, the increased rate of atrial fibrillation did not translate into an increased risk of death from cardiovascular causes.

In the same issue of the Journal, a research letter reports the results of a retrospective examination of the Fracture Intervention Trial (FIT) with alendronate. In this study, there was a trend toward a higher incidence of atrial fibrillation in the alendronate group (1.5% vs 1.0%;  $P=0.07$ ) compared to placebo.

Currently, no studies exist establishing the biologic mechanisms that might link bisphosphonate therapy to atrial fibrillation or arrhythmia; however, a causal relationship should be given serious consideration. Further post-marketing surveillance with bisphosphonates is currently ongoing.

(N Engl J Med 2007;356:1809-22)

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### **Combination Therapy in COPD**

Results of the TORCH trial were published in the Feb 22 issue of the New England Journal of Medicine. This study compared salmeterol 50 mcg/fluticasone 500 mcg BID vs placebo, salmeterol alone, or fluticasone alone in 6112 patients with COPD. Albuterol was available for rescue and ipatropium was also permitted. The primary endpoint was time to death from any cause by 3 years. At the end of 3 years, the proportions of deaths from any cause were 12.6% in the combination group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. As compared with placebo, the hazard ratio for death in the combination therapy group was 0.825 (95% CI, 0.681-1.002; P=0.052). The annual rate of COPD exacerbations in the combination therapy group was 0.85 (95% CI, 0.80-0.90), as compared to 1.13 (95% CI, 1.07-1.20) for placebo. The authors conclude that monotherapy with corticosteroids in COPD should not be advocated, monotherapy with long-acting bronchodilator appears safe, and combination therapy offers no advantage on survival. Exacerbations were reduced in the combination group; however, this may be offset by the higher incidence of pneumonia observed in the groups receiving inhaled corticosteroids.

(N Engl J Med 2007;356:775-89)

### **What Dose of ASA is Best?**

More evidence that lower doses of aspirin are just as effective in preventing cardiovascular events as higher doses has come from a new systematic review of the literature published in the May 9, 2007 issue of the *Journal of the American Medical Association*. The authors reviewed evidence from 11 prospective studies (8 RCTs and 3 observational trials) to examine the effect of different aspirin dosages for CVD prevention. The preponderance of evidence from these trials supports the fact that dosages greater than 75-81 mg/d do not enhance efficacy and are associated with higher risk for bleeding events. However, the authors do caution that interpatient variability in antiplatelet response has been noted for over 40 years, and that their data do not preclude the possibility that additional research could reveal that specific groups or subsets of patients may require higher doses to fully inhibit platelet activity.

(JAMA 2007;297:2018-24)

### **Updated Endocarditis Prophylaxis Guidelines from AHA**

Antibiotic prophylaxis to prevent endocarditis is required in fewer circumstances now, according to newly updated guidelines released from The American Heart Association. Major changes to note are that the following patients no longer need SBE prophylaxis for dental procedures:

- Mitral valve prolapse

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- Rheumatic heart disease
- Bicuspid valve disease
- Calcified aortic stenosis
- Atrial or ventricular septal defect
- Hypertrophic cardiomyopathy

SBE prophylaxis is recommended for the following patients:

<b>Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is recommended</b>			
Prosthetic cardiac valve			
Previous IE			
Congenital heart disease (CHD)*			
<ul style="list-style-type: none"> <li>• Unrepaired cyanotic CHD, including palliative shunts and conduits</li> <li>• Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure+</li> <li>• Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</li> </ul>			
Cardiac transplantation recipients who develop cardiac valvulopathy			
<b>Regimens for dental procedure</b>			
Regimen: Single dose 30 to 60 min before procedure			
<b>Situation</b>	<b>Agent</b>	<b>Adults</b>	<b>Children</b>
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin-oral	Cephalexin	2 g	50 mg/kg
	OR Clindamycin	600 mg	20 mg/kg
	OR Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
	OR Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

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<http://www.circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095>