

# drug therapy topics supplement

A Timely Discussion of Contemporary Issues

by Milo Gibaldi, Ph.D., School of Pharmacy

## CONTENTS

### CLINICAL PRACTICE

- Echinacea Offers No Benefit for Rhinovirus Infections
- NIH Panel Offers Advice on Managing Menopause
- Immediate vs. Deferred Drug Treatment for Early Epilepsy
- Wider Student Use Is Urged for New Meningitis Vaccine

### NEW DRUGS & INDICATIONS

- First-Approved Glycylcycline Is Aimed at Difficult-to-Treat Infections
- Tipranavir Granted Approval in Combination for HIV Infection

### DRUG EVALUATION

- Erlotinib in Non-Small-Cell Lung Cancer: Predictors of Outcome
- Long-Term Adefovir for HBeAg-Negative Chronic Hepatitis B

### DRUG SAFETY

- SSRIs and Antiplatelet Activity: An Update
- Safety Warnings for Fentanyl Transdermal Patch
- Endometrial Cancer and Postmenopausal Hormone Therapy
- New Warnings for Mifepristone and Misoprostol

### Drug Therapy Topics Supplement

A Drug Information Center / School of Pharmacy publication.  
Written by Milo Gibaldi, Ph.D.  
Edited by Tami Daley, with assistance from Nelda A. Murri, Pharm.D., and Elizabeth Rudy, D.V.M., R.Ph.  
Prepared by Sandra Walston, M.C.  
(206) 598-6612  
<http://uw.pmr.org/>

Copyright © 2005  
by the University of Washington.  
No material may be reproduced in whole or in part without permission.

## CLINICAL PRACTICE

### Echinacea Offers No Benefit for Rhinovirus Infections

Echinacea is among the most widely used herbal remedies in the U.S. In the late 1800s, echinacea preparations became popular as remedies for the common cold. Renewed interest in echinacea followed the passage of the Dietary Supplement Health and Education Act in 1994, which essentially barred the regulation of herbal medicines. Since efficacy studies with echinacea have produced conflicting results, researchers launched a clinical trial using an experimental model for colds caused by rhinoviruses to evaluate systematically the effect of different echinacea constituents on experimental infection and symptoms [*N Engl J Med* 2005;353:341-48].

Three distinct preparations of echinacea were produced by differential extraction from *Echinacea angustifolia* root. A total of 437 volunteers were randomly assigned to receive either prophylaxis, initiated seven days before virus challenge, or treatment, initiated at the time of challenge, either with one of these preparations or with placebo.

Data available for 399 participants showed no statistically significant effects of the three echinacea extracts on rates of infection or severity of symptoms. The authors of the report note that, given the variety of echinacea preparations, "it will be difficult to provide conclusive evidence that echinacea has no role in the treatment of the common cold." Nevertheless, they conclude that their findings "add to the accumulating evidence that suggests that the burden of proof should lie with those who advocate this treatment."

The study was sponsored by the National Center for Complementary and Alternative Medicine (NCCAM). The author of a related editorial accuses the center of investigating implausible remedies, rarely producing useful information [*Ibid* 337-39]. "Disproof rarely leads the supplement industry to reduce production or the public to decrease use. In fact, advocates often dismiss disproof." This, most assuredly, will be the case for echinacea.

### NIH Panel Offers Advice on Managing Menopause

Prompted by the unexpected findings from the Women's Health Initiative (WHI), confusion reigns as to the appropriate use of menopausal and postmenopausal hormone therapy. The situation has compelled the NIH to convene an expert panel as the first step toward determining safe, effective approaches in managing symptoms of menopause [*JAMA* 2005;293:2329-31].

(Continued on Supplement page 2)

## CLINICAL PRACTICE (continued)

### NIH Panel Offers Advice on Managing Menopause (continued)

WHI results showed unopposed estrogen and estrogen plus progestin therapy can increase the risk of coronary heart disease, thromboembolism, stroke, and breast cancer. Many women stopped using hormones after the findings of the WHI were made available. Lost in the consternation was that the landmark study evaluated hormone use for chronic disease prevention, not the treatment of perimenopausal symptoms.

The panel's draft statement calls menopause "a normal healthy phase of women's lives that does not require medical care." Symptoms are intolerable in only a minority of women. The evidence shows that hot flashes, night sweats, vaginal dryness, and painful intercourse result from estrogen loss rather than aging. In many of the controlled estrogen trials, debilitating symptoms such as hot flashes, improved over time in about one-third of women in the placebo group.

On discussing specific treatments for menopausal symptoms, panel members concluded that there is no evidence to support the use of botanicals, acupuncture, homeopathy, traditional Chinese medicine, or other

complementary and alternative therapies to treat hot flashes. Similarly, the panel found little evidence to support the use of dietary soy for symptom relief. On the other hand, behavioral interventions are a promising area for symptom treatment.

Estrogen alone or with progestin has been shown to be the most consistently effective treatment for hot flashes and night sweats. The panel said that estrogen therapy for symptomatic women should be used at the lowest effective dose for the shortest amount of time. Data are not available to support greater precision.

The panel's remarks drew considerable criticism. A professor of obstetrics and gynecology at USC said she disagrees with the panel's assessment that "menopause should not be considered a condition that requires routine medical care." She added, "It should be automatic to offer estrogen as an option." The panel's report is available online at <http://consensus.nih.gov>. The evidence review is available at <http://www.ahrq.gov/clinical/tp/menopstp.htm>.

### Immediate vs. Deferred Antiepileptic Drug Treatment for Early Epilepsy

When to initiate treatment with anticonvulsant drugs in patients with few or infrequent seizures is not an easy decision. Medical, psychological, and sociologic factors must be taken into account. In an effort to answer this question, researchers in the UK undertook a randomized but unblinded study of immediate and deferred antiepileptic drug treatment (mainly with carbamazepine or valproate) in 1443 patients, mainly teenagers and young adults [*Lancet* 2005;365:2007-13].

They found that immediate treatment increased time to first and second seizures and to first tonic-clonic seizure. It also reduced the time to achieve two-

year remission of seizures. However, immediate treatment does not affect long-term remission in these patients. At five-year's follow-up, 76% in the immediate treatment group and 77% of those in the deferred treatment group were seizure-free between three and five years after randomization. Furthermore, at two years, the benefits of improved seizure-control with immediate treatment seem to be balanced by the undesirable effects of drug treatment and there is no improvement in quality of life. A related editorial states that the results of the study suggest there is little to gain in the long term from starting medication immediately [*Ibid*, 1985-86].

### Wider Student Use Is Urged for New Meningitis Vaccine

About 3000 people in the U.S. develop meningococcal disease each year; about 10% die as a result and up to 15% of those affected suffer permanent disabilities. A new meningitis vaccine called *Menactra* has become available and the Centers for Disease Control and Prevention are urging its wide use for adolescents and college freshmen. The agency recommends that all 11- and 12-year-olds be routinely immunized. The

agency also recommends using *Menactra* to protect high-school freshman or children younger than 15, whichever comes earlier. College freshman living in close quarters of dormitories are at higher risk for meningococcal disease compared with peers; they too require protection. When adequate supplies of *Menactra* become available, the CDC is likely to recommend that the vaccine be given to all people ages 11 through 19.

## NEW DRUGS AND INDICATIONS

### First-Approved Glycylcycline Is Aimed at Difficult-to-Treat Infections

Tigecycline (*Tygacil*) has been approved by the FDA for intravenous treatment of adults with complicated intra-abdominal infection and complicated skin and skin structure infections caused by a broad range of organisms including methicillin-resistant *Staphylococcus aureus*. According to a report on the American Pharmacists Association's website, pharmacist.com, "Tigecycline binds to the 30S subunit of bacterial ribosomes, thereby inhibiting protein translation and blocking entry of transfer RNA."

In clinical trials, empiric therapy with tigecycline provided clinical cure rates in complicated skin and skin structure infections comparable to vancomycin and aztreonam. The drug should be administered cautiously in patients with known hypersensitivity to tetracyclines. In pre-approval clinical studies, the most common treatment-related adverse events in patients treated with tigecycline were nausea (30%) and vomiting (20%). Dosage adjustment is not required for patients with impaired renal function.

### Tipranavir Granted Approval in Combination for HIV Infection

The FDA has granted accelerated approval of an HIV-protease inhibitor called *Aptivus* (tipranavir) based on 24-week data from ongoing studies. Tipranavir must be taken with ritonavir (*Aptivus/r*) to increase the blood levels of the new drug; else, levels of *Aptivus* are insufficient to inhibit HIV replication. The new medication appears to inhibit HIV replication for many strains of the virus that are resistant to other available protease inhibitors.

According to *MD Consult* [24 June 2005], *Aptivus*, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1-infected adult patients with evidence of viral replication, who are highly treatment experienced, or have HIV-1 strains resistant to multiple protease inhibitors. Patients enrolled in the ongoing studies were failing their current protease inhibitor-based regimen, had received at least two protease inhibitor-based regimens, had received at least three classes of antiretroviral agents, and had documented protease inhibitor resistance.

These trials examined treatment response at 24 weeks of *Aptivus/r* versus a comparator group in which patients received one of several mar-

keted ritonavir-boosted protease inhibitors—lopinavir, indinavir, saquinavir, and amprenavir. All patients also received an optimized background regimen of other antiretroviral drugs. The results of these studies showed that a statistically significant greater proportion of HIV-positive patients taking *Aptivus/r* achieved a treatment response—defined as a one log or greater decrease in viral load from baseline—compared with the comparator group (40% vs. 18%).

Furthermore, a significantly greater proportion of patients receiving regimens that contained boosted *Aptivus* were able to reduce the amount of HIV in their blood to undetectable levels than in the boosted comparator group. About one-third of patients in the *Aptivus* group achieved a viral load of less than 400 copies and about one-quarter achieved a viral load of less than 50 copies per ml, compared with 16% and 9% in the comparator group, respectively.

Caution must be observed when administering *Aptivus* to patients with elevated transaminases, hepatitis B or C co-infection or any other underlying hepatic impairment. Liver enzyme

(Continued on Supplement page 4)

## NEW DRUGS AND INDICATIONS (continued)

### Tipranavir Granted Approval in Combination for HIV (continued)

tests should be carried out before starting therapy with *Aptivus*/r and frequently during treatment. One must also be alert to the fact that *Aptivus*/r has an extensive drug-drug interaction potential with a large number of diverse medications. Like

other protease inhibitors, *Aptivus*/r may be associated with the development or worsening of diabetes, elevations in cholesterol and triglycerides, and abnormal distribution of body fat.

## DRUG EVALUATION

### Erlotinib in Non-Small-Cell Lung Cancer: Predictors of Outcome

Erlotinib (*Tarceva*) inhibits the tyrosine kinase activity of epidermal growth factor receptor (EGFR) and has demonstrated activity against non-small-cell lung cancer (NSCLC). Now, a multinational research team reports that treatment with erlotinib can increase the survival of patients with NSCLC that have failed first- or second-line chemotherapy [*N Engl J Med* 2005;353:123-132]. The researchers also show that while EGFR mutations can predict a response to erlotinib, such mutations are not predictive of a survival benefit [*Ibid*, 133-44].

In the placebo-controlled study, patients with late-stage NSCLC were eligible if they had received one or two prior chemotherapy regimens. About half the 731 patients (median age 61.4 years) enrolled in the study had received two prior chemotherapy treatments and 93% had received platinum-based chemotherapy.

The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group; the median du-

ration of response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, a modest but statistically significant difference. Overall survival was 6.7 months and 4.7 months, favoring the erlotinib group. Side effects were common but only 5% of patients discontinued treatment.

The investigators then used tumor-biopsy samples from participants in the study to investigate whether outcomes were associated with expression by the tumor of EGFR and *EGFR* gene amplification and mutations. Nearly 60% of the patients who were tested had tumors that express EGFR. Multivariate analysis indicated that EGFR expression was a predictor of response (11% vs. 4%) as was polysomy or amplification of *EGFR* (20% vs., 2%). On the other hand, EGFR expression, copy number, or mutations did not influence survival after treatment with the drug. The results suggest that mutational analysis is not necessary to identify patients in whom treatment with EGFR inhibitors is appropriate.

### Long-Term Adefovir for HBeAg-Negative Chronic Hepatitis B

The goal of treatment for chronic hepatitis B virus (HBV) is to prevent cirrhosis, hepatic failure, and hepatocellular carcinoma. In theory, this is best achieved by eradicating HBV before irreversible liver damage occurs. Eradication of HBV, however, is all but impossible because of the presence of extrahepatic reservoirs of the virus and the integration of HBV DNA into the host genome. As a result, withdrawal of treatment is usually accompanied by rapid viral rebound [*N Engl J Med* 2005;352:2743-46].

There are five approved therapies for the treatment of chronic hepatitis B in the U.S. —interferon alfa-2b,

lamivudine, adefovir, entecavir, and pegylated interferon (peginterferon alfa-2a). FDA approval of hepatitis B therapies is based on responses after one year of treatment. However, few patients have a sustained response beyond this period. The net benefits of long-term treatment have not been studied adequately.

Noting that treatment with adefovir for 48 weeks resulted in histologic, virologic, and biochemical improvement in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B, investigators designed a study to evaluate the effect of continued

(Continued on Supplement page 5)

## Long-Term Adefovir for HBeAg-Negative Chronic Hepatitis B (continued)

therapy as compared with cessation of therapy [*Ibid*, 2673-81].

They assigned 185 patients to receive 10 mg adefovir or placebo, in a 2:1 ratio, once daily for 48 weeks. Thereafter, 48 patients receiving adefovir were again randomized to receive an additional 48 weeks of the drug or to switch to placebo. Patients initially assigned to placebo were switched to adefovir. Patients treated with adefovir during weeks 40 through 96 were subsequently offered continued therapy. The researchers report that the benefits achieved from 48 weeks of adefovir were lost when treatment was discontinued. In patients treated beyond 96 weeks through 144 weeks, benefits were maintained with infrequent emergence of viral resistance.

The main concerns with long-term treatment are side effects, drug resistance, and costs. In the trial cited

above, nephrotoxicity was observed in 3 of 70 patients who received adefovir and adefovir-resistance mutations were detected in 6 of 70 patients. Nephrotoxicity and drug resistance will be of increasing concern with longer duration of treatment.

In a related report, investigators show that a combination of peginterferon alfa-2a and lamivudine was associated with the greatest degree of virus suppression in patients with HBeAg-positive chronic hepatitis B, followed by lamivudine monotherapy and peginterferon alone [*Ibid*, 2682-95].

An editorial accompanying the two reports queries: "Given multiple treatment options that are less than ideal, who should be treated, with what, and when can treatment be stopped?" [*Ibid*, 2743-46].

## DRUG SAFETY

### SSRIs and Antiplatelet Activity: An Update

A recent issue of the *Prescriber's Letter* [2005;21:210715] revisits the role of serotonin in platelets and the association between selective serotonin reuptake inhibitors (SSRIs) and bleeding. While serotonin is conventionally thought of as a neurotransmitter, most of the body's stores are found outside the central nervous system. Among others, platelets are a site of non-neurological activity of serotonin, where it is required for platelet aggregation. SSRIs prevent reuptake of serotonin into platelets, resulting in serotonin-deficient platelets.

Case reports and observational studies link SSRIs to a two- to four-fold increase in the risk of gastrointestinal (GI) bleeding, about the same as the risk posed by NSAIDs. In patients taking SSRIs and NSAIDs or SSRIs and warfarin or an antiplatelet agent, the risk of bleeding is even greater. SSRIs are also associated with an increased risk of GI bleeding in elderly patients after orthopedic surgery. Limited reports associate SSRIs with bleeding at other sites, but not with stroke. Drug interactions may also increase the risk of bleeding. For example, fluconazole and other inhibitors of the drug-metabolizing enzyme

cytochrome P450 2C9 decelerate the metabolism of fluoxetine and increase blood levels.

GI bleeding risk is related to the degree of inhibition of serotonin reuptake and among SSRIs ranges from very low [e.g., mirtazapine (*Remeron*), maprotiline (*Ludiomil*)] to high (e.g. fluoxetine, sertraline, and paroxetine). A physician might consider prescribing an SSRI with a low or intermediate degree of inhibition of serotonin reuptake [e.g., citalopram (*Celexa*)]. Patients taking SSRIs should report unusual bleeding or bruising. Discontinuation of SSRI therapy makes sense for patients contemplating surgery.

On the flip side, the antiplatelet activity of SSRIs might reduce the risk of cardiovascular disease and myocardial infarction (MI). One study showed that sertraline reduced the risk of heart attacks in patients with major depression who were hospitalized for acute MI or unstable angina. SSRIs also seem to have additive effects on platelets when used with antiplatelet drugs such as aspirin and clopidogrel (*Plavix*). However, the *Prescriber's Letter* cautions that there is not enough research to support prescribing SSRIs for this purpose.

## DRUG SAFETY (continued)

### Safety Warnings for Fentanyl Transdermal Patch

The FDA has issued a public health advisory to call attention to reports of serious adverse effects from overdoses of fentanyl in patients using transdermal patches for pain control. The agency has highlighted the following safety information:

1. Fentanyl patches may cause death from overdose and should always be prescribed at the lowest dose needed for pain relief.
2. Patches should only be used by patients who are already opioid tolerant and who have chronic pain that is not well controlled with short-acting analgesics.
3. Health care professionals who prescribe the fentanyl skin patch and patients who use the patch and their caregivers should be aware of the signs of fentanyl overdose.
4. Patients using the patch may experience a sudden and possibly dangerous rise in their blood level of fentanyl.

The FDA continues to work with makers of these products to identify and manage factors that contribute to fentanyl overdose.

### Endometrial Cancer and Postmenopausal Hormone Therapy

Postmenopausal women who use hormone therapy containing estrogen alone are at increased risk of endometrial cancer. Recommended formulations for women with an intact uterus contain both an estrogen and progestogen, on the basis of findings that progestogens counteract the proliferative effects of unopposed estrogens on endometrial tissue. However, limited information is available on the incidence of endometrial cancer in women who use these therapies.

Seeking more conclusive information, investigators participating in the Million Women Study, perhaps better called the Nearly Million Women Study, an ambitious observational study, enrolled 716,738 postmenopausal women in the UK without previous cancer or hysterectomy. They were followed for an average of 3.4 years. Forty-five percent of the women reported at recruitment that they had used hormone therapy. During the study, the investigators diagnosed 1320 cases of endometrial cancers.

Compared with women who had never used hormone therapy, the risk of endometrial cancer was reduced with last use of continuous combined estrogen-progestin (relative risk, 0.71); increased with last use of estrogen alone (1.45); and not significantly changed with last use of cyclic combined preparations (1.05). The adverse effects of estrogen-only hormone therapy on the endometrium were greatest in non-obese women, and the beneficial effects of combined hormone therapy were greatest in obese women.

Confirming a growing suspicion, the Million Women Study found that combined estrogen-progestin hormone therapy causes a greater increase in breast cancer than do the other therapies. When endometrial and breast cancers are added together, there is a greater increase in total cancer incidence with use of combined hormone therapy, both continuous and cyclic, than with use of the other therapies.

### New Warnings for Mifepristone and Misoprostol

The use of mifepristone and misoprostol for the termination of early pregnancy is increasingly contentious in the U.S. Sparking the current debate is a public-health advisory issued by the FDA warning physicians of a possible link between the use of mifepristone with misoprostol and serious bacterial infection. The warning states that four deaths from sepsis had occurred in the U.S. in women who had taken the regimen. The warning was accompanied by a change in mifepristone's label, the second in less than a year.

An editorial in *The Lancet* [2005;366:344] notes that a group of U.S. Senators who had prepared a bill to outlaw mifepristone in the U.S. presented a draft to congress the day after the FDA publicized its warning. The author observes that while the role of the FDA in protecting women from unsafe drugs is clear and necessary, "the coincident timing of the FDA's warning and the draft bill serves only to blur the lines between science and politics—an issue that has been similarly conspicuous in the USA's emergency-contraception debate."