

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Combination Therapy for Neuropathic Pain

Neuropathic pain is a life-modifying complex condition resulting from a primary lesion or dysfunction in any part of the nervous system. Although causes are diverse, presenting symptoms are typical. Available effective therapies include anticonvulsants, tricyclic antidepressants, opioids, topical lidocaine, newer antidepressant agents (e.g., duloxetine, venlafaxine), and the analgesic drug tramadol. The anticonvulsant gabapentin is used frequently to control pain in postherpetic neuralgia and diabetic neuropathy. Opioids are also recommended as first-line treatment for neuropathic pain. In the clinical management of neuropathic pain, incomplete relief with gabapentin usually leads to the addition of a second agent, frequently an opioid [*N Engl J Med* 2005;352:1373-75].

Until recently, recommendations for combination therapy were based on intuition, not on clinical trial evidence. Now, investigators have provided evidence of the efficacy of a combination of gabapentin and morphine in reducing pain and pain-related disability in 57 patients with either diabetic neuropathy or postherpetic neuralgia; 41 completed the trial. The carefully controlled crossover study compared monotherapy and combination therapy with an active control (lorazepam). Doses were titrated to achieve maximum pain relief and minimal adverse events [*Ibid*, 1324-34].

Compared with lorazepam, monotherapy with gabapentin or morphine provided significantly better pain relief. The combination of morphine and gabapentin resulted in a greater reduction in pain than did gabapentin alone or morphine alone, at lower doses of each drug than either as a single agent. At the maximal tolerated dose, the gabapentin-morphine combination resulted in a higher frequency of constipation than gabapentin alone and a higher frequency of dry mouth than morphine alone.

Fear of scrutiny by regulatory agencies, as a result of perceived risks of addiction and diversion with opioids, may present barriers to the adoption of this strategy. In light of the success of gabapentin-morphine combination therapy, clinical trials with different combinations of drugs are warranted [*Ibid*, 1373-75].

Drug Therapy Outcomes in Hypertensive Black and Non-black Patients

Mortality related to hypertension and the risk of end-stage renal disease, coronary heart disease (CHD), heart failure, and stroke contribute heavily to health care costs. Blacks with hypertension have the highest morbidity and mortality

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CLINICAL PRACTICE (continued)

Drug Therapy in Hypertensive Black and Non-black Patients (continued)

from hypertension of any population group in the U.S. The benefits of lowering elevated blood pressure are well established but, until recently, controlled studies comparing different classes of antihypertensive agents for reducing cardiovascular complications of hypertension were not available. Then, in 2002, the results of ALLHAT were published. The well-controlled study, conducted in more than 42,000 patients, determined that a thiazide-type diuretic was at least as effective in preventing coronary heart disease as those based on an alpha blocker, an ACE inhibitor or a calcium channel blocker. Now, the most recent report from ALLHAT demonstrates that the overall findings of the study apply to both black and non-black patients with hypertension [*JAMA* 2005;293:1595-1608].

Summarizing the results, a related editorial says that the key findings of the race analysis are: (1) for each treatment group, reductions in blood pressure were greater among non-blacks than among blacks; (2) blood pressure reductions varied more among the three treatment groups—diuretic, ACE inhibitor, and calcium channel blocker—in blacks than in non-blacks and the worst blood pressure control was among blacks

who received lisinopril as first-step treatment; (3) in both blacks and non-blacks, neither amlodipine nor lisinopril were superior to chlorthalidone for the primary CHD outcome or for any other clinical outcome; (4) for both blacks and non-blacks, risk of heart failure and the combined cardiovascular disease outcome was significantly lower with chlorthalidone compared with lisinopril; and (5) for blacks, but not non-blacks, the risk of stroke was lower with chlorthalidone compared with lisinopril [*Ibid*, 1663-66].

After many years of research, ALLHAT has shown that diuretic therapy is very effective in reducing the risk of cardiovascular disease among both black and non-black patients with hypertension. The authors of the accompanying editorial conclude: “It is now time to move beyond comparisons of diuretics with other classes of blood pressure lowering drugs—that issue has been settled.” They add, “Determining how to lower blood pressure to more optimal levels... in the most cost-effective manner in the populations at risk is the new priority” [*Ibid*].

Choose Aspirin over Warfarin for Intracranial Arterial Stenosis

Atherosclerotic intracranial arterial stenosis is an important cause of stroke, especially in blacks, Asians, and Hispanics. Warfarin is commonly used for this disorder. Now, a comparison of warfarin therapy with aspirin therapy in patients with cerebrovascular events attributed to intracranial atherosclerosis has found that warfarin is associated with significantly higher rates of adverse events and provides no benefit over aspirin [*N Engl J Med* 2002;352:1305-16].

In the study, supported by the National Institute of Neurological Disorders and Stroke, investigators assigned patients with transient ischemic attack or stroke caused by 50% or greater stenosis of a major intracranial artery to warfarin (target INR, 2.0 to 3.0) or aspirin (1300 mg/day) in a well-controlled multicenter trial. The primary endpoint was ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke.

After 569 patients were enrolled, the study was stopped because of concerns about the safety of patients who had been assigned to receive warfarin. With

regard to the primary endpoint, an event occurred within two years in about 22% of patients, whether they were treated with high-dose aspirin or dose-adjusted warfarin. However, adverse events—death, major hemorrhage, or myocardial infarction and sudden death—occurred significantly more often in warfarin-treated patients than in those treated with aspirin. While death from vascular causes was about the same in the two groups, the warfarin group had a significantly higher rate of death from noncardiovascular causes. The investigators concluded, “Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis.”

In a related editorial, the author agrees that the data show that warfarin is not superior to 1300 mg of aspirin but notes that the time spent in the INR target range with warfarin was inadequate and calls for further studies with “very carefully regulated anticoagulation” [*Ibid*, 1368-70]. In the study, patients were within goal only 63% of the time; 28% of the patients

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Aspirin over Warfarin for Intracranial Arterial Stenosis (continued)

assigned to warfarin dropped out. Experience suggests that time in the target range correlates with clinical outcomes and the data from the current study is consistent with that idea. Anticoagulation in the therapeutic

range was far more effective than anticoagulation in the subtherapeutic range. The response in this subset of patients was greater than the response to aspirin therapy.

Does Mild Persistent Asthma Require Regular Treatment?

Current guidelines recommend daily treatment with inhaled corticosteroids for patients with mild persistent asthma. There is considerable evidence that this strategy achieves and maintains asthma control and more limited evidence that the continuous suppression of airway inflammation may not only control asthma but also prevent its progression [*N Engl J Med* 2005;1589-91]. Nevertheless, researchers have challenged this recommendation and proposed that intermittent, as-needed, therapy is equally effective and dramatically reduces exposure to corticosteroids [*Ibid*, 1519-28].

In the provocative report, investigators describe a study in which they compared three treatment protocols in 225 adult patients over a period of one year. In one protocol, patients were treated with twice-daily inhaled budesonide; in a second, patients were treated with twice daily oral zafirlukast (*Accolate*); and in a third, patients received no anti-inflammatory therapy. All patients were advised to take a course of inhaled or oral corticosteroid (intermittent therapy) if their asthma symptoms worsened.

Unexpectedly, the group that did not receive controller therapy had neither poorer lung function nor a greater frequency of asthma exacerbations. The re-

searchers estimated that the only treatment these patients needed was one course of inhaled budesonide on average every two years or oral corticosteroids on average every eight years. The only clinically important difference between the group receiving regular treatment with inhaled corticosteroid and the group receiving intermittent treatment with inhaled corticosteroid was that patients in the former group had 26 fewer days with asthma symptoms over the course of a year. The authors of the report conclude: "These findings suggest that the novel approach of treating patients with mild persistent asthma with inhaled and oral corticosteroids as needed may be viable" [*Ibid*]. They call, however, for larger and longer confirmatory trials.

A related editorial proposes that the results of this study may change clinical practice because the use of intermittent treatment complies with the philosophy of achieving and maintaining asthma control with the least amount of medication. The approach may be feasible in patients with mild persistent asthma who have never received corticosteroids and might also be offered to patients with mild persistent asthma as an intermediate step to the withdrawal of controller medication, if their disease is well controlled [*Ibid*, 1589-91].

NEW DRUGS AND INDICATIONS

New Drug for Type 2 Diabetes

Co-developers Amylin Pharmaceuticals and Eli Lilly have received approval to market *Byetta* (exenatide), the first in a new class of drugs called incretin mimetics, for the treatment of type 2 diabetes. Exenatide is a synthetic version of a peptide found in the saliva of the Gila Monster, a poisonous lizard, residing in the Southwest. The hormone is similar to glucagon-like peptide 1. Unlike other drugs now used for type 2 disease, *Byetta* must be injected, twice daily. Compared with insulin injections, which are used in patients with type 2 diabetes resistant to oral hypoglycemics, *Byetta*

may be less prone to provoke hypoglycemia. However, the novel drug is not indicated for monotherapy but must be used in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea and have not achieved adequate glycemic control.

According to a report in *The New York Times on the Web* [30 April 2005], about 18 million Americans have diabetes. The vast majority of them suffer type 2 diabetes, once called adult-onset diabetes. The condition,

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NEW DRUGS AND INDICATIONS (continued)

New Drug for Type 2 Diabetes (continued)

however, is now increasingly diagnosed in overweight, sedentary children and adolescents. Approximately one-third of affected Americans take either a sulfonylurea or metformin orally but many of them eventually fail to achieve recommended blood glucose levels and they are candidates for *Byetta*. But these patients may first opt

for the newer insulin sensitizers *Actos* (pioglitazone) or *Avandia* (rosiglitazone) rather than *Byetta*, to avoid injections. Alternatively, they might choose a once-a-day injection of insulin. The chief executive at Amylin noted that the company was testing a version of *Byetta* that would require only once-a-week injections.

Next Season's Vaccine Will Have New Strain of Influenza Virus

According to the World Health Organization, next season's influenza vaccine will be modified to protect against a new strain of the virus that was first reported in California in January and that is spreading rapidly. The strain has been identified in more than 20% of influenza viruses isolated from patients early in 2005 and is expected to be the dominant one circulating in the Northern Hemisphere next season [*The New York Times on the Web*, 11 February 2005].

The standard vaccine consists of three strains of influenza virus. The California strain, known as A/California/7/2004(H3N2), will substitute for A/Fujian. The two other strains will remain the same: A/New Caledonia 20/99(H1N1), which has been included for the last six years, and B/Shangain/361/2002, which has been included for two years. The *Times* notes that the California strain is not related to the avian influenza strain that has killed thousands of birds and a small number of people in Southeast Asia.

DRUG DISCOVERY

Antibiotics May Have a Role in Treatment of ALS

A commentary in *The New England Journal of Medicine* [2005;352:1376-78] discusses the findings of a stimulating report by a research team well versed in the pathologic effects of the excitatory neurotransmitter glutamate [*Nature* 2005;433:73-77]. Demonstrating that excessive levels of synaptic glutamate are neurotoxic, the investigators devised a screening assay to identify drugs that reduce these levels by accelerating the uptake of glutamate into astroglial cells in slice cultures of spinal cord. The screen revealed that beta-lactam antibiotics enhance the uptake of glutamate at concentrations ordinarily achieved during treatment of central nervous system

infections. The researchers further demonstrated that one agent, ceftriaxone, could prevent neuronal death in two models of glutamate excitotoxicity. Moreover, long-term ceftriaxone therapy slowed the course of disease in a mouse model of amyotrophic lateral sclerosis (ALS).

The commentary notes that the study represents "the first use of a screening assay on all drugs that have been approved by the Food and Drug Administration (FDA) and tests the hypothesis that compounds approved for safe use in one setting may have desirable effects in others."

DRUG EVALUATION

Mild Cognitive Impairment—Vitamin E Provides No Benefit, Donepezil Little

Because new treatments are expected to be better at preventing rather than restoring nerve function, early recognition of Alzheimer's disease and intervention is a major focus of current research. However, the benefit of drug therapy for the treatment of the prodromal phase of Alzheimer's disease—mild cognitive impair-

ment—has, up until now, neither been demonstrated nor refuted. Rather than wait for new developments, a study group has evaluated the effectiveness of two standard treatments for established disease to prevent progression from mild cognitive impairment to

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Mild Cognitive Impairment—Vitamin E vs. Donepezil (continued)

Alzheimer's disease [*N Engl J Med* 2005, published at www.nejm.org on Apr 13, 2005 (10.1056/NEJMoa050151)].

The researchers enrolled 769 eligible subjects who were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg donepezil (*Aricept*) daily, or placebo for three years. Donepezil is the most widely prescribed cholinesterase inhibitor and has limited clinical benefits in moderate to severe disease. Vitamin E has also been shown, in one well-controlled trial, to slow disease progression in such patients.

In the current study, possible or probable Alzheimer's disease developed in 212 patients. The overall rate of progression was 16% per year. As compared with placebo, there were no significant differences in the probability of progression to Alzheimer's disease in the

vitamin E group or the donepezil group over the three years of treatment. However, the donepezil group had a reduced risk of progression during the first year of the study. Furthermore, among carriers of one or more apolipoprotein E epsilon4 alleles, the benefit of donepezil was evident throughout the three-year study.

An editorial that accompanies the report states: "Despite these largely negative results, the bigger picture remains hopeful." The author notes that clinical studies of a variety of agents aimed at halting or even reversing the advance of brain lesions in Alzheimer's disease are ongoing and that at least some of these agents "will prove effective and can be deployed early in the hope of stopping the disease process while function remains intact" [*N Engl J Med* 2005; published at www.nejm.org on Apr 13, 2005 (10.1056/NEJMe058086)].

Sirolimus Inhibits Progression of Kaposi's Sarcoma

The incidence of Kaposi's sarcoma is about 500 times the rate in the general population among recipients of solid organs and about 20,000 times background among men with AIDS. These observations suggest a role for immunosuppression in the development of the disease. The usual approach to managing transplant-related Kaposi's sarcoma is to reduce or discontinue immunosuppressive therapy, which is effective but increases the risk of acute graft rejection.

Sirolimus, an immunosuppressant used in kidney-transplant procedures, appears also to have antineoplastic effects. Accordingly, investigators studied the cellular and clinical effect of sirolimus on Kaposi's sarcoma in renal-transplant recipients [*N Engl J Med* 2005;352:1317-23]. They stopped cyclosporine therapy in 15 transplant recipients who had Kaposi's sarcoma and started a six-month course of sirolimus.

Three months after the start of sirolimus therapy, all cutaneous Kaposi's sarcoma lesions had disappeared in all patients. At six months, remission was confirmed histologically. There were no acute episodes of rejection or changes in kidney-graft function.

A related editorial notes: "The results presented by Stallone, et al., strengthen the possibility that equilibrium between efficient immunosuppression and control over the development of cancer may be attainable." The results show that "sirolimus has the potential to tilt the risk-benefit balance of immunosuppression toward benefit after transplantation. To support this hypothesis, the authors cite a retrospective analysis, of more than 36,000 recipients two years after a first kidney transplant, showing a decrease of about 50% in the relative risk of cancer among patients given sirolimus, as compared with those given calcineurin inhibitors (i.e., cyclosporine or tacrolimus) [*Ibid*, 1371-73].

Chicken Pox Vaccine Cuts Death but Impact on Shingles Is Uncertain

A live attenuated varicella vaccine, approved by the FDA in 1995, has now been shown to sharply cut the death rate from the childhood disease [*N Engl J Med* 2005;352:450-58]. Starting in 1999, surveillance data showed impressive decreases in varicella disease. For the interval 1990 through 1994, the average number of varicella-related deaths was 145 per year; it then declined to 66 per year during 1999 through 2001. The

authors of the report note, "This decline was observed in all age groups less than 50 years, with the greatest reduction (92%) among children 1 to 4 years of age."

While the vaccine indisputably protects children, questions have arisen about whether its use will increase the incidence of herpes zoster (shingles) in

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Chicken Pox Vaccine Cuts Death but Shingles Impact Uncertain (continued)

adults. In this era of the varicella vaccine, its effect on the epidemiology of zoster remains unclear, in part because of the long delay between primary infection with varicella-zoster virus and the subsequent reemergence of zoster later in life. Zoster, which before the introduction of the vaccine affected about 15% of the population, occurs when latent virus in dorsal-root ganglia becomes reactivated. It usually occurs in persons with relative immunologic compromise. Before zoster can develop, a primary infection with varicella-zoster virus must occur.

According to a *Perspective* in *The New England Journal of Medicine* [2005;352:439-40], "Some believe that periodic exposure to persons with varicella... is

important in maintaining immunity to zoster." The authors add, "As the incidence of varicella decreases further, such stimulation of immunity from exogenous exposure will become rare. The result may be an increase in the incidence of zoster among persons who have had chickenpox, as well as a decrease in the average age at which zoster occurs." Others believe that endogenous stimulation by one's own immune system is more important in maintaining immunity to zoster. They propose that the growing number of vaccinated individuals should have a lower incidence of zoster. To resolve these questions, the results of a randomized trial assessing the vaccine's effectiveness in preventing zoster in the elderly are expected to become available soon.

Effective Treatment for Juvenile Rheumatoid Arthritis

Treatment for juvenile rheumatoid arthritis (RA) includes NSAIDs and disease-modifying antirheumatic drugs (DMARDs). Methotrexate is the most commonly used DMARD for juvenile RA. Sulfasalazine and etanercept (*Enbrel*) are also effective. These agents or other DMARDs, however, have not been compared with methotrexate.

Leflunomide (*Arava*), an orally active pyrimidine synthesis inhibitor, has been shown to be safe and effective long-term therapy for adults with RA. A pilot study in children determined that half of them responded, even though they had no response to, or were intolerant of, methotrexate. To further explore these findings, investigators conducted a 16-week random-

ized trial that compared leflunomide with methotrexate in children with active polyarticular-course juvenile RA [*N Engl J Med* 2005;352:1655-66].

Of 94 patients randomized to one drug or the other, 86 completed 16 weeks of treatment, 70 of whom entered a 32-week blinded extension study. Both leflunomide and methotrexate resulted in high rates of clinical improvement that were maintained at week 48, but methotrexate was slightly more effective. The price, however, was more frequent aminotransferase elevations with methotrexate than with leflunomide. While methotrexate appears to be the better choice, leflunomide is certainly an appropriate backup agent.

DRUG SAFETY

Inotrope for Heart Failure Increases Risk of Death

A recently reported pooled analysis of randomized controlled trials revealed that nesiritide (*Natrecor*) may be associated with increased risk of death in patients with acutely decompensated heart failure, as compared with standard diuretic and vasodilator therapies [*JAMA* 2005;293:1900-1905]. Nesiritide received approval based on improved symptoms and the perception that it was safer than dobutamine.

In three trials, 485 patients received nesiritide and 377 were assigned to non-inotrope-based therapy. Death within 30 days occurred more often in the group assigned to nesiritide therapy (7.2% vs. 4.0%).

The drug's manufacturer released a statement the day after the *JAMA* study appeared stating that "labeling has been revised to include an analysis of the mortality rates seen in pivotal trials of the congestive heart failure agent" [*BMJ* 2005;330:981]. Labeling had already cited a potential for hypotension and renal toxicity. There is evidence that nesiritide has been misused, with emergency room physicians rather than cardiologists prescribing the drug for emergent cases, and with its use in outpatient clinics, presumably to prevent decompensation.