



Family Medicine Clinical Pharmacy Forum Vol. 4, Issue 2 (March/April 2008)

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.

Contents

- **Drug update:**
 - New warnings for Spiriva[®]
 - Possible suicide risk for Singulair[®]
 - Increased risk of thromboembolism with OrthoEvra[®] Patch
 - New pediatric indication for Nexium[®]
- **Guideline update:**
 - Treatment of UTI in Nonpregnant Women
 - Update for MMR and varicella vaccines
 - Secondary Prevention of Stroke
- **Trial update:**
 - ACCORD and Steno-2 trials
 - ASA for Asthma???
 - Resistant depression
 - Trials highlighted at ACC meeting

Spiriva[®]: Possible increase in risk of stroke and correct administration of drug

Boehringer Ingelheim and FDA recently announced a possible increased risk of stroke in patients who take Spiriva[®] (tiotropium). The company reportedly has completed an analysis of the safety data from their ongoing trials of this agent and found a small, yet statistically different rate in the risk of strokes. The data from these studies suggest the risk of stroke to be 8 patients per 1000 patients treated for one year with Spiriva[®] vs. 6 patients per 1000 patients treated per one year with placebo. Although this risk is very small (absolute risk increase of 0.2%) it has caused the company and the FDA to further investigate the risks associated with Spiriva[®]. It is not recommended that you take patients off this medication at this time. Stay tuned for continued data from Boehringer Ingelheim and the FDA.

The FDA issued a Public Health Advisory last month after receiving many reports of patients swallowing Spiriva[®] (tiotropium) and Foradil[®] (formoterol) capsules rather than using them in their inhaler devices. This provides a reminder to make sure to discuss new medications and administration technique with your patients when prescribing new drugs.

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.



FDA warns of a possible suicide risk with Singulair®

The FDA has released an early communication statement regarding the investigation of a possible association between the drug Singulair® and behavior/mood changes, suicidality and suicide. It is not known at this time what studies or analysis have shown this increased risk. While the FDA continues to evaluate this possible risk, it is important for healthcare providers to continue to monitor patients for suicidal thinking or changes in behavior and mood and initiate optimal mental health therapy if needed.

The complete safety summary is available at <http://www.fda.gov/medwatch/safety/2008/safety08.htm#Singulair>

Increased risk of thromboembolism with OrthoEvra® Patch

The FDA has updated prescribing information for the OrthoEvra® Patch to include an increased risk in blood clots. There have been conflicting study results in the past, but the most recent study found women age 15-44 were at higher risk for developing venous thromboembolism compared to women using birth control pills. Providers should consider patient risk factors when prescribing the patch.

For additional information visit <http://www.fda.gov/medwatch/safety/2008/safety08.htm#orthoevrapatch>

Nexium® Approved for use in Children Ages 1-11 Years

Esomeprazole magnesium (Nexium®) was approved by the FDA for short term use in children ages 1-11 years of the treatment of gastroesophageal reflux disease (GERD). The drug is available in two forms, delayed-release and liquid, and two dosage ranges, 10-20 mg for 1-11 year olds and 20-40mg for 12-17 year olds.

The pediatric indication of Nexium® was based on previous adult trials extrapolated to the pediatric population with supporting safety and pharmacokinetic data in pediatric patients. Adverse effects are similar to what is seen with adult patients, including diarrhea, abdominal pain, nausea, gas, constipation, dry mouth and sleepiness.

For more information on esomeprazole, please refer to www.fda.gov/bbs/topics/NEWS/2008/NEW01802.html.

Summary of updated treatment guidelines for uncomplicated UTIs from ACOG

Treatment regimens recommended for uncomplicated acute bacterial cystitis

Trimethoprim-sulfamethoxazole	1 tab (160/800) twice daily x 3 days
Ciprofloxacin	250 mg twice daily x 3 days
Levofloxacin	250 mg once daily x 3 days
Nitrofurantoin monohydrate	100 mg twice daily x 7 days

*β-lactams (1st gen. cephalosporins and amoxicillin) are less effective due to increase resistance, rapid excretion, inability to clear gram negative rods and increasing risk for recurrence

*Prophylactic treatment for women with frequent recurrences may include continuous treatment with once-daily nitrofurantoin, ciprofloxacin or trimethoprim-sulfamethoxazole. This has been shown to decrease recurrence by 95%.

*Pyelonephritis, inpatient and outpatient, should be treated with 14 days of therapy.

*Initial treatment of symptomatic lower UTI with pyuria and/or bacteriuria does not require a urine culture but can be tested by urinalysis or urinary dipstick testing. If

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.



clinical improvement is not seen in 48 hours, urine culture is recommended to designate appropriate treatment.

Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine

The CDC/ACIP General Recommendations for Immunizations have been updated to no longer include the combination MMRV Vaccine. Last month new information was presented to ACIP on the risk of febrile seizures in children 12-23 months of age using the combination product. Instead of the combination vaccine (ProQuad[®] manufactured by Merck) providers should return to administering the MMR and varicella vaccines separately.

Although the risk of seizure was small overall, there was a 2.3 times greater risk in patients receiving the combination vaccine (9/10,000 vaccinations vs. 4/10,000 vaccinations) leading to the revised recommendation. Febrile seizures are more often seen with common childhood illnesses (ear infections, respiratory tract infections, etc) and rarely seen after vaccinations. Interestingly, the committee points out that although febrile seizures are stressful to parents, they are not uncommon in this population and have an excellent prognosis. According to the report, approximately 1/25 (4%) of young children will have at least one seizure.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5710a3.htm>

Updated AHA/ASA Recommendations for the Prevention of Stroke in Patients with Stroke and TIA

Recent stroke trials (CHARISMA, ESPRIT, SPARCL) have led the AHA/ASA to release new guidelines for secondary stroke prevention in patients with a history of stroke/TIA. Below is a summary of the recommendations:

- Antiplatelet therapy
 - CHARISMA: ASA + Plavix provides no additional benefit vs. monotherapy
 - ESPRIT: ASA + dipyridamole is better than ASA alone
 - Recommendation: For initial treatment post-stroke, ASA monotherapy, Plavix monotherapy, and ASA + dipyridamole are all acceptable to use, but ASA + dipyridamole is most likely better than ASA alone.
- Statin therapy
 - Statins are known to decrease CVD but new trials, i.e. SPARCL, have suggested a possible benefit in secondary prevention of stroke
 - Recommendation: Initiate statin therapy post-stroke to reduce the risk of another stroke and cardiovascular events.

Resource: Adams RJ, Albers G, et al. Update to the AHA/ASA Recommendations for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack. *Stroke*. 2008;39:1-6.

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.



Trial update: How low is too low for A1c in diabetic patients?

In February the debate for the appropriate A1c was reignited among providers. First the ACCORD trial, funded by the National Heart, Lung and Blood Institute was stopped early due to higher mortality in the intensive treatment (goal A1c of <6%) compared to standard therapy. The next day, a less publicized NEJM article was published detailing an intensive multifactorial approach which reduced mortality in Type 2 Diabetes. So...what should we do now? Here is a summary of the two trials.

ACCORD summary:

The intervention group had a goal A1c <6% vs normal treatment (following ADA goal of <7%) in the control group. When the trial was stopped the median A1c was 6.4% in the intensive group vs. 7.5% in the standard group. The study was halted due to an increased risk of mortality in the intensive group. The difference between groups was 14 deaths/1000 individuals/year vs. 11 deaths/1000 individuals/year, which although small, was significant. Interestingly, the mortality rate for both groups was lower than previous studies. ACCORD patient population had an average age of 62, diabetes >10 years, known cardiac disease or high risk which has experts posing the question of whether or not there may need to be different goals for different groups of diabetic patients. The leading organizations of the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AAACE) supported the decision to stop the trial but it is not expected that they would change their current guidelines. The other endpoints of this trial, blood pressure and lipid management, are still ongoing.

For more information visit <http://www.accordtrial.org>

Steno-2 Study: Effect of a multifactorial diabetes intervention on mortality

Within hours of the termination of the ACCORD trial, the Steno-2 trial was published in NEJM. This trial was a continuation of an earlier trial which examined intensified multifactorial intervention of tight glucose regulation, the use of ACE inhibitors, aspirin and lipid-lowering agents in patients with type 2 diabetes and persistent microalbuminuria. This trial had a much longer duration, with a follow-up of 13.3 years. The intervention group used defined targets of the ADA although the average A1c and the end of the follow-up was 7.7% compared to 8.0% in the conventional therapy group. It is interesting to note that the mortality rate for patients receiving conventional therapy was an alarming fifty percent. At the end of the follow-up, there was an absolute risk reduction for death from any cause of 20% in the intensive group. Additionally, there was a 13% risk reduction from cardiovascular causes. This trial, unlike the ACCORD trial, showed promising results with intensified intervention, although the A1c goals and end points were much higher in this trial.

Gaede P et al. Effect of a multifactorial intervention non mortality in Type 2 Diabetes. *N Engl J Med.* 2008;358:580-591.

Continue to treat your diabetic patients to reach ADA goals using a multifactorial approach of diabetic medications, aspirin, ACE inhibitor and statin therapy.

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.



Aspirin for Asthma?

An analysis of the Women's Health Study has suggested that low-dose aspirin may lower the risk for asthma. In this recently published trial, patients received 100mg of aspirin or placebo every other day. Patients on aspirin during the 10 year study, experience asthma 10% less than those not on aspirin. Although the study was not designed to assess asthma, specifically, this trial will likely generate future research. *Thorax*. Published Online First: 13 March 2008. doi:10.1136/thx.2007.091447

The TORDIA Trial: Optimal treatment for resistant depression in adolescents

At least 40% of adolescents with depression do not show an adequate response to serotonin reuptake inhibitor (SSRI) therapy. Depression resistant to initial SSRI treatment has been examined but has shown conflicting results and has yet to be studied in an adolescent population. Venlafaxine has shown promise in the treatment of resistant depression in adults. The TORDIA (Treatment of SSRI-Resistant Depression in Adolescents) trial randomized 334 patients 12-18 years old who did not respond to initial SSRI treatment to one of four groups 1) a second SSRI; 2) venlafaxine; 3) second SSRI plus cognitive behavioral therapy (CBT); or 4) switch to venlafaxine plus CBT.

The clinical response was statistically significant in patients receiving CBT compared to not receiving CBT (58.4% vs. 40.5%). There was not a statistically significant difference between patients receiving a second SSRI compared to those receiving venlafaxine (47.0% vs. 48.2%) with similar dropout rates in both groups. Based on these findings, it is recommended to initiate CBT in combination with a switch in antidepressant medication in adolescents with resistant depression.

Brent D et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA Randomized Controlled Trial. *JAMA* 2008;299:901-13.

Trials highlighted at American College of Cardiology (ACC) meeting

If you are a cardiology fan, this is your month! Several trials have been released at the ACC meeting this month. Here are a few of the highlights:

- **ENHANCE:** Results of the highly debated ENHANCE trial have been published in NEJM. This trial showed a significantly greater LDL and CRP reduction with ezetimibe plus simvastatin but failed to show a difference in intima-media thickness. This trial has started debate about LDL, importance of imaging and other beneficial effects of statins.
- **ONTARGET:** This trial examined the angiotensin receptor blocker (ARB) telmisartan and the ACE inhibitor ramipril in patients with vascular disease or high-risk diabetes. Telmisartan was statistically non-inferior to ramipril, but a disappointing finding was the combination of the two agents was associated with more adverse events and no increase in benefit.
- **PERISCOPE:** This trial examined imaging of pioglitazone compared to glimepiride. The results confirm cardiovascular safety and show a possible delay in progression of atherosclerosis comparable to that of statin imaging trials.
- **JUPITER:** The first outcome trial of rosuvastatin was stopped early due to markedly increased benefit of cardiovascular morbidity and mortality compared to placebo.
- **HYVET:** This hypertension trial in patients >80 years old was stopped early due to increased benefit of diuretic and ACE inhibitor therapy with a goal BP of 150/80.

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.



Smoking Cessation Group Clinic Has Success in Its First Year

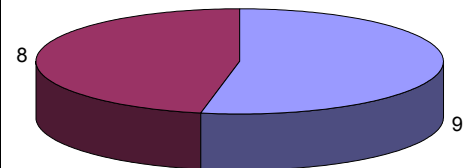
Since its inception in February 2007, the Smoking Cessation Group Clinic has assisted several patients in their efforts to quit smoking. According to self-reported quit rates, approximately 50% of patients that enroll in the clinic achieve cessation at 3 months. If you remove those people that did not quit during the clinic time period, cessation rates increase to over 80%.

In its first year, 76 patients have been referred to the Smoking Cessation Group Clinic. Of those referred, 37 (50%) have signed up for the clinic and 19 (25.7%) have committed to enrolling into the clinic. Approximately 20% of our referrals have come from the Family Medicine Clinic. Those that are most likely to commit to enrolling in the clinic are those that self-refer to the clinic.

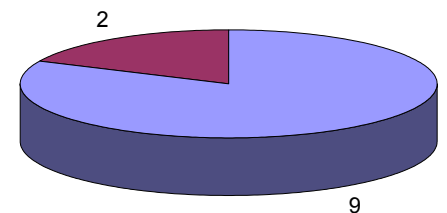
The Smoking Cessation Group Clinic continues to be available to assist patients in smoking cessation. Clinical pharmacists lead the clinic and work to provide a well-rounded approach to help people stop smoking. Each group consists of five sessions that meet over the noon hour on Tuesdays. Patients must be older than 18, smoke daily, and be willing to quit smoking within the first 30 days of the clinic to participate in the clinic. Participation in the clinic is free and the clinical pharmacists are able work with the patient and providers to assess the need and appropriateness of pharmacotherapy options for cessation. To request this service, an electronic consult form is available in IPR as an e-Order. The order is titled: Smoking Cessation Group Clinic Consult and can be found in the Consults folder under the FCC Family Practice and Master folders. Questions may be directed to Ann Philbrick at 356-8795 or 5527. **New clinics start April 15th and June 3rd.**

UIHC Smoking Cessation Clinic: *Self Reported Quit Rates*

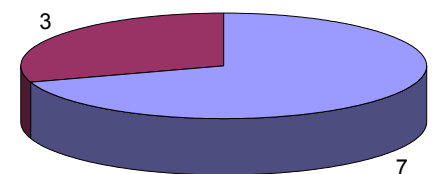
Quit Rates At 3 Months



Quit Rates at 3 months
Excluding Never Quit



Quit Rates at 6 Months



■ Smoke Free ■ Not Smoke Free

Authored by:

CoraLynn Trewet, MS, Pharm.D., Broadlawns Family Practice Program, Des Moines, IA

Special thanks to Megan Meyer and Brett Parker, PharmD Candidates, for help with this issue.