

# drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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## CONTENTS

### CLINICAL PRACTICE

- OCs and Cancer Protection
- Undiagnosed Low BMD
- New Epilepsy Guidelines

### NEW DRUGS & INDICATIONS

- *Provigil* for Fatigue in MS
- *Xigris*: First Drug for Sepsis

### DISEASE MECHANISMS

- Plasma Homocysteine a Risk Factor for Alzheimer's Disease

### DRUG SAFETY

- Clozapine Linked to Diabetes
- Delayed-Onset Heparin-Induced Thrombocytopenia
- Paroxetine Withdrawal
- Etanercept & Systemic Lupus

### DISEASE MARKERS

- Troponin Level Identifies ACS Treatment Strategy

### DIETARY SUPPLEMENTS & HERBAL REMEDIES

- Anticoagulant & Herbal Use

### DRUG EVALUATION

- Raloxifene May Benefit in Cardiovascular Risk
- Fluconazole in Preterm Infants
- Minocycline Effective in RA
- Irinotecan in Small-Cell Lung Cancer Treatment

### PHARMACOECONOMICS

- Drug Discounts for Elderly

## CLINICAL PRACTICE

### OCs With High-Potency Progestin Protect Against Ovarian Cancer

Oral contraceptive use is associated with a reduced risk of developing ovarian cancer, but the mechanism for the risk reduction is not well defined, prompting investigators to examine the relationship between the progestin and estrogen potency in combination OCs and the risk of developing ovarian cancer. The study included 390 case subjects with epithelial ovarian cancer and 2865 control subjects, between 20 and 54 years old [*J Natl Cancer Inst* 2002;94:32-38].

Regardless of hormone content and potency, OC use was linked to a reduced risk of ovarian cancer compared with nonuse. However, women who used low-progestin/high-estrogen potency formulations and those who used low-progestin/low-estrogen formulations were 2.1 and 1.6 times more likely to develop ovarian cancer than those who used high-progestin/high-estrogen formulations. Overall, women who used low-progestin potency formulations were 2.2 times more likely to develop ovarian cancer than women who used high-progestin formulations.

The authors of the report note that it has long been thought the protective effect of OCs derives from their ability to inhibit ovulation. However, if this were so, one would not expect OCs to differ in their protective ability because they are all potent ovulation inhibitors. The findings support claims that biological effects of progestins may in themselves help to protect women from ovarian cancer.

### Nearly Half of Postmenopausal Women Have Undiagnosed Low BMD

Large segments of the population at risk for osteoporosis and fracture have not been evaluated. To gauge the occurrence of low bone mineral density (BMD) in postmenopausal women and its fracture incidence during short-term follow-up, the National Osteoporosis Risk Assessment study screened 200,160 women aged 50 years or older and followed them for 12 months. Using World Health Organization criteria, the investigators determined that 39.6% of the women had bone mass density below normal (osteopenia), and 7.2% had osteoporosis. Among the 163,979 women with follow-up information, osteoporosis was associated with a fracture rate four times that in women with normal BMD; osteopenia was associated with a 1.8-fold higher rate. The authors of the report say, "Given the economic and social costs of osteoporotic fractures, strategies to identify and manage osteoporosis in the primary care setting need to be established and implemented [*JAMA* 2001;286:2815-22]." The study underscores the need for postmenopausal women to take preventive measures, such as exercise, good nutrition that includes calcium and vitamin D, and, when needed, medication.

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## CLINICAL PRACTICE (continued)

### New Epilepsy Treatment Guidelines Favor Monotherapy

The “Expert Consensus Guideline Series: Treatment of Epilepsy,” published in the November/December issue of *Epilepsy and Behavior*, favors, where possible, monotherapy and suggests treatment strategies based on seizure type and individual patient requirements. The guidelines are based on a survey of 45 specialists. Respondents had an average of 20 years in practice and most of them had participated in clinical trials within the last five years. The survey results indicated that if initial monotherapy fails, a second single

medication should be evaluated. If the second medication also fails, physicians should try a third medication or a combination of two drugs. The guidelines identify valproate as first-line treatment for adults with generalized epilepsy and carbamazepine as the first choice for adults with localized epilepsy. Lamotrigine is indicated as the first line of treatment for both localized and generalized epilepsy in women of childbearing age and in adults older than 65 [*Reuters Health*, 28 November 2001].

## NEW DRUGS AND INDICATIONS

### Provigil Appears Safe and Effective for Multiple Sclerosis-Related Fatigue

*Provigil* (modafinil) is a novel wakefulness-promoting drug indicated for excessive daytime sleepiness in patients with narcolepsy. There is considerable interest in finding additional uses for this interesting agent. *Provigil*'s maker, Cephalon, is investigating in phase III trials the use of modafinil for multiple sclerosis (MS) patients suffering fatigue. Fatigue is one of the most common and disabling symptoms of MS, affecting 75% to 90% of patients. Nearly half experience fatigue on a daily basis [*Scrip*, 25 January 2002].

A recent report described a phase II dose-escalation study of modafinil in 72 patients with MS-related fatigue. Compared with symptom scores during a two-week placebo run-in period, treatment with modafinil

200 mg/day, but not 400 mg/day, for nine weeks was associated with a significant improvement in multiple measures of fatigue. Neither dosing regimen was associated with serious adverse events [*J Neurol Neurosurg Psychiatry* 2002;72:179-83].

A study investigator told *Scrip* that neurologists should start using modafinil for severe fatigue associated with MS, but acknowledged the need to better understand the dosage and length of therapy. Previous studies have found that central nervous system stimulants worked in a minority of MS patients. Modafinil is not a stimulating agent, seeming to be more specific than stimulants in terms of the brain regions it activates.

### Lilly Launches *Xigris*: First Drug for Sepsis

Lilly's recombinant human activated protein C product *Xigris* (activated drotrecogin alfa) has been approved for the treatment of severe sepsis, specifically to reduce mortality in adult patients with sepsis associated with acute organ failure who have a high risk of death as determined by APACHE II, a scoring system based on a patient's general health and the severity of their illness. Product labeling warns about bleeding and lists several contraindications and warnings. *Xigris* is contraindicated for patients who have internal bleeding or who are more likely to bleed because of certain medical conditions, such as stroke, head or spinal surgery, and severe head trauma. *Xigris* should not be used in patients who have recently received a thrombolytic agent, an anticoagulant, a gpIIb/IIIa inhibitor, or a platelet inhibitor.

Although its advisory panel evenly split on recommending FDA approval of *Xigris*, the agency believes the product's benefits outweigh the possibility of severe bleeding in high-risk patients. The regulatory agency noted that in clinical studies involving 1690 patients, absolute mortality rate in those taking *Xigris* was reduced by 6% (from 31% to 25%) during the 28-day study period, and by 13% (from 44% to 31%) among patients at a higher risk of death. Sepsis represents a significant unmet medical need. More than 20 investigational drugs for sepsis have failed in clinical trials. The average price for one treatment with *Xigris*—a 96-hour intravenous infusion—is \$6800 [*Scrip*, 28 November 2001].

## DISEASE MECHANISMS

### Plasma Homocysteine Also a Risk Factor for Alzheimer's Disease

Alzheimer's disease accounts for more than 70% of all cases of dementia, and the identification of modifiable risk factors for the disease is a high priority. Patients with cardiovascular risk factors and a history of stroke appear to be at increased risk of both dementia and Alzheimer's disease. Plasma total homocysteine has emerged as an important vascular risk factor, and elevated levels have been associated with an increased risk of atherosclerotic complications.

These unrelated observations led to the hypothesis that elevated plasma homocysteine might be a risk factor for dementia and Alzheimer's disease. If this hypothesis is valid, it points to a potentially modifiable risk factor because plasma homocysteine levels can be lowered by supplementation with folic acid. Investigators have, therefore, examined plasma homocysteine in relation to newly diagnosed dementia and Alzheimer's disease in an elderly cohort [*N Engl J Med* 2002;346:476-83].

A total of 1092 men and women without dementia (mean age, 76 years) from the Framingham Study constituted the study sample. The researchers examined the relationship between plasma homocysteine levels measured at baseline and the risk of newly diagnosed dementia on follow-up.

Over a median of eight years, dementia developed in 111 subjects, including 83 given a diagnosis of Alzheimer's disease. The adjusted relative risk of dementia was 1.4 for each increase of 1 standard deviation (SD) in the log-transformed homocysteine value either at baseline or eight years earlier. The relative risk of Alzheimer's disease was 1.8 per increase of 1 SD in the transformed homocysteine value at baseline and 1.6 in the transformed value measured eight years before baseline. With plasma homocysteine levels greater than 14  $\mu\text{mol}$  per liter, the risk of Alzheimer's disease nearly doubled.

## DRUG SAFETY

### Clozapine Use Linked to Onset of Hyperglycemia and Diabetes

Researchers at the FDA suspect a causal relationship between the use of the atypical antipsychotic clozapine (*Clozaril*) and the onset of hyperglycemia and diabetes. Using the agency's MedWatch system and other reports of cases over the past ten years, the scientists collected data for 384 clozapine-treated patients who developed hyperglycemia or diabetes; 171 of these patients met the criteria for diabetes. In addition, 54

patients experienced exacerbation of preexisting diabetes. In most patients, problems developed within six months after starting clozapine therapy. Eighty cases of metabolic acidosis or ketosis developed in patients with hyperglycemia and 25 patients died during hyperglycemic episodes. The FDA urges physicians to be mindful of this potential complication.

### Delayed-Onset Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), which occurs in 3% of patients who receive heparin, usually presents 5 to 12 days after exposure and is often clinically catastrophic because of thromboembolic complications. Lack of awareness and delayed diagnoses have contributed to the substantial morbidity and mortality in patients with HIT.

Increasingly, physicians are seeing cases in which recently hospitalized patients with heparin exposure return to the hospital after several days to a few weeks with thrombotic complications. The delay in presentation substantially confounds diagnosis.

Investigators have described the clinical scenarios of 14 patients who met the criteria for delayed-onset HIT, rehospitalized after a median of 14 days with thromboembolic complications [*Ann Intern Med* 2002;136:210-15]. All 14 patients tested positive for heparin-induced antibodies. Thrombotic complications included venous thromboembolism in 12 patients (seven of them with pulmonary embolism) and arterial thrombosis in four patients (two patients had both). Eleven patients were retreated with heparin, precipitating a fall in platelet count in all of them. Subsequent treatment included alternative anticoagulants—lepirudin, argatroban, or danaparoid.

## DRUG SAFETY (continued)

### Severe Complications May Follow Paroxetine Withdrawal

GlaxoSmithKline has acknowledged that the antidepressant, paroxetine (*Paxil*), can cause severe withdrawal symptoms when stopped. The FDA published a new product warning about the drug, and, in the same week, the International Federation of Pharmaceutical Manufacturers Association found the company guilty of televising ads in the U.S. that mislead the public about the safety and ease of discontinuing paroxetine. The ads described withdrawal symptoms

as “very rare,” occurring in only two out of every 1000 patients.

According to new product information, withdrawal symptoms—bad dreams, paresthesia, and dizziness—occur in up to 7% of patients. The new label also cites episodes of agitation, sweating, and nausea, and tells physicians to consider restarting treatment if symptoms are intolerable [*BMJ* 2002; 324:260].

### Etanercept Use Linked to Systemic Lupus Erythematosus

A report in *The Lancet* [2002;359:579-80] describes four female rheumatoid arthritis patients who developed signs and symptoms of etanercept-induced systemic lupus erythematosus (SLE). The first case involved a patient who complained of malaise, fever, and polysynovitis 14 months after starting etanercept (*Enbrel*). Tests revealed an abnormal antinuclear antibody titer and antibodies against double-stranded DNA. Four weeks after etanercept was discontinued, these symptoms resolved. The second patient developed a lupus rash three months after starting etanercept therapy. She too had abnormal antibodies. The rash cleared in six weeks after the drug was stopped. Hypertension, edema,

an erythematous facial rash, and polyarthralgia developed in a third patient six weeks after starting etanercept. Tests showed abnormal antibodies. Symptoms resolved two weeks after stopping etanercept. The scenario was similar in a fourth patient who developed pleuritic chest pain, a malar rash, and diffuse skin erythema five months after starting etanercept.

Both etanercept and infliximab (*Remicade*) target TNF- $\alpha$  and are important agents in the treatment of rheumatoid arthritis. Infliximab has been associated with induction of SLE, but this is the first report of drug-induced SLE during treatment with etanercept.

## DISEASE MARKERS

### Troponin Level Identifies ACS Patients Needing Aggressive Treatment

In recognition of the wide spectrum of risk among patients with unstable angina and non-ST-segment elevation myocardial infarction [acute coronary syndrome (ACS)], the American College of Cardiology/American Heart Association Guidelines recommend risk stratification as one of the most important initial steps in evaluating and treating these patients. Baseline levels of cardiac troponins are useful for assessing prognosis in patients with ACS, and they identify patients who derive particular benefit from treatment with glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparins. However, the use of cardiac troponins to predict benefit of an invasive vs. conservative strategy in ACS patients is not clear.

With this question in mind, investigators conducted a prospective, randomized trial in patients with ACS; 1780 patients had baseline troponin level data and completed the follow-up. Patients were randomly assigned an early invasive strategy of coronary angiography and revascularization when feasible or a conservative strategy of medical management.

The main outcome measure was a composite end point of death, MI, or rehospitalization for ACS at six months.

Cardiac troponin levels significantly predicted outcomes. Patients with a cardiac troponin I level of 0.1 ng/ml or more had a significant reduction in the primary end point with the invasive strategy compared with the noninvasive strategy (15.3% vs. 25.0%). Patients with cardiac troponin I levels of less than 0.1 ng/ml tended to do slightly better with the conservative strategy. The report concludes, “In patients with clinically documented acute coronary syndrome who are treated with glycoprotein IIb/IIIa inhibitors, even small elevations in [cardiac troponins]... identify high-risk patients who derive a large clinical benefit from an early invasive strategy [*JAMA* 2001;286:2405-12].” A related editorial calls the findings an important advance, but notes that “the imprecision and lack of standardization of currently available troponin assays merit caution with their application [*Ibid*, 2461-62].”

## DIETARY SUPPLEMENTS AND HERBAL REMEDIES

### Anticoagulants and Herbal Medicines: A Risky Proposition

A review of reported interactions between herbal and conventional drugs has uncovered more than 100 cases, but the authors warn that undoubtedly many more have occurred [*Brit J Clin Pharmacol* 2001;52:587-95]. Warfarin was the most common drug with 18 cases, and St. John's wort was the most common herb. Other herbs included dong quai, ginseng, garlic, ginkgo, and kava. St. John's wort was implicated in 85 cases, 54 of

which were with cyclosporine. Other cases involving St. John's wort included interactions with oral contraceptives, warfarin, and antidepressants. The authors urge that patients on coumarin anticoagulants should be specifically advised to avoid taking herbal medicines or to have their international normalized ratio measured within two weeks of starting the product.

## DRUG EVALUATION

### Raloxifene May Benefit Postmenopausal Women with High Cardiovascular Risk

The Multiple Outcomes of Raloxifene Evaluation (MORE), a randomized, double-blind, placebo-controlled trial designed to determine the effect of raloxifene (*Evista*), a selective estrogen-receptor modulator, on bone mineral density and vertebral fractures in 7705 postmenopausal women at 180 sites in 25 countries who were followed for four years, has provided a wealth of data. The most recent analysis of the database concerns cardiovascular events collected as safety end points during the study [*JAMA* 2002;387:847-57].

In the overall cohort, the investigators observed no significant difference between groups in the number of combined coronary and cerebrovascular events. However, among the subset of 1035 women with baseline

cardiovascular risk factors—diabetes; prior coronary heart disease (CHD) or stroke; use of lipid-lowering agents, diuretics, aspirin,  $\beta$ -blockers, or calcium antagonists; CHD risk factors; and hypertension—those assigned to raloxifene had a significantly lower risk of subsequent cardiovascular events compared with placebo [relative risk, 0.60]. Although benefit was not evident until after the first year of the study, there was no evidence that raloxifene caused an increase in risk of cardiovascular events during the first year, a trend noted in previous reports of hormone replacement therapy in postmenopausal women with heart disease. The authors caution, “these findings must be confirmed by an adequately-powered, randomized trial with cardiovascular events as predefined outcomes” [*Ibid*].

### Fluconazole Prevents Fungal Colonization and Infection in Low-Birth-Weight Infants

Invasive fungal infection is associated with substantial morbidity and mortality in preterm infants. Investigators conducted a well-controlled trial over 30 months in 100 preterm infants with birth weights of less than 1000 g. During the first five days of life, the infants received intravenous fluconazole or placebo; therapy continued for six weeks. During treatment, fungal colonization was documented in 30 of 50 infants in the control group and 11 of 50 infants in the

fluconazole group (absolute risk reduction, 38%). Invasive fungal infection with positive growth of fungal isolates from the blood, urine, or cerebrospinal fluid developed in 10 infants in the placebo group and none in the fluconazole group (absolute risk reduction, 20%). No adverse effects of fluconazole therapy were recorded and no resistance to fluconazole was observed [*N Engl J Med* 2001;345:1660-66].

## DRUG EVALUATION (continued)

### Minocycline Effective for Early Rheumatoid Arthritis

The results of a recently concluded study suggest that over two years minocycline is an effective disease-modifying antirheumatic drug (DMARD) for patients with early (less than one year's duration) seropositive rheumatoid arthritis. The investigators assigned 60 patients to receive either minocycline 100 mg twice daily or hydroxychloroquine 200 mg twice daily. All patients received low-dose prednisone. At two years, 60% of

minocycline-treated patients achieved an American College of Rheumatology response (ACR50), compared with 33% of hydroxychloroquine-treated patients. Patients treated with minocycline were receiving less prednisone at two years and were also more likely to have been tapered off prednisone [*Arthritis Rheum* 2001;44:2235-41].

### Irinotecan Advances Treatment of Small-Cell Lung Cancer

The topoisomerase I inhibitor, irinotecan (*Camptosar*), could change the way small-cell lung cancer is treated. Data reported in *The New England Journal of Medicine* [2002;346:85-91] show a significant survival advantage associated with the combination of irinotecan and cisplatin over the usual chemotherapy—cisplatin plus etoposide (CE).

In the 154-patient phase III study, average survival was 12.8 months in the irinotecan-cisplatin arm, with a

one-year survival of 60% and an 89% tumor response rate, compared with an average survival of 9.4 months, a 40% one-year survival, and a 67% response rate with standard chemotherapy. Two-year survival rates were 19.5% in the irinotecan group and 5.2% in the CE group. The incidence of myelosuppression was lower for irinotecan-cisplatin patients than for CE patients. Irinotecan is a plant-derived material marketed and widely used for the treatment of metastatic colorectal cancer.

## PHARMACOECONOMICS

### Pfizer Offers Steep Discounts to Low-Income Elderly

When prescribing medication for low-income elderly patients without prescription drug coverage, physicians may wish to know that Pfizer is now offering all of its drugs to this population for a flat fee of \$15 a month for each prescription. The average retail price of a one-month supply of a Pfizer medication is \$65 a month. The new program requires no enrollment fee. The CVS Corporation, which operates 4100 community pharmacies in 33 states, and Wal-Mart Stores, the nation's largest retailer, said they would honor the program. Others are likely to follow.

Pfizer's chairman said the program was intended to bridge the gap in drug coverage until broader Medicare reform is adopted. Health officials estimate that at least 27% of Medicare patients, about 11 million people, have no prescription drug coverage. Pfizer estimates that seven million people could qualify for its program, which will be available to individuals with gross annual incomes under \$18,000 and couples with incomes

below \$24,000 a year. Medicare beneficiaries will have to submit copies of the first page of their tax returns or other proof of income with their application. Patients can get applications and information about the program, known as the Pfizer Share Card program, by calling a toll-free telephone number, (800) 717-6005.

Pfizer sells nine of the 50 drugs most often prescribed for Medicare patients, including *Lipitor*, *Norvasc*, *Zoloft*, *Glucotrol*, and *Viagra*. Pfizer is not including *Celebrex* in the program because Pharmacia manufactures it, but the card does cover *Zyrtec* and *Aricept*, which are also comarketed. Patients with Alzheimer's disease now pay \$120 to \$130 a month for *Aricept*. GlaxoSmithKline and Novartis are also offering discount cards, but the General Accounting Office recently said that such cards had not significantly cut costs for elderly consumers buying brand-name medication in metropolitan areas, where savings average less than 10% of retail prices [*The New York Times on the Web*, 16 January 2002].