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American Academy of Pediatrics Recommendations for Children with High Cholesterol by Christina Nguyen

On July 1, 2008, the American Academy of Pediatrics (AAP) released a new policy statement regarding cholesterol screening and treatment recommendations for pediatric patients. The updated version, "Lipid Screening and Cardiovascular Health in Childhood," will replace the 1998 "Cholesterol in Childhood" report. This new report stresses the importance of the prevention of cardiovascular disease (CVD) through early screening, dietary guidelines, increasing physical activity, and the usage of pharmacologic agents with indications for treating dyslipidemic children.¹

Coronary heart disease is the number one cause of death in the United States.^{1,2} Risk factors may be present and/or may start developing at a young age; thus, pediatricians should begin a lifelong approach to prevent CVD in their patients. The increase in childhood obesity requires pediatricians and other health care professionals to be well-informed of the risk factors for CVD and to apply the changes recommended by the American Academy of Pediatrics.¹ These recommendations are as follows:

- Children and adolescents should be screened if they have a family history of dyslipidemia or premature CVD (≤ 55 years of age for men and ≤ 65 years of age for women). Screening is also recommended in children without a family history if they have a BMI $\geq 85^{\text{th}}$ percentile, hypertension, diabetes mellitus, or are exposed to cigarette smoke. These children should be first screened at 2 years of age, but no later than 10 years of age. Currently there is no available noninvasive method to screen children and a fasting lipid profile is recommended. Children with values within normal ranges should be tested again within three to five years.¹
- Children who are overweight or obese with high triglyceride levels or low HDL levels should focus primarily on weight management. These pediatric patients should seek nutritional counseling and increase physical activity. US Department of Agriculture dietary guidelines recommend that children (2 years or older) and adolescents have a balanced caloric intake with increased consumption of fruits, vegetables, fish, whole grains and low-fat dairy products.¹
- Pharmacologic interventions are recommended for pediatric patients 8 years or older after family history, risk factors, and triglyceride concentrations are thoroughly assessed. Indications for drug therapy would include:
 - LDL concentrations above 190 mg/dL despite diet therapy
 - Other risk factors present such as obesity, hypertension, or family history of premature CVD and LDL concentrations over 160 mg/dL despite diet therapy.
 - Although initial LDL concentration goals should be less than 160 mg/dL, children with a family history of CVD and other risk factors should be treated more aggressively to lower their LDL concentration to 110 mg/dL or less.¹
 - Diabetes mellitus with LDL concentration above 130 mg/dL.
 - Therapy should be implemented in children younger than 8 years of age only if there is an LDL concentration greater than 500 mg/dl

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Inside This Issue:

AAP Recommendations for Children with High Cholesterol	Page 1
Recent Concerns of Bioequivalence Issues in Generic Wellbutrin	Page 2
New Black Box Warning for Fluoroquinolones	Page 3
Incidence of Angioedema when Initiating ACE Inhibitors	Page 4
Pharmaceutical Industry Lobbying Issues	Page 5

Wellbutrin XL vs. Generic Bupropion: Concerns of Bioequivalence? by Lyle Dixson

Bupropion is an antidepressant used to treat Major Depressive Disorder (MDD), thought to work through inhibiting the reuptake of norepinephrine and dopamine. According to the Food and Drug Administration (FDA), some patients switching from Wellbutrin XL to Teva's AB-rated extended release bupropion formulation (Budeprion XL 300 mg) have reported a loss of antidepressant effect, new onset of side effects or worsening of existing side effects. A total of 85 reports were noted during the first half of 2007, the same time period in which about 1 million prescriptions per month were dispensed for extended-release formulations of bupropion. Approximately 40% of those were filled with Teva's product, but it is unclear how many of these prescriptions represented a switch from the brand name product and how many were for the initiation of therapy.¹

The approval of Teva's bupropion XL product was based on studies showing that there were no significant differences in the rate and extent of absorption as measured by the plasma concentrations of the 150 mg strengths of the generic and brand-name products. To satisfy the FDA's criteria for bioequivalence, the generic product must show that the area under the drug plasma concentration over time curve (AUC) and the average maximum concentration (C_{max}) fall within the 90% confidence interval of the same concentration of the brand product. The differences reported with Teva's product were well within these limits.



There is a difference in the amount of time required to reach the maximum plasma concentration (T_{max}). Teva's product reaches T_{max} in 2-3 hours whereas the Wellbutrin product reaches T_{max} in 5-6 hours. However, this is not a required criteria for the approval of the generic drug.¹

An alternative factor which could lead to a recurrence of depression is the natural progression of the disease. The recurrence of major depression can occur without changes in medication even in well controlled cases. In trials cited by the FDA, a 5-8% recurrence rate can occur without a change in medication.¹ The number of reports of recurrence reported by patients who were switched to the generic drug may be consistent with the number of patients expected to recur if they continued to take brand-name Wellbutrin.²

The FDA considers the generic bupropion XL 300 mg from Teva Pharmaceuticals bioequivalent and interchangeable with Wellbutrin XL 300 mg. The recurrent nature of MDD gives a possible explanation for the reports of efficacy issues when switched to the generic. The FDA will continue to monitor reports of inequivalence and adverse events.¹

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

- **AACE Consensus Statement on Pre-Diabetes**
- **Vytorin and aortic stenosis: the SEAS trial**
- **Recent controversies surrounding Chantix therapy**



A New Black Box Warning for Fluoroquinolones by Laura Yahr

The Food and Drug Administration (FDA) is mandating that the makers of fluoroquinolones add a black box warning about the increased risk of tendonitis and tendon rupture in patients taking these antibiotics. This would effectively be strengthening an already existing warning about this adverse effect.¹ This warning was designed, in part, to enhance appropriate prescribing of this class of antibiotics.

While tendonitis and tendon rupture will only occur in select patients, there are some groups who are more likely to experience these outcomes. The risk is increased in the following patient populations²:

- Patients over age 60
- Patients also taking corticosteroids
- Kidney, heart, and lung transplant recipients
- Patients who are physically active or who exercise
- Patients with kidney failure
- Patients with a history of tendon problems, for example, due to rheumatoid arthritis



Patients should be instructed to contact their physician with the first sign of pain, swelling, or inflammation in a tendon area. The patient should avoid exercise and use of the involved tendon.³ Signs or symptoms of tendon rupture include a snap or pop in a tendon area, bruising right after an injury in a tendon area, and the inability to move the affected area or bear weight on it.² In some cases, alternative therapy should be considered.

The Achilles tendon is the most frequently ruptured tendon. Literature suggests it ruptures 3 – 4 times more often in patients on fluoroquinolones than patients not on fluoroquinolones, occurring in approximately 1 in 100,000 patients.¹ Other commonly affected tendons include the rotator cuff, hand, biceps, and thumb.²

The manufacturers of fluoroquinolones have thirty days to submit changes made to the safety label, including a stronger warning and a Medication Guide. If they do not comply or if the FDA doesn't approve of the new wording on the proposed label, the agency will impose a new timeline on the manufacturer and can order a label change that confers the new safety information.³

The consumer group, Public Citizen, filed a lawsuit to force the FDA to order a new safety label from the manufacturers. This group claims that more than 300 cases of tendonitis and 400 cases of tendon rupture occurred from November 1997 – December 2007 while the FDA stated that “hundreds” of cases have been reported but could not give out a specific number due to the current lawsuit.⁴

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Truth from Myth—The Incidence of Angioedema when Initiating ACE-Inhibitors by Craig Marx

A new study in the June 2008 issue of *Hypertension* seeks to provide a more accurate incidence rate of angioedema when patients initiate angiotensin converting enzyme (ACE) inhibitors, as well as other antihypertensive agents. The large observational study by Miller et al¹ aims to assess the validity of previously estimated incidence rates of angioedema and to determine outcomes in a larger, more diverse patient population than what had been studied previously.

Angioedema is a rare and severe side effect associated with the use of angiotensin converting enzyme (ACE) inhibitors and other medications. In the past, most studies looking at incidence rates of angioedema in the treatment of hypertension were small observational studies from short trials that examined particular patient populations³ and most excluded patients of advanced age or with concurrent disease states.² Such studies had placed the rate of angioedema incidence between 1 or 2 per 1000 patients. One of the largest and most conclusive of the previous trials, Omapatril Cardiovascular Treatment Versus Enalapril (OCTAVE), gave conflicting information by estimating the incidence rate of angioedema to be 6.8 per 1000 person years. Furthermore, little data had been provided regarding the onset of angioedema following initiation of therapy.

The Miller study,¹ which obtained data from Veterans Affairs hospitals across the United States, followed 195,192 patients starting ACE inhibitors and compared their incidence of angioedema with that of 399,889 patients initiating other antihypertensive medications. Selected cases of new angioedema were limited to those antihypertensives newly prescribed, and the incidence rate findings are generally consistent with previous estimates (1.97 per 1000 person years). The study also indicates a nearly 4-times increased risk of angioedema in ACE-treated patients as compared to other antihypertensives.¹

The findings of greatest clinical relevance obtained from the study involve the onset of angioedema after initiation of therapy and incidence rates in patient-specific subsets. Several reports during the past three years,^{5,6} including Miller et al,¹ have indicated that although incidence rates are highest shortly after initiating ACE therapy, the risk of developing angioedema extends beyond the first month and up to one year following initiation of therapy. Additionally, it was found that the risk of angioedema increased considerably for blacks (3.88x), females (1.45x) and those with chronic heart failure (1.22x) and decreased substantially for diabetic patients (0.88x).¹

In conclusion, this study verifies previous estimates of overall angioedema rates when initiating ACE therapy. However, it raises concerns regarding the length of time that patients may be at risk after initiation of therapy. Consequently, practitioners may need to change approaches to patient counseling and about the risks associated with these medications.

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Recent Pharmaceutical Industry Lobbying Issues by Kevin Olson

2007 was a record-setting year for spending by pharmaceutical companies in the nation's capital. More than \$189 million was spent in 2007, up from \$146 million in 2006. The Pharmaceutical Research and Manufacturers of America (PhRMA) group spent the most money at almost \$23 million, followed by Amgen and Pfizer as the top 3 spenders.¹ During this time, Democrats took over the majority of positions in Congress after the 2006 elections, so drug companies had to develop relationships with the new leadership in office in order to effectively lobby for crucial bills affecting the industry.² Interestingly, 2006 marked the first time the Democratic party received more money than Republicans from the pharmaceutical and health care accessory industry.²

Drug companies' lobbying efforts are focused on: 1) guarding drug patents in the United States and internationally, 2) stopping the use of drugs from other countries inside the U.S., and 3) expanding the free trade of U.S. drug companies internationally. Pharmaceutical companies successfully lobbied for primary legislation including the Prescription Drug User Fee Act (PDUFA) and the Best Pharmaceuticals for Children Act.

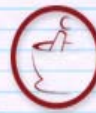
The PDUFA is legislation allowing drug companies to give money to the Food and Drug Administration (FDA), (referred to as user fees) to pay for extra staff members to expedite drug approvals. These user fees are now approximated to be a little over 25% of the FDA's 2009 estimated budget of \$2.4 billion.¹ The Best Pharmaceuticals for Children Act is legislation allowing drug companies to extend their patent on a drug for 6 months in exchange for testing the drug on children. This process delays the marketing of a generic form of the drug and gives the drug companies an additional 6 months of exclusive sales.¹

The pharmaceutical industry has also successfully blocked legislation from being passed by Congress. The Fair Balance Prescription Drug Advertisement Act of 2007 was written to limit the allowable amount of direct drug advertising, but the legislation never made it out of committee meetings to be brought to a vote.¹ The pharmaceutical lobby also blocked another bill in 2007 that would have prohibited a brand name drug company from compensating a generic drug company for postponing the release of a generic drug onto the market.³

Pharmaceutical industry lobbying continues to play a significant role in controlling federal legislation related to the availability of medication in this country. Awareness of this process is important, as such legislative decisions can have a significant impact on the ability to provide optimal patient care.

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