

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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ALTERNATIVE MEDICINE

PubMed Database Features Alternative Medicine Literature

More than 220,000 references and abstracts and some full-text articles on complementary and alternative medical practices are now available on the National Library of Medicine's PubMed online database. The recently created National Center for Complementary and Alternative Medicine (NCCAM) joined with the NLM to develop the special section.

To access the database, users can go to the NCCAM web site, www.nccam.nih.gov, and click on "CAM on PubMed." PubMed covers 4500 journals published in the U.S. and overseas. It accommodates 120,000 users each day, conducting about 700 searches per minute [*Reuters Health*, 6 February 2001].

NEW DRUGS AND INDICATIONS

Reminyl Receives U.S. Approval for Alzheimer's Disease Treatment

Janssen/Shire's Alzheimer's disease treatment, *Reminyl* (galantamine), an acetylcholinesterase inhibitor like *Aricept* (donepezil) and *Exelon* (rivastigmine), has received FDA approval. *Reminyl* may impact the market because of its dual mechanism of action. It also modulates nicotinic receptors to amplify neurotransmission of the acetylcholine signal. At this time, however, there is no clear evidence that this second effect translates into an added clinical benefit, and its description is not included in approved labeling. Nevertheless, Janssen will try to persuade physicians that this dual mechanism makes a difference.

FDA approval is based on data from four clinical studies involving more than 2650 patients that showed galantamine could improve symptoms as measured by global assessment and a performance-based measure of cognitive function. Its most common side effects are nausea, vomiting, anorexia, diarrhea, and weight loss. In its *Reminyl* promotions, Janssen is likely to emphasize improved GI tolerance over *Exelon*. The company plans to conduct a comparative-safety study with *Aricept*.

Janssen will continue to study galantamine in subclinical patients who have been identified using PET scanning or family history as the Alzheimer's therapy

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NEW DRUGS AND INDICATIONS (continued)

Reminyl Receives Approval for Alzheimer's Disease (continued)

field moves toward disease prevention [*Scrip*, 7 March 2001]. Janssen is also collecting data on the concomitant use of *Reminyl* and its antipsychotic drug *Risperdal* (risperidone). The company sees potential synergies between the two, a combination that addresses

both cognitive decline and disease symptoms. Although *Risperdal* is not yet approved for treatment of psychoses in Alzheimer's, the product is widely used off-label by physicians for dementia in later stages of the disease [*The Pink Sheet*, 5 March 2001].

Starlix for Type 2 Diabetes

Novartis's treatment for type 2 diabetes, *Starlix* (nateglinide) is now available. The oral antidiabetic agent is approved both as monotherapy and in combination with metformin for patients whose condition is not controlled by diet and exercise alone. *Starlix* enters a competitive market and must overcome the head start of three other new drugs for the indication: a similar product, *Prandin* (repaglinide), and the glitazones—*Actos* (pioglitazone) and *Avandia* (rosiglitazone).

Nateglinide, like repaglinide, reduces postprandial glucose spikes, but has a faster onset and shorter dura-

tion of action. Accordingly, nateglinide presents less risk of hypoglycemia than does repaglinide. It is dosed three times daily, one minute to 30 minutes before meals. Although *Starlix* must compete with products taken once daily, Novartis says its dosing regimen is important because suppression of a glucose surge after meals is vital for delaying the progression of type 2 diabetes. Financial analysts say that informing physicians of the link between mealtime glucose spikes and macrovascular disease will be key to the company's marketing strategy and the product's success [*Scrip*, 21 February 2001].

Botulinum Toxin: New Form and New Indication

At the end of last year, Elan launched its botulinum toxin B product *NeuroBloc* for the treatment of cervical dystonia (spasmodic torticollis). The new form of the toxin will compete with Allergan's type A botulinum product *Botox*. Botulinum toxin A blocks neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons. Botulinum toxin B acts at a different point of the nerve synapse. According to Elan, *NeuroBloc* has a longer duration of action than *Botox*, but this claim is arguable. Initially, *NeuroBloc* is likely to be used in patients who do not adequately respond to *Botox*. Other conditions in which *NeuroBloc* may be effective include blepharospasm (repeated blinking), cerebral palsy, hypertonia, laryngeal dystonia, spastic paresis, hyperhidrosis (excessive, uncontrollable sweating), hypersialorrhea (drooling), whiplash, migraine, and tension headache [*Scrip*, 9 March 2001].

Allergan continues to support studies designed to expand the use of *Botox*. In a wrinkle study, 80% of patients with severe facial lines had either mild or no lines at maximum frown after four months of *Botox* treatment compared with 1.5% of patients on placebo.

Two other studies have demonstrated the effectiveness of *Botox* in reducing hyperhidrosis of the palms [*Ibid*].

A study reported in *The New England Journal of Medicine* evaluated a botulinum toxin A product used in Europe and demonstrated its effectiveness for the treatment of axillary hyperhidrosis. The trial enrolled 145 patients with rates of sweat production greater than 50 mg/min, unresponsive to topical treatment with aluminum chloride. Multiple intradermal injections of botulinum toxin A were administered to one underarm and multiple injections of placebo to the other. Two weeks later, the axilla injected with placebo was treated with botulinum toxin A.

At base line, the mean rate of sweat production was 192 mg/min. Two weeks after the first injection, the mean rate of sweat production in the treated axilla was 24 mg/min, as compared with 144 mg/min in the control axilla. Injection of botulinum toxin A into the axilla that had been injected with placebo reduced the mean rate of sweat production in that axilla to 32 mg/min. Treatment was well tolerated and effects persisted for at least 24 weeks [*N Engl J Med* 2001;344:488-93].

Foradil: Another Long-Acting Bronchodilator

Novartis's *Foradil* (formoterol), the first competition for GlaxoSmithKline's well-established long-acting bronchodilator *Serevent* (salmeterol), has been approved for the maintenance treatment of asthma and the prevention of bronchospasm in reversible obstructive airways disease. Approval was based on studies in more than 7000 patients, including 1600 mild-to-moderate asthmatics. The results showed that formoterol can provide significant bronchodilation for 12 hours. Compared with salmeterol, formoterol's major advan-

tage is its more rapid onset of action. Although it is not indicated as a rescue medication, trial patients valued being able to feel the drug working promptly. One study showed that formoterol has an onset of action similar to albuterol, within five minutes. Salmeterol acts in about 30 minutes. Patients may also find formoterol's inhalation device easier to use than the device that delivers salmeterol. Novartis hopes to win an indication for use of formoterol in chronic obstructive pulmonary disease [*Scrip*, 23 February 2001].

DRUG SAFETY

FDA Warns Against Warfarin, Miconazole Interaction, and Zyvox Myelosuppression

The FDA has warned women taking warfarin to consult their physicians before taking *Monistat* or other vaginal medications intended for the treatment of yeast infection that contain miconazole. The agency has asked manufacturers of such products to include a warning on the products' packaging about the potential drug-drug interaction. The action followed two reports of prolonged blood clotting in women using both warfarin and a miconazole product. One of the women developed bruises, bleeding gums, and a nosebleed. Miconazole is a potent inhibitor of warfarin metabolism [*Reuters Health*, 7 March 2001].

The FDA and Pharmacia are warning physicians that some patients taking the anti-infective drug *Zyvox* (linezolid) may be at increased risk for myelosuppression. In a "Dear Health Care Provider" letter, the company advised physicians to perform weekly complete blood counts in patients taking the drug, especially in those who received linezolid for more than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone-marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. A bold warning has been added to *Zyvox* labeling: "Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid" [*The Pink Sheet*, 12 March 2001]. The warning

also states that when linezolid was discontinued, the affected hematologic parameters rose toward pretreatment levels.

More Questions About Steroid Safety in Preterm Infants

There is increasing evidence that the risks associated with early administration of the corticosteroid dexamethasone to premature infants outweigh the benefits. A study reported in *Pediatrics* found that premature infants who received dexamethasone for neonatal chronic lung disease were placed at risk for an impairment in brain growth, largely affecting cerebral cortical gray matter [*Pediatrics* 2001; 107:217-21]. The findings come soon after reports of a study of preterm infants, halted by the NIH, in which early administration of dexamethasone at a moderate dose had no effect on death or chronic lung disease but was associated with gastrointestinal perforation and decreased growth [*N Engl J Med* 2001;344:95-101].

In the latest report, a research team studied 18 infants who were born at 23-31 weeks gestation. Seven of the infants were treated with dexamethasone. Fourteen healthy term infants were evaluated for comparison. Using an advanced magnetic resonance imaging technique, the investigators measured cerebral tissue volumes at 38-41 weeks post-conception. They found that the cerebral cortical gray matter was reduced 35% in premature infants treated with dexamethasone compared with untreated premature infants. Cerebral cortical gray

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DRUG SAFETY (continued)

Steroid Safety in Preterm Infants (cont.)

matter was similar in the untreated premature infants and healthy term infants.

The authors of the report stated, "... these findings are consistent with growing evidence of a potential deleterious effect of dexamethasone on neo-

natal brain and subsequent neurodevelopmental outcome." They added, "This apparent deleterious effect should be taken into consideration by clinicians when weighing the potential risks and benefits of this therapy for low-birth-weight infants with chronic lung disease" [*Pediatrics* 2001; 107:217-21].

DRUG EVALUATION

Actonel Reduces Hip Fracture Risk in Elderly Women With Osteoporosis

Actonel (risedronate) entered the osteoporosis market last year as the second bisphosphonate, following *Fosamax* (alendronate). Evidence that risedronate increased bone mineral density and decreased the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis supported claims for prevention and treatment. Now, a study has shown that risedronate, like alendronate, appears to reduce the risk of hip fracture in postmenopausal women with osteoporosis (defined as low bone mass or previous vertebral fracture), but not among elderly women with risk factors other than osteoporosis [*N Engl J Med* 2001;344:333-40].

The investigators randomly assigned 5445 women 70-79 years old who had osteoporosis and 3886 women at least 80 years old who, in addition to their age, had at least one other nonskeletal risk factor for

hip fracture, such as poor gait or a propensity to fall, to receive oral risedronate or placebo for three years. Overall, the incidence of hip fracture among all women assigned to risedronate was 2.8%, as compared with 3.9% among those assigned to placebo. In the group of women 70-79 years old with osteoporosis, the incidence of hip fracture among those assigned to risedronate was 1.9%, as compared with 3.2% among those assigned to placebo (relative risk, 0.6). In the group of older women selected on the basis of nonskeletal risk factors, the incidence of hip fracture was 4.2% among those assigned to risedronate and 5.1% among those assigned to placebo; the difference was not statistically significant. Therefore, for the prevention of hip fracture, treatment with a bisphosphonate should be limited to postmenopausal women with confirmed osteoporosis.

Pravastatin Reduces Risk of Ischemic Stroke and Diabetes

Analyses of pooled data from large clinical trials have demonstrated further benefits of lipid-lowering pravastatin (*Pravachol*). Data from the West of Scotland Coronary Prevention Study (WOSCOPS), a five-year primary prevention trial in about 6600 men with elevated cholesterol levels but no history of heart disease, suggest that pravastatin may reduce the risk of late-onset type 2 diabetes. And a separate analysis of three trials suggests that pravastatin lowers the incidence of stroke. The initial results from WOSCOPS, reported in 1995, showed that in this population pravastatin reduced the risk of myocardial infarction by 31% and that of cardiovascular death by 32%.

The new analysis of the WOSCOPS data shows that those in the placebo group had a 3% chance of

getting diabetes, but that the risk of developing the disorder was reduced by 30% in those who received pravastatin [*Circulation* 2001;103:357-62]. The favorable effect of pravastatin on stroke is highlighted by the Pravastatin Pooling Project, which analyzed data from WOSCOPS and two secondary prevention trials. Examining outcomes from almost 20,000 patients, the study found that compared with those assigned to placebo, patients taking pravastatin had a 20% reduction in the risk of stroke. Even people on antihypertensive medication or aspirin demonstrated a reduction in stroke with pravastatin. The number of patients who need to be treated (NNT) for one year to prevent one stroke event, however, is relatively large [*Ibid*, 387-92].

Antiretroviral Therapy in Patients with Drug-Resistant HIV

The goal of combination antiretroviral drug therapy in patients with HIV infection is the complete suppression of viral replication. The correlation between the amount of circulating HIV and the rate at which AIDS develops has allowed viral load to be used as a reliable marker of therapeutic benefit and led to the practice of classifying patients with detectable plasma HIV RNA levels as treatment failures. Failure to achieve complete suppression is common in clinical practice, occurring at a rate of 40-70%, but failure in broader immunologic and clinical terms is uncommon, at least during the first 24-30 months of follow-up. These observations suggest that the ability of the virus to deplete CD4 cells may nevertheless be impaired despite ongoing viral replication.

A study reported in *The New England Journal of Medicine* focuses on "treatment failures" and addresses a practical question: What is the value of continuing therapy once drug-resistant virus has been detected? This study demonstrated that among patients with incomplete suppression of viral replication, HIV RNA levels may be significantly lower during therapy than after therapy has been discontinued and suggests that suppression of viral replication, even when incomplete, provides immunologic benefits [*N Engl J Med* 2001;344:472-80].

The investigators studied a group of 16 patients who had received combination therapy with a protease

inhibitor-containing regimen for more than 12 months. The subjects had plasma HIV RNA levels of greater than 2500 copies/ml for at least the previous six months, and yet had had a gain of at least 100 CD4 cells/mm³ since the initiation of therapy. Patients who were randomly assigned to discontinue therapy had a greater increase in viral RNA and a greater decrease in CD4 cell count than the patients who continued therapy. However, among those who continued therapy, a slow increase in viral RNA was observed and persisted throughout the study.

An editorial that accompanied the report noted, "This study also speaks to the issue of why the detection of drug-resistant virus may not mean clinical failure of the drug regimen; its findings indicate that drug-resistant viruses may not replicate as well as drug-sensitive viruses." The commentary's authors believe that continued drug therapy in patients with drug-resistant viruses offers benefit because of continued suppression of drug-sensitive viruses and the appreciable time required for selection of drug-resistant viruses that are as pathogenic as the drug-sensitive viruses. They caution, however, that this approach to therapy will need to be compared with other strategies, "... such as those aimed at detecting drug resistance early, at a time when a change of therapy might suppress replication to an undetectable level" [*Ibid*, 520-21].

Plavix Decreases Mortality in Patients with Acute Coronary Syndrome

A report at a meeting of the American College of Cardiology demonstrated that the antiplatelet drug *Plavix* (clopidogrel) reduced the risk of an acute myocardial infarction, stroke, or death by 20% in a multicenter trial in 12,500 patients with acute coronary syndrome (unstable angina or non-Q-wave MI). The results were hailed as a major advance in the treatment of patients with severe heart disease. The study is a boon for Sanofi-Synthelabo and its marketing partner, Bristol-Myers Squibb. Clopidogrel, which was launched in 1998, had more than \$1 billion in sales last year, driven by short-term use in patients who had undergone balloon angioplasty and stent procedures. The new study indicates that clopidogrel, when taken continuously with aspirin, offers both immediate and long-term benefits for a wider population of patients and is likely to further increase *Plavix* sales. About 1.5 million Americans are thought to suffer unstable angina each year, and an additional 500,000 experience non-Q-wave MI [*The Wall Street Journal Interactive Edition*, 20 March 2001].

Those participating in the study were assigned to either a loading dose of clopidogrel 300 mg followed by daily doses of 75 mg plus low-dose aspirin or aspirin plus a placebo. They were followed for nine months. The investigators reported that 9.3% of patients on *Plavix* plus aspirin suffered a heart attack, a stroke, or death from heart disease during follow up, compared with 11.5% of those on aspirin alone, an absolute risk reduction of 2.2%. The use of the combination in appropriate patients instead of aspirin alone is likely to prevent 28 major cardiovascular events for every 1000 patients who are treated for nine months.

On the down side, the combination was associated with an increase in major bleeding: 3.6% in the *Plavix*-plus-aspirin group and 2.7% in the aspirin-alone group. The risk of hemorrhagic stroke, however, was the same, about 0.1%, in each group, and no one was left with significant disability.

DRUG EVALUATION (continued)

Chemotherapy Plus Herceptin for Metastatic Breast Cancer

Women with breast cancers that overexpress human epidermal growth factor receptor (HER2) have an aggressive form of the disease with significantly shortened disease survival and overall survival. Specific therapy for this condition in the form of a humanized monoclonal antibody trastuzumab (*Herceptin*) has been developed. This antibody inhibits tumor growth when used alone and has had synergistic effects when used in combination with cisplatin and carboplatin, docetaxel, and ionizing radiation, and additive effects when used with doxorubicin, cyclophosphamide, methotrexate, and paclitaxel.

Phase II trials demonstrated that many women with HER2-positive metastatic disease who had relapsed after chemotherapy had a response to trastuzumab. Investigators now report the results of a phase III trial in 234 women with metastatic breast cancers that overexpressed HER2 and had not previously received chemotherapy for metastatic disease. They were randomly assigned to receive chemotherapy alone or chemotherapy plus trastuzumab. Treatment consisted of an anthracycline and cyclophosphamide for patients who had not previously received postoperative therapy with an anthracycline, or paclitaxel for patients who had received postoperative anthracycline, with or without trastuzumab [*N Engl J Med* 2001;344:783-92].

The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression

(median, 7.4 vs. 4.6 months), a higher rate of objective response (50% vs. 32%), a longer duration of response (median, 9.1 vs. 6.1 months), a lower rate of death at one year (22% vs. 33%), and longer survival (median, 25.1 vs. 20.3 months).

The most important adverse effect was cardiac dysfunction, which occurred in 27% of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8% in the group given an anthracycline and cyclophosphamide; 13% in the group given paclitaxel and trastuzumab; and 1% in the group given paclitaxel alone. Trastuzumab was discontinued because of cardiac dysfunction in 8% of patients. Cardiac function improved in 75% of patients after the initiation of standard medical care.

Thus, as compared with the best available standard chemotherapy, concurrent treatment with trastuzumab and first-line chemotherapy was associated with a significantly longer time to disease progression, a higher rate of response, a longer duration of response, and improved overall survival. While cardiotoxicity is a grave concern, especially when trastuzumab is combined with an anthracycline, the researchers concluded, "Given the extremely poor prognosis of patients with HER2-positive metastatic breast cancer, the cardiotoxicity of trastuzumab must be weighed against its potential clinical benefit."

CLINICAL PRACTICE

New Guidelines for Antibiotic Use in Upper Respiratory Infection

Guidelines from The American College of Physicians-American Society for Internal Medicine say that antibiotics should not be prescribed for most upper respiratory tract infections [*Ann Intern Med* 2001;134:479-89; 495-97]. A senior medical associate at the college told the news media that upper respiratory tract infections account for 70% of the overuse of antibiotics, the principal reason for the dramatic increase in antibiotic resistance over the past ten years. She added, "The main thrust of the guidelines is to remind all our members and all primary care physicians that

these infections are caused by viruses, so there is no need to give antibiotics...." She recognized that "... many physicians are afraid that if they take the time to explain antibiotic use, their patients will insist on getting an antibiotic anyway or go to another doctor," but, pointing to recent surveys, said they should not be. "Patients are interested in having their care explained to them, and as long as they understand that antibiotics are not going to help them, they do not have a problem not receiving them" [*Reuters Health*, 20 March 2001].