



Family Medicine Clinical Pharmacy Forum Vol. 5, Issue 4 (July/August 2009)

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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Pitavastatin (Livalo)

Pitavastatin has recently been FDA approved for the treatment of hypercholesterolemia and combined dyslipidemia. Pitavastatin is an HMG CoA reductase inhibitor very similar to other statins on the market. It will be available as 1, 2, and 4 mg tablets. Pitavastatin is manufactured by Kowa Pharmaceuticals. They are expected to launch pitavastatin early next year. Currently there is no label information available from the FDA.

Pitavastatin has already been on the market in Japan, South Korea, Thailand, and China for several years, so much of the data comes from clinical trials done in these countries. Pitavastatin has been proven effective in lowering LDL and triglycerides. **So far there are no published data on pitavastatin's effect on cardiovascular outcomes.** Pitavastatin has been shown to have a similar side effect profile as the other statins, with the most common side effects being muscle, joint, and back pain, and constipation.

So what makes pitavastatin different than all the other statins on the market? According to the manufacturer, pitavastatin is a more effective HMG CoA reductase inhibitor because of a unique cyclopropyl group in the drug molecule. This may lead to greater reduction in LDL cholesterol levels. So far there has been no difference in LDL lowering effects when pitavastatin is compared with other statins. In an 8 week study in Korea, **pitavastatin was compared to atorvastatin and no differences in reduction of LDL, total cholesterol, or triglycerides, or increases in HDL were found.** Another possible advantage of pitavastatin is that it undergoes minimal CYP450 metabolism. This may translate into fewer drug-drug interactions compared to the other statins.

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1. Manufacturer drug information. Accessed 8/7/09 from www.kowapharma.com/PressReleases/news080209.htm

2. Lee SH, Chung N, Kwan J, et al. Comparison of the efficacy and Tolerability of Pitavistatin and Atorvastatin: An 8-Week, Multicenter, Randomized, Open-Label, Dose-Titration Study in Korean Patients with Hypercholesterolemia. *Clin Ther.* 2007 Nov;29(11):2365-73.

Milnacipran (Savella) – A New SNRI for Fibromyalgia

Milnacipran is the 3rd drug approved by the FDA for management of fibromyalgia. It is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It inhibits NE reuptake with a 3-fold greater affinity than for serotonin. It undergoes predominately renal elimination (55% eliminated unchanged). It is pregnancy category C. Precautions and warnings for milnacipran are similar to other SNRI's.

One randomized, double-blind efficacy study evaluated milnacipran 100mg daily, 200mg daily, and placebo in patients with fibromyalgia. At 3 months, the percentage of patients who rated themselves as "much improved" or "very much improved" were 48% (100mg), 51% (200mg), and 33% (placebo).

Adverse effects which have been reported are noted below:

Adverse Event	Milnacipran-Savella (%) (N=1557)	Placebo (%) (N=652)
Constipation	16	4
Nausea	37	20
Vomiting	7	2
Hypertension	5	2
Hot flush	12	2
Hyperhidrosis	9	2

Milnacipran has notable effects on blood pressure. These are noted in the table below:

Blood Pressure Effect	Milnacipran-Savella (%)	Placebo (%)
Risk of HTN at study end (in non-hypertensive patients)	19.5	7.2
>15 mm Hg increase in SBP at study end (among hypertensive pts at baseline)	2-7	1
>15 mm Hg increase in SBP on 3 consecutive visits	6-9	2

Dosing:

-Day 1: 12.5mg, Day 2-3: 12.5mg BID, Days 4-7: 25mg BID, after day 7: 50mg BID

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Cost for 1 month supply: Savella 50mg BID (\$120); compared to Cymbalta 60mg QD (\$143), and Lyrica 150mg BID (\$152).

Summary: Savella is modestly effective at decreasing pain and improving function in fibromyalgia. Blood pressure will need to be monitored in patients receiving it. Male patients with a history of obstructive uropathy may experience higher rates of genitourinary adverse events. Patients will need to be withdrawn gradually following discontinuation as with other SNRI's and SSRI's.

Hgb A1c: A New Diagnostic Marker for Type II Diabetes

A report last month from the International Expert Committee (a committee appointed jointly by the American Diabetes Association, European Association for the Study of Diabetes, and the International Diabetes Federation) has proposed expanding the use of HgbA1c for the diagnosis of Type II diabetes mellitus. Because HgbA1c is a measure of serum glucose levels over time, it has been used extensively in the management of diabetes both as a goal of therapy and an indicator of the severity of the disease. For the same reason, it is being proposed as a tool for diagnosis. Many studies have shown the correlation between elevated HgbA1c and risk of macro- and microvascular complications. It would then make sense that patients with an elevated HgbA1c, who are at higher risk for these complications, should be diagnosed as diabetic and be treated as such.

In previous Expert Committee reports, HgbA1c has not been recommended as a diagnostic tool, primarily because of the lack of standardization that lead to variability in results. Recent advancements in standardization and accuracy have lead to the revision of their recommendation. Compared to fasting glucose measurements, the HgbA1c assay is actually easier to do because the samples are stable for a longer period of time at room temperature. It is also more convenient for the patient because they do not have to be fasting.

The recommended HgbA1c value for the diagnosis of diabetes is $\geq 6.5\%$. They recommend confirming diagnosis with a followup HgbA1c, unless the patient has symptoms or a glucose level of >200 mg/dL. This value is based on the correlation of HgbA1c and risk of retinopathy. Studies have found the risk of retinopathy increases significantly at HgbA1c values between 6-7%. It is suggested that patients with HgbA1c levels $<6.5\%$ and $\geq 6.0\%$ are at high risk of developing diabetes and could therefore benefit from some type of therapy.

There are some limitations of using HgbA1c as a diagnostic tool. The accuracy is dependent on the hemoglobin. Patients with hemoglobin abnormalities or any condition that effects red cell turnover such as major bleeding, transfusions, or malaria,

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will have inaccurate results. HgbA1c is not recommended for the diagnosis of Type I diabetes because of the more rapid onset. **It is also not recommended as a diagnostic test in pregnant women because they have more red blood cell turnover.**

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care*. 2009 Jul;32(7):1327-34.

Iowa Prescription Monitoring Program (PMP)

You may have heard about this recently. The Iowa PMP is a free, web-based database which Iowa prescribers and pharmacists may access to evaluate their patients' use of controlled substances. The website has been operational now since March 2009. This site may assist practitioners in determining appropriate treatment options and to improve the quality of patient care. The Website's address is <https://pmp.iowa.gov/IAPMPWebCenter/>.

The PMP is a new health care tool for practitioners by assisting in identifying potential diversion, misuse, or abuse of controlled substances by their patients while facilitating the most appropriate and effective medical use of those substances.

Pharmacies across Iowa transfer information into this database **twice each month** which lists the controlled substance prescriptions they have filled for patients. The database contains all controlled substance prescriptions filled since January 1, 2008. If you need help getting started using this site (e.g. user ID/password) call 515-281-5944 or email: terry.witkowski@iowa.gov.

If you are concerned for the potential of a patient abusing or misusing controlled substances, just go to the website, click on "Requests", then click on "Submit" and enter your patient's name and date of birth. A report will then be generated in a few seconds. **The site seems to work best if you only enter "last name", "first name", and "date of birth" in the search parameters.**

Commentary: I just started using this site 1-2 weeks ago. I am very pleased with how fast it is and easy to use. **You will never have to wonder again if the patient you are talking with in the clinic about pain is seeing multiple providers or pharmacies of which you are unaware.** At our clinic, using this website will replace the traditional phone call to the local pharmacy "hotline" for concerns of potential controlled substance abuse.

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Vancomycin - An Update on Therapeutic Monitoring

In January 2009, three professional organizations (ASHP, IDSA, and SIDP) published a joint consensus review regarding therapeutic monitoring of vancomycin in adults (Rybak M et al. Am J Health-Syst Pharm 2009;66:82-98.)

Historically, the recommended target vancomycin trough concentration was <10 mg/L. More recently studies have suggested that trough concentrations <10 may predict therapeutic failure and the potential for emergence of resistant strains of MRSA.

The most notable recommendations from the guidelines are listed below:

Recommendation	Level of Evidence
● Troughs should be obtained just prior to the next dose at steady state (after 4th dose)	IIB
● Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid developing resistance	IIIB
● Trough concentrations of 15-20mg/L are considered optimal for complicated infections (e.g. endocarditis, osteomyelitis, meningitis, and pneumonia) caused by <i>Staph aureus</i>	IIIB
● Daily doses of 15-20 mg/kg (as actual body weight) given every 8-12 hours are recommended for most patients with normal renal function to achieve the suggested serum concentration when the MIC is ≤ 1 mg/L.	IIIB
● In seriously ill patients, a loading dose of 25-30mg/kg (based on actual body weight) can be used to rapidly attain target concentrations	IIIB

The big picture message from these new guidelines seems to be: 1.) Target a trough >10 in everyone (regardless of type of infection), and 2.) Target a trough of 15-20 in complicated infections (e.g. bone, joints, bacteremia, etc.).

How Useful are the Beers criteria in Identifying Problem Prescribing?

Drugs-to-avoid criteria are commonly used to evaluate prescribing quality in elderly patients. Despite the widespread use of such criteria, evidence of their validity as markers of prescribing quality for elderly patients is mixed.

Steinmen MA et al evaluated the medications from 256 Iowa City VA elderly (>65 years) outpatients who were taking 5 or more medications. After a comprehensive patient interview (by physician and pharmacist), the team recommended that certain drugs be discontinued, substituted, or reduced in dose. The researchers evaluated the degree to

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which drugs considered potentially inappropriate by the “drugs-to-avoid criteria” (of Beers et al and Zhan et al) were also considered problematic by the study team, and vice versa.

The 256 patients were using 3678 medications. The physician-pharmacist team identified 15% of drugs as problematic, while 6% and 2.5% were flagged as potentially inappropriate by the Beers criteria and Zhan criteria, respectively. Kappa statistics for concordance were 0.10 – 0.14; showing only slight agreement with the individualized review. **Of note, 61% of drugs identified as potentially inappropriate by the Beers criteria and 49% of drugs flagged by the Zhan criteria were not judged as problematic by the expert reviewers.** Moreover, the Beers and Zhan criteria identified only 8-15% of drugs that experts judged to be problematic.

The authors concluded that drugs-to-avoid criteria have limited ability to differentiate between drugs and patients with and without prescribing problems identified on individualized expert review.

Notes: Drugs-to-avoid criteria (e.g. Beers and Zhan criteria) have increasingly been used as quality measures to assess and compare prescribing quality across providers and health systems. This study highlights substantial problems which exist when these criteria are used in this manner.

Steinman MA et al. *Arch Intern Med* 2009;169(14):1326-1332.

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