



# Family Medicine Clinical Pharmacy Forum

## Vol. 4, Issue 6 (November/December 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.*

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### Relation of $\beta$ -Blocker Induced Heart Rate Lowering and Cardioprotection in Hypertension

According to a recent meta-analysis published in the *Journal of the American College of Cardiology*, beta-blocker induced heart rate lowering may not be beneficial for patients with hypertension. The investigators searched MEDLINE, EMBASE, and CENTRAL databases for studies released from 1966 to May 2008 that evaluated beta-blockers as first-line therapy for hypertension. A total of 22 randomized controlled trials were identified, of which 9 included heart rate data. In total, 34,096 patients received beta-blockers, 30,139 received other antihypertensive agents, and 3,987 received placebo. The beta-blocker treated patients experienced a significant decrease (12%) in heart rate, whereas the comparison group had a non-significant decrease (1%). Paradoxically, the lower heart rate was associated with a statistically significant increase in relative risk for several end points, including all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and heart failure. The researchers hypothesized that pharmacologically-induced bradycardia may lead to dyssynchrony between pulse waves, thereby increasing central aortic pressure and hemodynamic burden to target organs. Beta-blockers should continue to be recommended as indicated for heart failure, myocardial infarction, and tachyarrhythmias; however, in the absence of these compelling indications, beta-blockers should be used cautiously.

*J Am Coll Cardiol.* 2008 Oct 28;52(18):1482-9

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### **Controversy Surrounding Off-Label Use of FDA Approved Medications**

In a recent study published in the journal of *Pharmacotherapy*, researchers from Stanford University and the University of Illinois-Chicago expressed concerns regarding 14 medications that are widely prescribed for off-label indications. In compiling their list, the researchers identified three key factors: volume of off-label drug use with inadequate evidence supporting that use, safety of the candidate drug, and a composite factor representing cost, recency of market entry, and degree of promotion or marketing. The authors assert that their model suggests how future research efforts could be focused on a small set of high-priority off-label uses where in-depth evaluation can be expected to provide the greatest value. The medications implicated in the study are listed below, with the associated on-label and off-label uses listed.

*Pharmacotherapy* 2008; 28(12):1443-1452

Medication Name	Most Common On-Label Use	Most Common Off-Label Use
1. Quetiapine	Schizophrenia	Bipolar, maintenance
2. Warfarin	Atrial Fibrillation	Hypertensive heart disease
3. Escitalopram	Depression	Bipolar
4. Risperidone	Schizophrenia	Bipolar, maintenance
5. Montelukast	Asthma	COPD
6. Bupropion	Depression	Bipolar
7. Sertraline	Depression	Bipolar
8. Venlafaxine	Depression	Bipolar
9. Celecoxib	Joint sprain or strain	Fibromatosis
10. Lisinopril	Hypertension	Coronary artery disease
11. Duloxetine	Depression	Anxiety
12. Trazodone	Depression	Sleep disturbance
13. Olanzapine	Schizophrenia	Depression
14. Epoetin alfa	Chronic renal failure	Anemia of chronic disease

### **New American College of Physicians (ACP) Guidelines for Use of Antidepressants**

The efficacy and safety of the second generation antidepressants bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of depressive disorders in adults were evaluated in a meta-analysis by the ACP to establish clinical guidelines.

Overall, there were no substantial differences between the second generation agents for the treatment of major depressive disorder. This applies to all phases of treatment, response to a second agent after initial treatment failure, treatment of accompanying symptom clusters, and various subgroups. Any statistically significant differences in efficacy and effectiveness were small and not believed to be clinically significant. Onset of action was the only variable that was found to have a statistically and clinically significant difference between agents. Mirtazapine was found to have a significantly faster onset of action compared to several SSRIs. Adverse drug events were similar among the second generation antidepressants, with sexual dysfunction being the only adverse event to demonstrate a difference. Bupropion was associated with the lowest rate of sexual dysfunction and paroxetine was associated with a higher rate.

*Ann Intern Med.* 2008 Nov 18;149(10):734-50

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### **Consensus Algorithm for Management of Hyperglycemia**

The ADA and the EASD have revised their consensus algorithm for the medical management of type 2 diabetes. The goal of therapy is to achieve and maintain A1C levels <7% as quickly as the titration of medication will allow.

They recommend the initiation of lifestyle intervention and metformin at diagnosis. Metformin should be titrated to the maximal effective dose over 1-2 months, as tolerated by the patient. Addition of either a sulfonylurea or basal insulin should be started within 2-3 months after diagnosis if a patient is not at glycemic goals, or anytime a patient has an A1C >7%. Basal insulin should be favored in patients with an A1C >8.5%. Insulin therapy should be started or intensified if the patient still fails to achieve target A1C levels. The early addition of insulin is stressed in patients who do not meet target goals.

Less well-validated therapies which may be considered as alternatives include exenatide (Byetta<sup>®</sup>) and pioglitazone (Actos<sup>®</sup>). These agents may be added if a patient is not at goal after using metformin and lifestyle intervention alone and hypoglycemia is undesirable, taking into consideration the side effects and costs associated with these drugs. If a patient is close to target A1C levels (A1C<8%), a third oral antidiabetic agent may be considered. This is usually not preferred as it is no more effective and more expensive than initiating or intensifying insulin.

Agents that are not considered in either tier of preferred agents include amylin agonists (Symlin<sup>®</sup>),  $\alpha$ -glucosidase inhibitors (acarbose, Glyset<sup>®</sup>), glinides (Starlix<sup>®</sup>, Prandin<sup>®</sup>), and DPP-4 inhibitors (Januvia<sup>®</sup>). These medications are not considered in either tier of preferred agents due to limited clinical data, relative expense, and/or lower overall effectiveness at lowering glucose. The consensus group unanimously advised against the use of rosiglitazone (Avandia<sup>®</sup>).

*Diabetes Care. Medical Management of Hyperglycemia in Type 2 Diabetes: a Consensus Algorithm for the Initiation and Adjustment of Therapy. 2008*

### **New Medication: Tapentadol (trade name pending)**

Tapentadol immediate-release tablets received approval from the FDA on November 21, 2008. Tapentadol is approved for the relief of moderate to severe acute pain in adults 18 years of age or older. Tapentadol is a centrally-acting analgesic with a unique dual mode of action as an agonist at the  $\mu$ -opioid receptor and as a norepinephrine reuptake inhibitor. Johnson & Johnson, the company marketing tapentadol, must wait for a drug scheduling decision from the DEA before tapentadol can be made available for distribution. Although official labeling for the new product has not been released by the company or FDA, the tablets have been approved in 50mg, 75mg and 100mg doses. In one Phase 3 clinical study comparing tapentadol-IR and oxycodone-IR, the most common treatment emergent adverse events for both groups were nausea, vomiting, dizziness, constipation, headache, and somnolence. While the incidence of nausea, vomiting, and constipation were significantly lower in the tapentadol-IR treated groups compared to the oxycodone-IR groups, the incidences of dizziness and somnolence were not significantly different between the treatment groups.

[http://www.pricara.com/pricara/pages/112108\\_press\\_release.jsp](http://www.pricara.com/pricara/pages/112108_press_release.jsp)

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### **Haemophilus influenzae Type b (Hib) Conjugate Vaccine Shortage**

Merck & Co. is reporting that the current shortage of Hib vaccine (PedVaxHIB® and Comvax®) will continue until mid-2009. All providers should continue to use the modified vaccination schedule, vaccinating all infants with the primary series (see below) while deferring the 12-15 month booster dose in all children except those at high risk. All high-risk children should receive the 12-15 month booster dose as scheduled. High-risk children include those with sickle cell disease, leukemia or other neoplasm, asplenia, HIV or other immunosuppressed states, as well as American Indian or Alaskan Natives.

The appropriate number of Hib doses required for the primary series depends on the product being administered. The two unaffected vaccines, ActHIB® and TriHIBit®, are PRP-tetanus toxoid (PRP-TT) conjugate Hib vaccines. PedvaxHIB® and Comvax® are recommended as a 2-dose primary series (at ages 2 and 4 months), whereas ActHIB® is recommended as a 3-dose primary series (at ages 2, 4, and 6 months). ActHIB® and PedvaxHIB® also are licensed for the 12--15 month booster dose. TriHIBit® is licensed only for the 12--15 month booster dose.

Because the Hib vaccine shortage has been ongoing since December 2007, the CDC is encouraging all health-care providers to be vigilant regarding the possibility of invasive Hib disease. Suspected cases of invasive Hib disease should be thoroughly investigated and reported to local public health authorities.

[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5746a2.htm?s\\_cid=mm5746a2\\_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5746a2.htm?s_cid=mm5746a2_e)

### **Varicella vaccine (MMRV and Shingles) Shortage**

It is anticipated that the shingles vaccine shortage will be nearly resolved by the end of January 2009. Zostavax ® is currently being shipped to providers/vendors to fill all backorders. Patients requesting the vaccine can be reassured that it should be available within the next several weeks.

MMRV (ProQuad®) continues to be temporarily unavailable until at least mid-2009. Continue vaccinating children and adults with the separate vaccines, MMR and Varicella. Due to the increased incidence of vaccine related adverse events associated with the combination product, vaccination with the individual products may be preferred.

[www.cdc.gov](http://www.cdc.gov)

### **Medicare Part D changes for 2009**

Substantial changes to Medicare Part D prescription drug plans are scheduled for 2009. For plans that provide coverage to Iowans, premiums have increased 15-50%. In addition to substantial increases in plan premiums, deductibles and co-payments have increased as well. Several plans have a four-tier system of coverage. Depending on plan specifics and the medication prescribed, it appears it will not be unusual for beneficiaries to have \$100 + co-payments for non-formulary brand name medications.

Prescription drug coverage after beneficiaries reach to upper limit (~\$2700) of coverage, sometimes referred to as the “Gap” or “Donut hole” will continue to be problematic in 2009.

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There are a few plans that offer coverage on generic medications when the patient is in the gap, but there are no plans that offer coverage on brand name medications in the gap. The premiums for plans that offer this gap coverage are significantly higher than no gap coverage plans. It seems reasonable to expect calls from patients early in 2009 looking for solutions to the high co-payments for brand name medications.

<http://www.medicare-partd.com/PartD-Medicare-PartD-PDP-for-Iowa-Iowa.php?st=IA&prodid=240>

### **E-Prescribing Incentives under Medicare Part B**

Effective January 1, 2009, CMS is offering financial incentive to patient care providers who utilize E-Prescribing technology as a prescription delivery method. The incentive program provides a 2% rebate on all eligible Medicare Part B (Fee for Service) claims submitted by qualified providers. Eligible Part B claims are primarily limited to outpatient, office-based claims.

For incentive payments to occur, providers must utilize e-prescribe specific G codes for eligible claims a minimum of 50% of the time. The G codes specify if the prescriber utilized e-prescribe for prescription authorized during the visit (G8443), if no prescriptions were authorized during the visit (G8445) or if e-prescribe is not used due to regulatory issues (narcotics), pharmacy not able to receive e-prescriptions or patient request (G8446). No “credit” is provided for refilling of prescriptions not associated with an eligible office visit.

In 2012, the incentive program will evolve into a disincentive program, where eligible providers NOT using e-prescribe will have Medicare payments reduced by 1%. The amount of fee reduction is scheduled to increase in subsequent years. As with most CMS programs, there are many details to review to assure compliance with the program. See this website for details: [http://www.cms.hhs.gov/PQRI/03\\_EPrescribingIncentiveProgram.asp#TopOfPage](http://www.cms.hhs.gov/PQRI/03_EPrescribingIncentiveProgram.asp#TopOfPage)

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