

CPS Insider is a quarterly client newsletter produced by the University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS).

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## At a Glance



### Noteworthy

A Meta-Analysis of  
 Second Generation  
 Antipsychotics



### What's New at UMMS?

UMMS CPS' Fellowship  
 in Pharmacoeconomics  
 and Outcomes Research

## New Generics

- **Dorzolamide HCl; timolol maleate (Cosopt®)**  
 Approved: 10/28/2008  
 Launched: 10/28/2008
- **Dorzolamide HCl (Trusopt®)**  
 Approved: 10/28/2008  
 Launched: 10/28/2008
- **Sumatriptan injection (Imitrex®)\***  
 Launched: 11/6/2008
- **Levetiracetam (Keppra®)**  
 Approved: 11/4/2008  
 Launched: 11/14/2008†
- **Sumatriptan tablet (Imitrex®)\***  
 Launched: 11/24/2008
- **Calcitonin-salmon (Miacalcin®)**  
 Approved: 11/17/2008  
 Launched: 12/9/2008

\*GSK-authorized generic equivalent

†Only for 250 mg, 500 mg, and 750 mg tablets

Information available at [www.fda.gov/cder/ogd/](http://www.fda.gov/cder/ogd/)

## Drug Watch



### Banzel® (rufinamide)

Approved: 11/14/2008

Manufacturer: Eisai Co., Ltd.

Formulation: Oral tablet

Cost (AWP): \$1.56/200 mg

Rufinamide is a new antiepileptic agent that has been FDA-approved for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 4 years and older. LGS is a form of epilepsy characterized by multiple types of seizures in the presence of mental retardation or neurologic abnormalities. The medication exerts its effect on sodium channels to prolong channel inactivation and reduce periods of sustained repetitive firing.

The recommended initial dose for children is 10 mg/kg/day, divided into two equal doses, and then increased by 10 mg every other day. The recommended initial dose for adults is 400–800 mg/day, in two equal doses, and then increased by 400–800 mg every two days. The maximum daily dose is 3200 mg/day. Rufinamide is available in 200 mg and 400 mg oral tablets.

Common adverse events include CNS effects. Antiepileptic drugs increase the risk of suicidal thoughts or behavior and patients should be monitored closely for these effects. Rufinamide is contraindicated in patients with Familial Short QT syndrome.

Rufinamide provides a new option for patients previously limited to treatments of valproic acid, lamotrigine, topiramate, felbamate, and carbamazepine.



### Tapentadol

Approved: 11/20/2008

Manufacturer: Johnson & Johnson

Formulation: Oral tablet

Cost (AWP): Unavailable

Tapentadol is a centrally acting analgesic that acts as a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. It is FDA-approved for the treatment of moderate to severe acute pain in adults over the age of 18. It will be supplied as immediate-release 50 mg, 75 mg, and 100 mg tablets.

Like other mu-opioid receptor agonists, tapentadol may result in respiratory and CNS depression. It is contraindicated in patients with severe respiratory disease, or paralytic ileus, as well as in patients currently taking monoamine oxidase inhibitors. Tapentadol should be used cautiously in patients taking other CNS depressants as this may result in an additive depressant effect. The most common adverse events include: nausea, vomiting, dizziness, headache, and somnolence.

A trade name for tapentadol has not yet been identified. Because of the abuse potential for this product, it is currently undergoing U.S. Drug Enforcement Agency review to determine its controlled substance schedule. The manufacturer estimates that tapentadol will become available in March 2009. Tapentadol represents a new option for patients without adequate pain relief with current opioid therapy.

## New FDA-Approved Indications

- **Seroquel XR® (quetiapine fumarate)**  
Approved on 10/8/2008. Quetiapine fumarate is indicated for monotherapy treatment of bipolar depression and bipolar mania.
- **Apidra® (insulin glulisine [rDNA origin] injection)**  
Approved on 10/24/2008. Insulin glulisine is indicated for the treatment of children with diabetes ages 4 and older.
- **Norditropin® (somatropin [rDNA origin] injection)**  
Approved on 10/31/2008. Somatropin is indicated for the treatment of growth failure in children born small for gestational age with no catch-up by age 2 to 4.
- **Ranexa® (ranolazine)**  
Approved on 11/5/2008. Ranolazine is indicated for the first-line treatment of chronic angina.

## New Formulations and Dosages

- **Keppra XR™ (levetiracetam)**  
500 mg extended-release tablet  
Approved: 9/12/2008
- **Sancuso® (granisetron)**  
3.1 mg/24 hours transdermal system  
Approved: 9/12/2008
- **Stalevo® (carbidopa/levodopa/entacapone)**  
75 mg (18.75 mg/75 mg/200 mg) and 125 mg (31.25 mg/125 mg/200 mg) tablets  
Approved: 10/28/2008

Information available at [www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

## Clinical Notes

### Depressive Disorder Treatment with Second Generation Agents— November 2008

#### 2008 Recommendations of the American College of Physicians: Selected Key Points

- The American College of Physicians recently released clinical practice guidelines for the pharmacologic management of the acute, continuation, and maintenance phases of major depressive disorder (MDD), dysthymia, and accompanying symptoms. The authors reviewed 203 studies from 1980 to April 2007 for 12 specific second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine).
- The efficacy of second-generation antidepressants in the acute phase showed no significant differences between SSRIs, SNRIs, SSNRIs, bupropion, trazodone, or nefazodone. The evidence to support this was collected from 80 head-to-head randomized-controlled trials (RCT) that compared SSRIs to other SSRIs, SNRIs, SSNRIs, and other second-generation antidepressants.
- Evidence from seven studies showed, after four weeks of treatment, response rates were similar among second-generation antidepressants. Mirtazapine had a statistically significant faster onset of response compared to citalopram, fluoxetine, paroxetine, and sertraline.
- Based on sub-analysis of age, sex, race/ethnicity, or comorbid conditions in several clinical trials, there was no difference in efficacy, effectiveness, and harm of second-generation antidepressants.
- Patient quality of life was evaluated in 18 trials as secondary outcomes, in which there were no observed differences among second-generation antidepressants.
- In general, treatment response and remission, within 6 to 12 weeks of treatment, were not achieved in 38 percent and 54 percent of the patients, respectively. The STAR\*D study provided the best evidence showing 1 in 4 patients who switched to sustained-release bupropion, sertraline, or extended-release venlafaxine after an initial treatment failure, became symptom-free. The three drugs studied showed no difference in efficacy.
- Evidence from four studies showed no difference between fluoxetine and sertraline, fluvoxamine and sertraline, paroxetine and duloxetine, or venlafaxine and trazodone for maintaining response or remission of MDD. In a meta-analysis of 31 RCTs, the continuation of antidepressant therapy helped reduce the risk of relapse.
- Summary of final recommendations:
  - The selection of a second-generation antidepressant for acute major depression on the basis of adverse event profiles, cost, and patient preference
  - The assessment of patient status, therapeutic response, and adverse effects on a regular basis, starting within 1 to 2 weeks of therapy initiation
  - The modification of treatment for MDD if there is an inadequate response to pharmacotherapy within 6 to 8 weeks of therapy initiation
  - The continuation of therapy for MDD at least 4 to 9 months after satisfactory response in patients with a first depressive episode and even longer in patients with two or more depressive episodes

Qaseem A, Snow V, Denberg TD, et al. Using Second-Generation Antidepressants to Treat Depressive Disorders: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med.* 2008;149:725-733.

# Advisories

## FDA Advisory Committee Recommends Removal of Asthma Indication for Selected LABAs

On 12/11/2008, a panel of federal drug experts voted that Serevent<sup>®</sup> (salmeterol) and Foradil<sup>®</sup> (formoterol) should no longer be indicated in the management of asthma. Other long-acting beta-2 agonists (LABA), Advair<sup>®</sup> (salmeterol/fluticasone) and Symbicort<sup>®</sup> (budesonide/formoterol), would continue to carry the indication. The recent LABA safety concerns arose when a meta-analysis reported a small but significant increased risk of asthma-related hospitalizations associated with LABA use, especially in children 4 to 11 years old. Serevent<sup>®</sup> was also associated with an increased risk of asthma-related death. All LABAs currently carry a Black Box warning regarding this risk. According to the data, Advair<sup>®</sup> is not

associated with an increased risk of respiratory complications. The data suggests that the increased risk associated with Serevent<sup>®</sup> and Foradil<sup>®</sup> is related to the lack of concurrent steroid therapy seen prescribed with these agents and their inappropriate use. Both Advair<sup>®</sup> and Symbicort<sup>®</sup> are combination agents containing a corticosteroid. The manufacturers of Serevent<sup>®</sup> and Foradil<sup>®</sup>, Novartis and GlaxoSmithKline, reject the panel's decision but have agreed to cooperate. Both medications are also indicated for the management of chronic obstructive pulmonary disorder.

## Chantix Has Most Adverse Events of Any Medication

On 10/22/2008, the Institute for Safe Medication Practices (ISMP) released a report indicating that the number of serious adverse drug reactions and deaths reported to the FDA increased by

38 percent during the first three months of 2008 compared to the average of the previous four quarters. There were nearly 21,000 reports, which include approximately 4,825 deaths. Chantix<sup>®</sup> (varenicline) had the most reports of any other medication. Earlier in the year, the FDA released a warning about possible suicidal behavior and vivid dreams associated with varenicline use and banned its use by pilots this past summer. Since the approval of varenicline in 2006, a total of 3,325 injuries have been reported, including 112 deaths. According to the recent reports from the ISMP, varenicline was linked to 1,001 serious adverse events such as blackouts or loss of consciousness, which led to traffic accidents in 15 individuals. Pfizer has stated that the number of reports is linked to recent publicity regarding the drug's side effects.



## From The Hill

### Federal

#### New Bill Targets Rogue Pharmacies on the Internet

On 9/30/2008, the Senate voted unanimously to approve a bill aimed at stopping the operation of online rogue pharmacies in the United States. The bill reflects the growing concern that online pharmacies enable patients to purchase drugs with few restrictions. The legislation would make it harder for people to obtain prescription medications over the Internet. Under the new legislation, a prescription would only be considered valid if the patient has been seen in person by a health care professional (HCP). In addition, information identifying the business and the associated HCPs would be required to be displayed on the website. Furthermore, state attorneys general would now be allowed to close rogue online pharmacies across all states and increase penalties for those illegally distributing prescription drugs and other controlled substances. Penalties would double for certain drugs and imprisonment of up to 30 years would be possible if death or serious injury resulted from using a drug obtained from a rogue website.

For additional information, please visit <http://online.wsj.com/article/SB122351521815117817.html>

### State

**Massachusetts:** A recent investigation discovered that some hospitals in Massachusetts receive higher payments from private insurers even though there is no apparent difference in the quality of care among institutions. The data indicates that certain institutions receive payments 15 percent to 60 percent higher than their competitors. Some hospitals have now asked Governor Patrick to address these payment disparities. The investigation highlights the bargaining power that hospitals with powerful brand names, elite reputations, or convenient geographical locations have with insurers. Massachusetts' current deregulated system could cause problems with the state's new 2006 health insurance law, leading to significant differences with equity and affordability of health care services among patients within the Commonwealth. Currently, payment rates are contained in private contracts between insurers; however, the state has approved the launch of a website designed to report what insurers pay individual hospitals as well as how the hospitals rank on quality measures.

For additional information, please visit [http://www.boston.com/news/local/massachusetts/articles/2008/11/20/state\\_urged\\_to\\_review\\_fees\\_to\\_elite\\_hospitals](http://www.boston.com/news/local/massachusetts/articles/2008/11/20/state_urged_to_review_fees_to_elite_hospitals)

## Pipeline

### Uloric® (febuxostat)

Febuxostat is an oral agent for the treatment of hyperuricemia associated with gout. It is a non-purine selective inhibitor of xanthine oxidase. Clinical trials have demonstrated efficacy and tolerability with daily doses of 40 mg and 80 mg. Dose adjustments are not required in patients with renal impairment. While early studies found a risk of mortality and heart problems associated with febuxostat, a larger Phase III study demonstrated no difference in the risks when compared to allopurinol. On 11/24/2008, an FDA advisory panel voted 12 to 0 in favor of the drug's approval. If approved, febuxostat would be the first new gout agent in 40 years.

### Denosumab

Denosumab, being developed by Amgen, is a fully-human monoclonal antibody administered twice-yearly via subcutaneous injection. It is a receptor activator of nuclear factor kappa B ligand (RANKL), which is responsible for the regulation of osteoclasts, cells that remove bone tissue.

Currently in Phase III trials for the treatment of several bone loss conditions, denosumab is being evaluated for use in both men and women. These conditions include post-menopausal osteoporosis and bone loss associated with cancer and chemotherapy. A Phase III head-to-head study against alendronate in women with osteoporosis demonstrated significantly greater increases in bone mineral density with denosumab ( $P < 0.05$ ). A trade name for denosumab has not yet been identified.

## Noteworthy

### A Meta-Analysis of Second-Generation Antipsychotics in the Treatment of Schizophrenia

The treatment of schizophrenia with atypical antipsychotics remains controversial due to the variability in treatment response and the prevalence of adverse reactions. A recent meta-analysis published in the American Journal of Psychiatry reported small but significant differences in the efficacy of the available atypical antipsychotic medications.

In the 78 head-to-head trials evaluated, efficacy was measured as the decrease in total score on the Positive and Negative Syndrome Scale (PANSS). A greater decrease in PANSS total score was observed with olanzapine compared to aripiprazole (weighted mean difference [WMD]= -5.0,  $P=0.002$ ), quetiapine (WMD= -3.7,  $P < 0.001$ ), risperidone (WMD= -1.9,  $P=0.006$ ), and ziprasidone (WMD= -8.3,  $P < 0.001$ ). A greater PANSS score decrease was also observed with risperidone compared to quetiapine (WMD= -3.2,  $P=0.003$ ) and ziprasidone (WMD= -4.6,  $P=0.002$ ).

Although the differences in efficacy were small, they could potentially have a large effect in the management of a chronic condition such as schizophrenia. Medication safety was not evaluated in the analysis, however adverse events, if severe enough, could take precedence over the small difference in efficacy between the medications. Tolerability and efficacy should therefore both be considered when selecting an atypical antipsychotic.

Leucht S, et al. AM J Psychiatry. 2008;AiA:1-12.

## What's New at UMMS?

In addition to our existing managed care residency accredited by the American Society of Health-Systems Pharmacists, in partnership with the Academy of Managed Care Pharmacy, we have recently developed a two-year fellowship. This fellowship is a highly individualized program with a focus on Health Outcomes and Pharmacoeconomic research, related to managed care. UMMS CPS prides itself on offering residents and fellows an extremely well rounded, real-world experience that puts them in direct contact with our clients and multidisciplinary health care teams, with the structured educational support of clinical experts in the field. Through exposure to drug policy development, hands-on clinical work, research, and clinical services marketing and administration, residents and fellows participate in an unmatched variety of experiences. Please visit [www.umassmed.edu/cps](http://www.umassmed.edu/cps) for more information on these programs.



## UMMS Clinical Pharmacy Services: Who We Are and What We Do

The University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS) is a comprehensive prescription drug management program developed in 1999 as part of UMMS' Commonwealth Medicine division, primarily to provide drug utilization review for Massachusetts Medicaid. Today, CPS brings exceptional depth and experience in the development and implementation of unique, client-customized managed care-related clinical pharmacy functions including, but not limited to, evidence-based formulary support, drug utilization review, medication therapy management, clinical call center support, and provider/patient education. 'CPS Insider' is an educational resource produced quarterly to deliver critical information at the highest level of quality to our clients. We hope that you find this resource of value and welcome your suggestions for improvement.



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