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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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Should Bisphosphonates be Discontinued after Five Years?

Osteoporosis affects 10 million Americans and contributes to 1.5 fractures each year. While bisphosphonates are the mainstay of treatment for osteoporosis, little data is available regarding the optimal duration of bisphosphonate therapy.

The Fracture Intervention Trial Long-term Extension (FLEX) study evaluated 1099 postmenopausal women taking alendronate 5 or 10 mg daily. This trial compared women taking alendronate for a duration of 5 years to those continuing treatment for 10 years.

The FLEX study found that switching to placebo after 5 years of alendronate therapy resulted in significant declines in bone mineral density (BMD) at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; P<0.001) and spine (-3.7%; 95%CI, -4.5% to -3.0%; P<0.001). However, the mean BMD levels remained at or above the values measured at the beginning of therapy. Compared with those who continued alendronate for 10 years, patients who stopped alendronate after 5 years had increased serum markers of bone turnover, such as bone-specific alkaline phosphatase. After 5 years, the cumulative risk of nonvertebral fractures was not significantly different between those who continued and discontinued alendronate.

Based on the results of the FLEX study, the authors concluded that stopping alendronate after 5 years does not significantly increase the risk of nonvertebral fractures. With limited proven benefit and substantial costs to patients, the use of long-term bisphosphonate therapy may not be appropriate. Therefore, practitioners may consider discontinuing therapy after 5 years in women with a good initial response (3-5% increase in hip BMD, 8-10% increase in spine BMD, and T-score >-3.5) to bisphosphonates and low risk of vertebral fractures. If the decision is made to discontinue therapy, it is reasonable to monitor BMD at least every other year.

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of Continuing or Stopping Alendronate After 5 Years of Treatment. *JAMA* 2006;296:2927-2938.

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Current Recommendations for Treatment of Influenza

Influenza season is upon us once again. As of January 27, 2007, the state of Iowa was reporting widespread activity of influenza. Signs and symptoms of influenza include fever, myalgia, headache, nonproductive cough, and sore throat. Children can also present with otitis media, nausea, and vomiting. After these symptoms appear, the infectious period lasts 5 days and ≥10 days in adults and children, respectively.

The CDC recommends oseltamivir (Tamiflu®) or zanamivir (Relenza®) for treatment or prophylaxis of influenza. Avoid amantadine and rimantidine due to high resistance rates. When started within 48 hours of symptom onset, these agents shorten the duration of symptoms by one day. See Table 1 for recommended doses of antiviral agents in children and adults.

Table 1. Recommendations for dosing of antiviral agents

Antiviral agent	**Dosing Parameter**						
		Children ≥1 year old				**>13 years**	**CrCl <30 mL/min**
		<15 kg	**15-23 kg**	**>23-40 kg**	**>40 kg**		
Oseltamivir *(Tamiflu)*	**Treatment***	30 mg BID	45 mg BID	60 mg BID	75 mg BID	75 mg BID	75 mg daily
	Prophylaxis**	30 mg daily	45 mg daily	60 mg daily	75 mg daily	75 mg daily	75 mg every other day
Zanamivir *(Relenza)*	**Treatment***	All patients ≥7 years old: 10 mg (2 inhalations) BID					
	Prophylaxis**	All patients ≥5 years old: 10 mg (2 inhalations) once daily					

**All treatment doses are for 5 days* ***All prophylaxis doses are for 10 days*

Of note, several cases of delirium have been reported with Tamiflu in Japan, especially in pediatric patients. Therefore, patients on Tamiflu should be instructed to report any change in mental status or behavior to their health care professional.

http://www.cdc.gov/flu/professionals/treatment/. Accessed January 27, 2007.

Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture

Hip fractures are the most common and devastating complication of osteoporosis, which is characterized by decreased bone mineral density and often related to low calcium intake and/or calcium malabsorption. Additionally, another class of medications commonly used in many patient populations may be linked to hip fractures. Proton pump inhibitors (PPIs) are the mainstay of therapy for gastroesophageal reflux disease (GERD). However, it is hypothesized that these agents may increase the risk of hip fractures by decreasing calcium absorption. In addition to causing acid suppression and hypochlorhydria, this class of medications may also decrease bone resorption by inhibiting osteoclastic vacuolar proton pumps, thereby further potentiating hip fracture risks.

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A recent case-control study examined this correlation by evaluating approximately 200,000 PPI users, 200,000 H_2 blocker users, and 1.4 million nonusers of acid suppression drugs. All of the patients examined were older than age 50 with an incident hip fracture. Results of this study showed a significant increase in the risk of hip fractures in patients taking long-term high-dose PPIs, which was defined as taking at least 75% of prescriptions twice daily [AOR 2.95; 95% CI, 1.80-3.90; P<0.001]. Furthermore, the risk of hip fractures was also higher with increased duration of high-dose PPI use [AOR for 1 year, 1.22 (95% CI, 1.15-1.30); 2 years, 1.41 (95% CI, 1.28-1.56); 3 years, 1.54 (95% CI, 1.37-1.73); and 4 years, 1.59 (95% CI, 1.39-1.80); P<0.001 for all comparisons].

Based on the results from this study, the authors concluded that using PPIs for greater than one year was associated with an increased risk of hip fracture. It is estimated that 1200 patients would have to receive at least one year of therapy in order to cause one hip fracture. In addition to the potential risk for hip fracture, previous studies have linked PPI use to increased risk of community acquired pneumonia and *C. difficile* colitis. These previous studies, along with current findings, highlight the importance of using PPIs at the lowest effective dose for the shortest period of time.

Yang YX, Lewis JD, Epstein S, Metz DC. Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. *JAMA* 2006;296:2947-53.

Guidelines for Treatment of Community-Acquired Pneumonia

The Infectious Diseases Society of America and American Thoracic Society recently released consensus guidelines on treatment of community-acquired pneumonia (CAP). No major changes in recommendations for empiric antibiotic therapy were made. However, the new guidelines stress the importance of dosing levofloxacin at 750 mg daily for patients with CrCl >50 mL/min or 750 mg every 48 hours for patients with CrCl <50 mL/min. Levofloxacin exhibits concentration dependent killing, and studies have shown better efficacy and similar adverse effects at 750 mg than 500 mg doses.

In almost 50% of cases of CAP, a causative organism is not identified. Therefore, therapy usually begins on an empiric basis. The most causative organism is *Streptococcus pneumoniae*, followed by *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. See Table 1 for recommendations on empiric antibiotic therapy.

Table 1. Initial empiric therapy for suspected bacterial CAP in immunocompetent adults

	Initial therapy	Alternative agent
Outpatient – *no comorbidities*	Azithromycin 500 mg x1, then 250 mg days 2-5 **OR** doxycycline 100 mg BID	Levofloxacin 750 mg daily
Outpatient – *comorbities or recent antibiotic use*	Levofloxacin 750 mg daily	Augmentin 2 gm BID + Macrolide
Inpatient – *not ICU*	Ceftriaxone 1 gm IV daily + azithromycin 500 mg IV daily	Levofloxacin 750 mg daily
Inpatient – *ICU*	Combination therapy: Ceftriaxone 1 gm IV daily + azithromycin 500 mg or levofloxacin 750 mg daily	Piperacillin/tazobactam or Imipenem or Cefepime + levofloxacin 750 mg daily

*Comorbidities include COPD, CHF, cancer, diabetes, renal or liver disease

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**On antibiotics in the last 3 months

All patients should be treated for a minimum of 5 days, and therapy should be continued until patients are afebrile for 48-72 hours. If the patient does not show improvement within 72 hours, consider an organism that is not covered by initial therapy or drug-resistant organisms.

Mandell, LA. et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clinical Infectious Diseases 2007,44:Suppl 2.
UptoDate accessed online November 20th 2006

Efficacy on LDL Lowering: Zetia 5 mg vs. 10 mg

Ezetimibe (Zetia®), an oral cholesterol absorption inhibitor, is approved for use as monotherapy or in combination with either statins or fenofibrate for the treatment of hypercholesterolemia. The recommended dose of ezetimibe is 10 mg daily, regardless of whether it is used in conjunction with a statin. However, Phase II studies have shown that ezetimibe has a very flat dose response curve, which suggests that smaller doses may be sufficient to lower cholesterol in some patients (Table 1).

Table 1. Phase IIa and IIb study results on dose-related effect on LDL

Phase IIa	% reduction LDL	Phase IIb	% reduction LDL
1 mg	14.6	1 mg	12.6
5 mg	15.7	5 mg	16.4
10 mg	16.4	10 mg	18.7

A combined pooled analysis of these two studies found that the difference in the ability to lower LDL between ezetimibe 5 mg and 10 mg appears to be less than 3% (16% vs. 19%, respectively). This indicates that some patients may be able to meet their LDL cholesterol goals with half of the recommended dose of ezetimibe. However, it is important to keep in mind that the goal LDL may be less than 70 mg/dL for very high-risk patients (e.g., those with heart disease and multiple risk factors, including diabetes). Evidence suggests that achieving lower LDL goals results in greater cardiovascular benefits. For high-risk patients, the cost savings of taking half the recommended dose (5 mg) of ezetimibe must be weighed against the potential additional benefit achieved with 10 mg.

Using half of a tablet of ezetimibe, either alone or in combination (ezetimibe/simvastatin, or Vytorin®), could potentially save patients up to $45 per month[1]. It is reasonable to recommend doses of 5 mg in patients who have difficulty paying for their medications, particularly if they are not at high risk for cardiovascular disease. Following any dose change, cholesterol levels should be re-checked to examine efficacy of the lower dose of ezetimibe.

Drugstore.com. Zetia. www.drugstore.com. Accessed 12.11.2006.
SteinE. Results of pase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur Heart J* 2001;3(Suppl E):E11-6.
Using half doses of Zetia or Vytorin. Pharmacists Letter/Prescribers Letter 2006;22(11):221104.

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Clinical Pearl – Does this Patient Have Dilantin Toxicity?

An 83 year old female presents to the ER with symptoms of confusion, ataxia, and weakness. She is on phenytoin (Dilantin) for seizure control. Her Dilantin level is 10.9 (normal 10-20). However, her albumin level is 1.2 g/dL. Could this patient have Dilantin toxicity?

Dilantin is ~90% protein bound; therefore, patients with low levels of albumin (<4.0 g/dL) have falsely low levels of Dilantin. It is prudent to check an albumin level in any patient on Dilantin at risk of hypoalbuminemia.

The equation for the adjusted Dilantin level is: measured Dilantin level/[(0.2 x albumin) + 0.1]. This patient's corrected Dilantin level is 32.7, indicating that she is experiencing Dilantin toxicity. Signs and symptoms of Dilantin toxicity include confusion, ataxia, hypotension, dizziness, and nystagmus. After decreasing her Dilantin dose, a level should be rechecked in 7-10 days.

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