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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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PRoFESS Trial Results

Results of the highly promoted PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial were recently reported in a series of presentations at the European Stroke Conference.

Among the results:

- Dipyridamole plus aspirin failed to establish non-inferiority with clopidogrel in preventing second strokes, even though the study found little difference between the drugs in effectiveness.
- Telmisartan was unable to prove that it was better than placebo in preventing second strokes.
- Neither strategy proved successful in showing better results in improving functional outcomes or cognitive outcomes.

The study, sponsored by Boehringer-Ingelheim, enrolled over 20,000 patients. The primary outcome of the trial was to compare the effectiveness of the dipyridamole arm to clopidogrel with a secondary endpoint of effectiveness in preventing other vascular events. In the primary outcome, prevention of a second stroke, 916 dipyridamole patients had strokes (9%) compared with 898 clopidogrel patients (8.8%) (*P*=0.783).

In the part of the study that judged whether immediate treatment of high blood pressure with the angiotensin receptor blocker telmisartan was beneficial compared with placebo,

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the results again failed to provide a definitive answer. The researchers assigned 10,146 of the PRoFESS enrollees to receive telmisartan 80 mg a day and 10,186 to receive placebo. Overall, 8.7% of the patients receiving telmisartan suffered a second stroke in the 2.5-year time frame of the study, and 9.2% of patients receiving placebo also suffered second strokes in the trial, which translated into a 5% reduction with telmisartan, a difference that failed to reach statistical significance (*P*=0.23). In a secondary endpoint, major vascular events -- cardiovascular death, myocardial infarction, stroke, or new or worsening heart failure -- were experienced by 13.5% of patients on telmisartan and 14.4% of patients on placebo (*P*=0.11).

Researchers also noted that none of the treatments in the study appeared to improve outcomes on the Mini Mental State Examination, the Barthel Index, or the Modified Rankin Scale -- all measures of cognitive or functional status.

http://www.theheart.org/article/866845.do

Iron Supplementation for ACE-Inhibitor Cough

Can iron supplements be used to treat ACE Inhibitor induced cough?

A dry hacky cough is a common adverse effect from ACE Inhibitors. This cough can occur in 5-30 % of patients and is a frequent reason for discontinuation of the drug. A study published in Hypertension consisted of 19 Korean patients (6 men and 13 women) who were on ACE Inhibitors for various reasons. The inclusion criteria included a cough that developed on an ACE Inhibitor and that occurred after a rechallenge of the medication. The patients were randomly assigned to either a daily dose of 256 mg ferrous sulfate or placebo. After four weeks 8 out of 10 patients in the iron treatment group had decrease in cough scores and only 1 out of 9 patients in the placebo group had a decrease in cough scores. This difference was statistically significant, p-value (<0.01). At the end of the 4 weeks, there were no statistically significant difference in the patients' hemoglobin, hematocrit, ferritin, iron, and TIBC levels.

Lee SC, Park SW, Kim DK, Lee SH, Hong KP. Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension.* 2001;38:166-70.

New Drug: Pristiq™ (desvenlafaxine)

Desvenlafexine, (Pristiq) is the active metabolite of venlafexine (Effexor) an SNRI, with the FDA-approved indications for major depressive disorder (MDD). Dosing is initiated at 50 mg/day and may go up to 400 mg/day, although no additional benefit has been seen above 50 mg/day. Desvenlafexine, also has the off-label use for the treatment of vasomotor symptoms associated with menopause. Dosing for the vasomotor symptoms has not been established, but is being investigated at 100 mg/day. Common ADRs include; nausea/vomiting, abdominal pain, asthenia, anorexia, constipation, xerostomia, dizziness, insomnia, nervousness, somnolence (drowsiness), sweating, tremor, vertigo,

and ejaculation dysfunction. As of yet there appear to be no head-to-head comparisons of venlafexine against desvenlafexine. Though in a basic cost comparison of the two drugs, 30 tablets of Pristiq 50 mg costs around $120.00 and is similar in cost to 30 capsules of Effexor XR 150 mg. Generic venflaxine is about half the price.

Pristiq® Prescribing Information. Wyeth Pharmaceuticals, Inc 2008. www.pristiq.com

Bisphosphonate Use in Patients with Metastatic Cancer

Bisphosphonates are a class of drugs generally indicated for the treatment of osteoporosis by inhibiting bone resorption through the inhibition of osteoclast activity and induction of osteoclast apoptosis. Several studies have examined whether they can improve pain scores in patients with bone metastases.

A 2006 trial published in *Clinical Oncology* evaluated of the benefit of zoledronic acid (Zometa) in cancer patients with a skeletal related event (SRE); (pathological vertebral fractures, pathological non-vertebral fracture, spinal cord compression, surgery for bone complications, radiotherapy for bone complications, hypercalcaemia) or progressive bone metastases. In 2008, a study published in *Breast Cancer Research and Treatment*, evaluated similar outcomes and uses of ibandrontate (Boniva). Both studies use SRE, or bone metastases as inclusion criteria. Also, both study protocols measure pain and quality of life, which refers to the highest pain score, average pain score and number of pain sites as the primary endpoints. In all three categories the bisphosphonate showed a statistically significant reduction yielding a palliative response at 4 and 8 weeks. A systematic review by Yuen published in 2006 in the Cochrane database, evaluated ten studies and 1,955 patients with prostate cancer utilizing bisphosphonates for pain. The results also supported the use of BP's for prostate cancer pain. From review of the literature, it can be concluded that BP's may be beneficial for the treatment of pain in patients with bone metastases independent of gender (male or female) and origin of cancer (breast or prostate).

J Clin Oncol. 2006;24:4895-900.
Breast Cancer Res Treat. 2008;108:79-85.
Cochrane Dat Syst Rev. 2006;(4):CD006250. Accessed at:
<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006250/frame.html >.

Bisphosphonates and Risk of Atrial Fibrillation

Recently, some of your patients may be asking about use of alendronate and heart problems. Early trials of alendronate reported a higher incidence of atrial fibrillation in users of alendronate in post-hoc analyses. However, it is unclear whether there is a direct causal link or if this is due to an already elevated baseline risk for cardiovascular problems that is known to be present in the postmenopausal population. With this scenario of at risk patients sharing similar risk factors, any secondary or post hoc analyses of osteoporosis treatments and adverse cardiovascular events will be difficult to interpret and susceptible to serious confounding and problems related to multiple

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comparisons. A recent nested case-control study was reported in BMJ clarifying this issue. The authors examined etidronate and alendronate (around 14,000 cases of atrial fibrillation and around 68 000 controls) between 1999-2005. The investigators report almost no difference in the use of bisphosphonates in people with atrial fibrillation and those without (3.2% of current users had atrial fibrillation vs 2.9% of non-users). No association was seen in appropriately adjusted analyses that examined new users versus not new users, former users versus not former users, and long duration versus short duration of use. For now, beyond taking the patient's pulse and ordering an EKG when it is irregular, available evidence suggests that business should carry on as usual—the risk of atrial fibrillation associated with oral bisphosphonates seems to be vanishingly small if it exists at all, and it is unlikely to ever offset the confirmed benefits of these drugs in the prevention of fractures.

BMJ 2008;336:784-785 (12 April), doi:10.1136/bmj.39513.481065.80 (published 11 March 2008)

Metformin versus Insulin for the Treatment of Gestational Diabetes

Currently, insulin is the treatment of choice for gestational diabetes. High glucose levels can cause maternal and fetal complications. Insulin is the preferred treatment because of the need for precise control of maternal glucose levels and the limited information regarding safety of the oral medications. Metformin, unlike insulin crosses the placenta, which could potentially cause adverse effects to the fetus. Metformin is a pregnancy category B and has been linked to infant problems such as jaundice, polycythemia, and hypoglycemia.

In May 2008, a study was published in the New England Journal of Medicine to address this issue. The randomized, open label study consisted of 751 women with gestational diabetes that had failed glucose control with diet and exercise alone. Each patient was assigned to either metformin or insulin treatment groups and if the patient was unable to attain glycemic control on metformin alone, they could be augmented with insulin. The primary outcome was a composite of neonatal complications. The study showed that there were no significant differences in primary outcome between the metformin and insulin treatment groups (32.0% and 32.2% respectively, P = 0.95) and there were no significant differences in serious adverse effects. Surprisingly, 46% of the metformin group were unable to achieve glycemic control on metformin alone and had to be supplemented with insulin. The treatment groups were surveyed and more women preferred metformin over insulin.

Rowan JA, Hague WM, Gao W, et al. "Metformin Versus Insulin for the Treatment of Gestational Diabetes." *N Engl J Med*. 2008 May 8;358(19):2003-15.

Oral Sodium Phosphate Bowel Preparations and Safety

Acute kidney injury (specifically, acute phosphate nephropathy) has been reported due to oral sodium phosphate solutions (OSPS) used as bowel cleansers in preparation for

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colonscopy. Common OTC products are Fleet Phospho-soda or Fleet ACCU-PREP, or Visicol tablets. These were typically in patients with advanced age, pre-existing kidney disease or decreased intravascular volume, and those using medicines that affect renal perfusion or function (diuretics, ACE-inhibitors, angiotensin receptor blockers, and possibly NSAIDs). In 2006 the FDA issued a Black Box warning that OSPS should be used with caution in patients with impaired renal function.

Case reports of acute renal failure in patients with presumably normal renal function are now being reported, and a recent case-control retrospective study on patients with presumed normal renal function appears to confirm this finding. It is unclear if the culprit is sodium load itself or the specific sodium salt. The table below from E-facts lists the content of several non-sodium phosphate preparations. Some have been advocating use of lower sodium preps, such as MoviPrep.

Arch Intern Med 2008;168:593-7.
http://www.fda.gov/cder/drug/infopage/OSP_solution/default.htm

	CoLyte (Schwarz Pharma)	**Powder for Oral Solution**: 1 gal: 227.1 g PEG 3350, 21.5 g sodium sulfate, 6.36 g sodium bicarb, 5.53 g NaCl, 2.82 g KCl.	Regular and pineapple flavors. In bottles.
		4 L: 240 g PEG 3350, 22.72 g sodium sulfate, 6.72 g sodium bicarb, 5.84 g NaCl, 2.98 g KCl.	Citrus berry, lemon lime, cherry, and pineapple flavors. In bottles.
Rx	**GoLYTELY** (Braintree Labs.)	**Powder for Oral Solution**: 236 g PEG 3350, 22.74 g sodium sulfate, 6.74 g sodium bicarb, 5.86 g NaCl, 2.97 g KCl.	In disposable jugs.
		227.1 g PEG 3350, 21.5 g sodium sulfate, 6.36 g sodium bicarb, 5.53 g NaCl, 2.82 g KCl.	In packets.
Rx	**MoviPrep** (Salix)	**Powder for Reconstitution**: 100g PEG 3350, 7.5 g sodium sulfate, 2.691 g NaCl, 1.015 KCl.	Aspartame, 4.7 ascorbic acid, 5.9 g sodium ascorbate. 2.33 mg phenylalanine. Lemon flavor. In cartons w/ disposable container and 4 pouches.
Rx	**NuLytely** (Braintree Labs.)	**Powder for Reconstitution**: 420 g PEG 3350, 5.72 g sodium bicarb, 11.2 g NaCl, 1.48 g KCl.	Cherry, lemon-lime, and orange flavors. In 4 L disposable jugs.
Rx	**TriLyte** (Schwarz Pharma)		In 4 L bottles with flavor packs.
Rx	**OCL** (Abbott)	**Oral Solution**: 146 mg NaCl, 168 mg sodium bicarb, 1.29 g sodium sulfate decahydrate, 75 mg KCl, 6 g PEG 3350, 30 mg polysorbate 80/100 mL.	

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EKG Recommendations for ADHD Drugs

Stimulant medications for attention-deficit-hyperactivity disorder (ADHD) have been associated with reports of sudden death in the pediatric population. Factors potentially associated with the sudden deaths include cardiac structural abnormalities, toxic amphetamine levels, family history of ventricular arrhythmia, and extreme exercise/dehydration. The American Heart Association (AHA) has recently published guidelines for cardiovascular screening and monitoring of children and adolescents receiving ADHD drugs. The AHA guideline recommends that all children/adolescents undergo thorough physical and family history examination before initiating ADHD medication. An EKG is not specifically required; however, it is suggested especially if there are any potentially worrisome findings on history or physical examination. They also recommend that children and adolescents currently receiving ADHD medications should be evaluated for cardiac risks.

Circulation 2008;117:2407-23.

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