Family Medicine Clinical Pharmacy Forum

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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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Pharmacothearpy Issues.

New Drug. Cymbalta™ (duloxetine hydrochloride) is a new SSNRI. It is in the same class as Effexor™ (venlafazine) and is considered a "me too" drug. It has been approved for major depressive disorder (20 – 60mg/d may be divided into BID) and diabetic peripheral neuropthy (60mg/d). It is also currently in the clinical trial phase for approval for urinary stress incontinence (40mg BID). It takes about 3 weeks for an initial response. A month's supply of Cymbalta™ will cost around $192.00 (30mg BID), while 30 tablets of Effexor XR™ 75mg is around $89.00. This is an expensive medication that has not shown benefit over other agents and should be reserved as second line treatment.

New Drug. Ketek™ (telithromycin) is the first antibiotic in a new class called ketolides. It is similar to the macrolides. It is approved for acute bacterial exacerbations of chronic bronchitis (800 mg x 5d), acute bacterial sinusitis (800 mg x 5d), mild-moderate community acquired pneumonia (800 mg x 7-10d). It comes in 400 mg tablet size and costs about $70 for a 5-day course. Of note, it has many of the same problems as erythromycin...adverse GI effects, numerous drug interactions, and potential arrhythmias. Ketek™ is also a strong inhibitor of CYP3A4 enzymes...like erythromycin and clarithromycin, so it can increase levels of drugs metabolized by 3A4 (simvastatin, lovastatin, midazolam, etc.) It should be reserved as an alternative to other first-line therapies.

New Drug. Camprol™ (acamprosate) is a new drug for maintenance of abstinence from alcohol. It is a GABA analogue which is thought to work by restoring the balance between the glutamate (neuronal excitation) and GABA (neuronal inhibition) neurotransmitter systems. Unfortunately, dosing is not very convenient - usual dose is two 333 mg tablets (666 mg) three times daily. It is well-tolerated, with headache, diarrhea, and nausea reported. A month's supply will cost about $140, compared to generic naltrexone (50 mg daily) which is about $130. Generic disulfiram (250 mg daily) costs much less at about $26 (AWP) per month. There is no evidence right now that any of these agents is superior in efficacy to one another.

New Drug. Lyrica™ (pregabalin) is a derivative of Neurontin™ (gabapentin) and was approved by the FDA in December of 2004 for the management of neuropathic pain associated with diabetic peripheral neuropathy (150-450mg/d) and postherpetic neuralgia (150-450mg/d). It is

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also currently in the clinical trial phase for treatment of partial seizures (150 – 600mg/d). Lyrica™ and Neurontin™ are thought to have a similar mechanism of action (which is poorly understood), however Lyrica™ may be more potent than Neurontin™, requiring smaller doses. The FDA has recommended that Lyrica™ be classified as a controlled substance do to possible abuse potential. Lyrica™ is still not available on the market despite being approved in December.

New Drug Formulation. Aricept ODT™ (donepezil HCl) is a new orally disintegrating tablet formulation of donepezil soon to be available in the same strengths (5 and 10 mg). Pfizer claims it is because many Alzheimer's patients develop difficulty swallowing. Cost information is unavailable at this time but will likely be similar to regular Aricept (approximately $125/month). Hmmm, I think Aricept is coming off patent soon…

Practice-Based Issues.

"Andropause." A recent report of a 170% increase in testosterone prescriptions from 1999 to 2002, and an increase in sales from $18 million in 1988 to $400 million in 2003 has caught the attention of the National Institutes of Health (NIH). The NIH is concerned that testosterone is being used "off-label," or in male patients with normal testosterone levels. Current market research suggests the bulk of testosterone prescriptions are written for men aged 46 to 65. Therefore, the NIH commissioned the Institute of Medicine (IOM) to access the risks involved in using testosterone off-label. The IOM report identified 48 publications describing the results of 39 trials, most of which were poorly designed, with small sample sizes — ranging from 6 to 108 men — and brief duration. Only 31 of the trials were placebo-controlled. All the studies were done on men who received intramuscular injections of testosterone. The prescriptions being written now are for testosterone patches or testosterone gel. The studies offered no clear evidence of benefit for depression, although some studies reported improvement in quality of life and functional status. There was evidence for increased lean body mass but not for improved bone density. Only men with a confirmed diagnosis of hypogonadism reported improved sexual desire. In November 2003, the IOM released its report, which recommended randomized, placebo-controlled studies of testosterone replacement in men aged 65 years or older need to be done to fully elicit the risk/benefit of using testosterone replacement. Many unanswered questions remain regarding the long-term safety of testosterone, as well as the definition of "normal" testosterone levels with aging. If you choose to prescribe testosterone replacement, it is recommended to get a baseline PSA and perform DRE, and repeat every 6-12 months. LFTs, Hgb/Hct and lipids should all be done at baseline and periodically thereafter. For more information, see: http://www.medscape.com/viewarticle/470045

New Contraindication. Phenergan™ is now contraindicated for use in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Postmarketing cases of respiratory depression including fatalities, have been reported with use of Phenergan™ in pediatric patients less than 2 years of age. For more information, see: http://www.fda.gov/medwatch/SAFETY/2005/phenergan_deardoctorletter.pdf

Public Health Advisory. Crestor™ has been under increased scrutiny lately from the FDA. Please note strengthened labeling for Crestor regarding risk of myopathy, particularly at the highest dose (40 mg/d). It is also noted in a recent pharmacokinetic study that Asian patients had much higher blood levels of the drug; therefore labeling has been changed to recommend 5

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mg/d as the starting dose in this population. To that end, if you chose to use this drug, I would suggest you start with the 5 mg dose and in all of your patients and titrate accordingly, even those that you may be switching from another statin. For more information, see: http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#crestor

Public Health Advisory. Adderall XR™ was recently taken off the market in Canada due to due to concern about reports of sudden unexplained death (SUD) in children taking Adderall™and Adderall XR™. SUD has been associated with amphetamine abuse and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines. In addition, a very small number of cases of SUD have been reported in children without structural cardiac abnormalities taking Adderall™. At this time, FDA cannot conclude that recommended doses of Adderall™ can cause SUD, but is continuing to carefully evaluate these data. For more information, see: http://www.fda.gov/cder/drug/infopage/adderall/default.htm

Regulatory Issues.

Pseudoephedrine. You may be aware that a bill was recently passed by the Iowa Senate which would require that all pseudoephedrine-containing products be reclassified as Schedule 5, making them available only through a registered pharmacist. Proof of identification would be required at the time of purchase and a registered log of purchases would be kept. Sales would be restricted to no more than 6,000 mg per month per patient. This reclassification would include all pseudoephedrine-containing products packaged with 360 mg or more of the drug (packages containing a total of less than 360 mg of total pseudoephedrine would not be subject to Schedule 5 regulation). Some cities and/or counties in the state have already enacted similar legislation restricting pseudoephedrine sales. Similar legislation enacted in Oklahoma has helped reduced methamphetamine manufacture and distribution.

Research.

Enrollment is continuing in the *Collaborative Management of Hypertension* Study. If you have a newly diagnosed hypertensive patient or a patient on treatment and not at BP goal, please contact Karen Kluesner at 430-7335. Fliers are posted in the patient care areas.

Clinical Pearl.

A recent drug information question we received was: "*Are expired drugs dangerous*?" The short answer is that not all expired drugs are dangerous. Some drugs that degrade easily (e.g. sublingual nitroglycerin, insulin, liquid antibiotics) would be dangerous if expired because of loss of potency and subsequent loss of therapeutic benefit. Others that decompose into a different chemical compound (e.g. aspirin degrades to salicylic acid) could be dangerous. To understand the issue more closely, there are 2 questions to consider:

(1) Who sets the expiration dates for prescription drugs in their original packaging? Expiration dates are set by the manufacturer of a prescription drug and not the FDA. The company may choose whatever time period they desire, and it is presumed that this period is determined based on the results of "in-house" testing. Some people, however, feel that the time period chosen by the company is done in an effort to facilitate product sales. Most pharmaceutical

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manufacturers choose two to three years after the date of manufacture as the expiration date. The expiration date assigned to a medication by the manufacturer is not the date after which it has "gone bad." It is the date after which the manufacturer cannot guarantee that the product meets FDA standards for stability (maintaining identity, strength, quality, purity). Usually, maintenance of at least 90% potency is acceptable.

(2) Who sets the expiration dates for prescription drugs that are transferred from original packaging into a prescriptioin vial? In 1985, the United States Pharmacopeia (USP) began recommending that pharmacists set expiration dates at no more than one year if they are dispensing drugs in a container other than the original one. In 1997, it became a USP requirement that, unless otherwise specified in compendium standards, the expiration date on a dispensed medication should be no later than the expiration date on the manufacturer's container or one year from the dispensing date, whichever is earlier. How a medication is stored affects its long-term stability. Exposure to light, air, humidity, and temperature extremes can affect the degradation rate of a drug. The expiration date assigned by the manufacturer or dispensing pharmacist assumes that the medication will be stored properly - in the closed container it was dispensed in at the appropriate temperature. In reality, many patients store medications in less than ideal environments: warm, humid areas (bathroom cabinet), window sills (lighted areas), various locations in the interior of automobiles (hot), etc. These storage conditions lend credence to pharmaceutical manufacturers' insistence that "conservative" expiration dating is warranted.

Interestingly, this question of expired drugs has actually been examined by the military. The United States military has nearly a billion dollars invested in drug inventory stockpiled in various locations throughout the world, for "military preparedness." Approximately fifteen years ago, when military officials realized that they were soon going to have to begin replacing the aging inventory, they decided to commission the FDA to study the feasibility of extending the shelf life of their inventory. The program is referred to by the Department of Defense as the "Shelf Life Extension Program." In the first year of the testing program, the FDA tested 58 different prescription drugs, representing 157 different manufacturing lots. Some of the original drugs tested were penicillin, lidocaine, and lactated Ringer's. After this initial round of testing was complete, the FDA extended the expiration dates for 80% of the expired lots tested by an average period of 33 months. In 1992, seven years after testing began, the expired lots were retested, and more than 50% met testing standards (i.e., remained useable). In the year 2000, at least one of those batches remains stable, fifteen years after its original expiration date. Some specific drugs that have been incorporated into this testing program include: pralidoxime, chloroquine, diazepam, ciprofloxacin, atropine, sodium chloride for injection, and cimetidine. The original expiration date of ciprofloxacin tablets that were added to the testing program was 1993, and this expiration date has now been extended to 2001. The Shelf Life Extension testing program is still ongoing.

Source: Prescriber's Letter, May 2000

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