

# drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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### Drug Therapy Topics Supplement

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## CLINICAL PRACTICE

### Management of Subclinical Hypothyroidism

A recent report in the *Prescriber's Letter* [2005;21:210123] illuminates the controversy over whether to treat patients with subclinical hypothyroidism, a diagnosis based solely on laboratory values indicating an elevated serum thyroid stimulating hormone (TSH) and a normal thyroxine (T4) level. Some patients do report vague symptoms such as fatigue, dry skin, cold intolerance, and constipation, but symptoms are frequently absent.

Screening patients for subclinical hypothyroidism, by means of a serum TSH test, is controversial. Recommendations from two conferences do not support routine screening of the general population. The treatment of patients with subclinical hypothyroidism is also controversial. According to the report, many physicians elect to treat patients with a normal T4 if the TSH is > 5 mIU/L. But this is not without risk, including the development of osteoporosis and atrial fibrillation, especially in patients who are overtreated. Proponents of treatment say that ignoring the condition may lead to overt hypothyroidism (especially if the patient has a positive thyroid antibody test) and potential harmful effects on cholesterol levels and cardiac disease.

On reviewing the evidence, the contributors to the *Prescriber's Letter* conclude that the treatment of subclinical hypothyroidism should be tailored to each patient. "In general, patients with a serum TSH concentration > 4.5 mIU/L to 5.0 mIU/L and <10 mIU/L do not need thyroid replacement therapy." On the other hand, thyroxine therapy is appropriate for anyone with a TSH level over 10 mIU/L as well as for women who are or want to be pregnant and have an elevated TSH. Even mild hypothyroidism might be harmful to a fetus. A trial of thyroxine therapy might also be considered for people with subclinical hypothyroidism and symptoms.

### Aspirin Sensitivity in Patients with Coronary Artery Disease

A significant proportion of the U.S. population is unable to tolerate aspirin due to sensitivity to it or to other NSAIDs. In susceptible people, aspirin sensitivity may cause symptoms similar to allergic reactions. The reaction can be manifested by aspirin-exacerbated respiratory tract disease, urticaria/angioedema, or anaphylaxis. Many patients with aspirin sensitivity also have asthma and nasal polyps.

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## CLINICAL PRACTICE (continued)

### Aspirin Sensitivity in Patients with Coronary Artery Disease (continued)

Susceptibility can be confirmed with a challenge test by giving the patient a small dose of aspirin and observing the results. Patients with aspirin-induced asthma can usually take acetaminophen for pain relief [*JAMA* 200;292:3098].

Researchers have recently published the findings of an extensive literature survey using the search terms *aspirin allergy*, *coronary artery disease*, *aspirin desensitization*, and *aspirin sensitivity* [*Ibid*, 3017-3023]. They estimate that the prevalence of aspirin-exacerbated respiratory tract disease is about 10%. The prevalence of aspirin-induced urticaria varies from 0.07% to 0.2%. The investigators note, "Aspirin sensitivity is most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting NSAIDs that inhibit cyclooxygenase-1."

Many patients with aspirin sensitivity can be desensitized under close medical supervision. During

desensitization, very small doses of aspirin are taken daily, with the doses slowly increasing over time. After desensitization, aspirin therapy must be continued indefinitely to prevent resensitization. The literature survey suggests that aspirin desensitization is safe and successful in many patients, except in those with chronic idiopathic urticaria.

The authors of the review suggest that in patients with NSAID sensitivity and concomitant coronary artery disease, "aspirin desensitization therapy may be considered given aspirin's excellent clinical efficacy, low-risk profile, and cost-effectiveness." They caution, however, that there have not been any randomized trials that specifically focus on the efficacy of aspirin. This recommendation departs from the guidelines proposed by the American College of Cardiology and the American Heart Association which say that an alternative antiplatelet agent (i.e., clopidogrel) is indicated in patients with a true sensitivity to aspirin.

## NEW DRUGS AND INDICATIONS

### Potential Breakthrough Drug for MS Withdrawn Weeks after Launch

Natalizumab (*Tysabri*), a recombinant humanized IgG4 kappa monoclonal antibody, was approved in November for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. By antagonizing the effects of the glycoprotein alpha4beta1 integrin, natalizumab affects cell adhesion and transendothelial migration and reduces immune-cell activation within inflamed tissue. By virtue of its mechanism of action, which is distinct from drugs currently used in the treatment of MS, natalizumab interferes with the passage of potentially damaging immune cells in the blood across the blood-brain barrier [*Prescriber's Letter* 2005;21:210109].

Natalizumab was widely viewed as a major therapeutic advance in the treatment of MS and patients were buoyed by its development. More cautious observers, however, emphasized that the long-term safety of natalizumab is unknown. Indeed, they were

prophetic. In March, the makers of *Tysabri* announced suspension of sales and clinical trials and directed physicians to stop all therapy with the drug.

The decision was based on reports from a MS clinical trial in which *Tysabri* was combined with *Avonex* (interferon beta-1a) that a patient had died from a rare but fatal disorder called progressive multifocal leukoencephalopathy (PML) while a second patient was showing signs of the condition. The second patient succumbed a few days later. PML is ordinarily seen only in severely immunocompromised individuals.

When the suspension might be lifted, if ever, is unknown, but FDA officials express confidence in the ultimate potential of natalizumab. The antibody is also being studied for the treatment of rheumatoid arthritis and Crohn's disease. No reports of PML have emerged from such patients.

## Modified Paclitaxel to Treat Metastatic Breast Cancer

The FDA has approved *Abraxane*, a new form of paclitaxel (*Taxol*, generic versions) that is easier to administer and appears to avoid some side effects. The water solubility of paclitaxel is poor; intravenous administration requires the use of a commercial solvent called *Cremaphor*, which is itself freighted with side effects, including severe allergic reactions. To minimize these reactions, patients are usually given antihistamines and corticosteroids before treatment. Paclitaxel must also be given through special intravenous tubing because the solvent leaches material from tubes ordinarily used for administration, and the preparation must be infused relatively slowly.

*Abraxane* consists of microparticles of paclitaxel bound to albumin. The formulation eliminates the need for *Cremaphor* and prophylactic medication. Further-

more, larger doses of paclitaxel, up to 50% more, can be given before side effects become intolerable, and the drug can be given more rapidly with standard tubing. The new preparation, based on novel technology, is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. Ordinarily, prior therapy would have included an anthracycline.

In a pivotal clinical trial with 460 women with advanced breast cancer, a tumor response was observed in 21.5% of patients who received *Abraxane* compared with 11.1% of those who received *Taxol*. Among the patients receiving the modified form of paclitaxel, severe neutropenia occurred less frequently than among those assigned to *Taxol*.

## A New Treatment for Ocular Neovascularization

A recent report concerns the evaluation of a novel pegylated oligonucleotide, pegaptanib (*Macugen*), in patients with neurovascular, or wet, age-related macular degeneration (AMD) [*N Engl J Med* 2004;351:2805-16]. A related editorial provides useful background information [*Ibid*, 2863-65].

Neovascularization leads to blindness in several eye disorders including AMD, diabetic retinopathy, and other vascular occlusive diseases. Effective treatment is wanting. More than 50 years ago, scientists hypothesized that ischemic tissue in the eye released an unknown factor that could be responsible for the development of neovascularization. In 1994, investigators showed that the level of vascular endothelial growth factor (VEGF) was strikingly elevated in the vitreous of patients with ischemic retinal diseases. Release of VEGF can stimulate neovascularization and increase

capillary permeability; both of these effects are associated with loss of vision. The search was then on for a drug that could block VEGF in the eye, a search that led to the discovery of pegaptanib.

In the recently reported study, researchers administered intravitreal pegaptanib or sham injections into one eye per patient every six weeks over a period of 48 weeks. More patients receiving active treatment, as compared with sham injection, maintained their visual acuity or gained acuity (33% vs. 23%). Unfortunately, further analysis revealed that only about 10% of patients can anticipate improvement in their vision on treatment with pegaptanib, a level of efficacy not terribly different from that provided by photodynamic therapy, which relies on a photosensitive drug that has an affinity for neovascular tissue. The new findings, however, do provide the opportunity to test combination therapy.

## DRUG EVALUATION

### NSAIDs in Osteoarthritic-Knee Pain

Much confusion surrounds the use of NSAIDs in the treatment of pain associated with osteoarthritis and other conditions. The safety of the most widely prescribed agents, selective COX-2 inhibitors, has been called into question following reports of a linkage between the use of *Vioxx*, *Celebrex*, and *Bextra* and heart attacks. Even the safety of naproxen has been chal-

lenged. That selective COX-2 inhibitors are no more effective in reducing pain than are aspirin and other nonselective NSAIDs is widely acknowledged. While *Vioxx*, now withdrawn from the market, offered gastroprotection compared with nonselective NSAIDs,

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## DRUG EVALUATION (continued)

### NSAIDs in Osteoarthritic-Knee Pain (continued)

there is no clear cut evidence that *Celebrex*, which remains on the market, provides a similar benefit.

Now, further complicating matters, is a recently reported meta-analysis of well-controlled clinical trials that demonstrates the limited efficacy of NSAIDs, including selective COX-2 inhibitors, in the treatment of osteoarthritic knee pain. [*BMJ* 2004;329:1317-20]. The investigators reviewed 23 trials that included 10,845 patients (median age 62.5 years). The average duration of symptoms was 8.2 years. Among the study subjects, 7807 received adequate doses of NSAIDs and the others received placebo. Based on these data, the researchers concluded that NSAIDs do not seem to offer a long-term solution to this disabling medical problem.

The analysis showed that NSAIDs can reduce short-term pain slightly better than placebo. The pooled

difference for pain on a visual analog scale was 15.6% better on active drug than on placebo after 2-13 weeks of treatment, deemed to be a modest improvement. The analysis, however, does not support long-term use of NSAIDs for this condition. One trial reported long-term effects on pain but found no difference between active drug and placebo at one, two, three, and four years after the start of treatment. In light of these weak and possibly clinically meaningless effects, the authors of the report conclude, "As serious adverse effects are associated with oral NSAIDs, only limited use can be recommended."

A related commentary cites other measures used in the management of osteoarthritis of the knee but finds all of these efforts, short of surgery, to be wanting. "Thankfully, surgery does offer the ultimate answer in the severely osteoarthritic knee" [*Ibid*, 1300-1301].

### Calcium Blocker Less Protective Than Other Blood Pressure Medication

A new analysis of data from the Women's Health Initiative indicates that, when women need combination therapy to control hypertension, the risk of cardiovascular disease mortality is greater when diuretics are combined with calcium antagonists than when diuretics are prescribed with beta-blockers or ACE inhibitors [*JAMA* 2004;292:2849-59]. ALLHAT showed that diuretics were equal or superior to other antihypertensive drugs as first-line therapy. However, surveys show that most patients with hypertension require more than one drug class to control the disorder. Which drug should be added after a thiazide?

The study included 30,219 women with hypertension at baseline but no history of cardiovascular disease

(CVD). Among them, 11,294 were receiving monotherapy. A total of 4493 were receiving combined therapy with two different drug classes. Subjects were followed for an average of 5.9 years. After statistical adjustment for confounders, the hazard ratio for CVD mortality compared with diuretics was 1.55 (95% CI, 1.02-2.35) for calcium blockers, 0.97 for ACE inhibitors, and 0.83 for beta-blockers. Women treated with a diuretic plus a calcium channel blocker had an 85% greater risk of CVD death compared with those treated with a diuretic plus a beta-blocker. Risk was similar for ACE inhibitors plus diuretics and beta-blockers plus diuretics. Confirming the ALLHAT results, monotherapy with diuretics was equal or superior to other monotherapy in preventing CVD complications.

### Impact of Levodopa on Parkinson's Disease Progression Remains Uncertain

The use of levodopa as dopamine-replacement therapy is effective in reducing the symptoms of Parkinson's disease and it remains the standard drug. Despite the recognized benefit of levodopa, concern has been expressed that its use might accelerate disease progression. The worry is based on the observation that levodopa and dopamine can generate reactive oxygen and induce the degeneration of dopamine neurons in culture. As a result of these *in vitro* findings, some clinicians delay the initiation of levodopa therapy. On the other hand, levodopa is not toxic in animals and may

promote the functional recovery of damaged nigral neurons. Since the question of levodopa's effect on disease progression is clinically important, researchers conducted a controlled trial to assess its effects on the course of the disease [*N Engl J Med* 2004;351:2498-508].

They evaluated 361 patients with early Parkinson's disease who were assigned to receive a titrated dose of carbidopa-levodopa or matching placebo for 40 weeks, and then undergo withdrawal of treatment for two

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## Impact of Levodopa on Parkinson's Disease Progression (continued)

weeks. The primary outcome was a change in scores on the Unified Parkinson's Disease Rating Scale (UPDRS) from baseline. Neuroimaging studies were performed in 142 subjects at baseline and at week 40 to assess striatal dopamine-transporter density.

The severity of the disease increased more in the placebo group than in the levodopa group. In contrast, in the substudy, the mean decline of iodine-labeled marker uptake was significantly greater with levodopa than with placebo. The subjects receiving the highest daily dose of

levodopa, 600 mg, with 150 mg carbidopa, had significantly more dyskinesia and other side effects than those receiving placebo. The authors conclude that the potential long-term effects of levodopa on Parkinson's disease remain uncertain. They suggest that, until more evidence is available, clinicians should customize the dose of levodopa to the needs of the individual patient on the basis of clinical response and the profile of adverse events. Patients can be assured that, from a clinical perspective, the study did not find that levodopa hastens the progression of Parkinson's disease.

## Add-On Lamivudine of No Benefit for HBeAg<sup>+</sup> Chronic Hepatitis B

Treatment of HBeAg-positive patients with chronic hepatitis B is not effective in most cases. Conceivably, a combination of immunomodulatory pegylated interferon alfa-2b and antiviral lamivudine might improve the rate of sustained response. To explore this possibility, researchers assigned 307 HBeAg-positive patients with chronic infection to combination therapy or monotherapy with PEG-interferon for 52 weeks. About 35% of patients assigned monotherapy or combination

therapy had lost HBeAg at the end of follow-up. Loss of HBeAg followed by relapse was more common in the combination therapy. As expected, response rates varied by HBV genotype. The authors of the report conclude, "Treatment with pegylated interferon alfa-2b is effective for HBeAg-positive chronic hepatitis B. Combination with lamivudine in the regimen used is not superior to monotherapy" [*Lancet* 2005; 365:123-29].

## Sirolimus-Eluting Stents for Revascularization of Small Coronary Arteries

Atherosclerotic lesions of small coronary arteries are commonly seen in patients undergoing revascularization. Revascularization of these vessels with bypass surgery is complicated and has a high failure rate. A high restenosis rate is associated with balloon angioplasty and conventional stent implantation. Sirolimus-eluting stents improve the rate of event-free survival in patients at low risk of restenosis as well as in more challenging patients. This drug-laden stent, however, has not been adequately studied in small vessels.

To that end, investigators randomized 257 patients undergoing percutaneous coronary intervention for ischemic heart disease, and who had a previously untreated

lesion located in a small vessel. Patients received a sirolimus-eluting stent or an uncoated stent [*JAMA* 2004; 292:2727-34]. After eight months, the restenosis rate was 53.1% in the patients receiving a sirolimus-eluting stent and 91.8% in those receiving an uncoated stent. Fewer patients assigned to the drug-coated stent experienced major coronary adverse events, largely because of a reduction in target lesion revascularization and myocardial infarction. While it is likely that sirolimus-eluting stents reduce restenosis in small coronary arteries as well as other complicating events, the findings are confounded by fewer patients with diabetes mellitus in the active-treatment group than in the control; diabetes is a known risk factor for restenosis [*Ibid*, 2777-78].

## DRUG SAFETY

### Study Confirms Loss of Bone with *Depo-Provera*

A prospective study has confirmed that treatment with the contraceptive depot medroxyprogesterone acetate (*Depo-Provera*) is associated with bone loss [*Fertil Steril* 2004;82:1580-86]. The investigators com-

pared mean bone mineral density (BMD) in 178 first-time users of depot medroxyprogesterone acetate (DMPA) and 145 women not using hormonal contraception. Mean BMD at the hip and spine at two years after initiation of DMPA fell by 5.8% and 5.7%. On the other hand, BMD loss among controls was less than  
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## DRUG SAFETY (continued)

### Loss of Bone with *Depo-Provera* (cont.)

1.0%. Significant bone loss was also observed after only one year of DMPA. In November, the FDA issued a “black box” warning on DMPA stating that bone loss may not be reversible, particularly if the depot contraceptive is used for more than two years. The findings are likely to discourage physicians from prescribing *Depo-Provera*. The longest acting hormonal contraceptive available in the U.S. other than DMPA, *Lunelle*, provides protection against pregnancy for only one month after treatment.

### Androgen Deprivation for Prostate Cancer Increases the Risk of Fracture

Androgen-deprivation therapy, in the form of gonadotropin-releasing hormone (GnRH) agonists, is being applied increasingly in men with localized prostate cancer. This strategy, however, does not improve survival in minimally symptomatic patients. Therefore, risk-benefit issues must be considered.

Androgen deprivation induces a rapid loss of bone-mineral density within the first six months of therapy. Whether this loss leads to an increased risk of fractures has not been studied. Now, investigators have used the linked database of a National Cancer Institute surveillance program and Medicare to determine the risk of fracture associated with androgen deprivation in the form of orchiectomy or treatment with GnRH agonists in a large sample of more than 50,000 men, who had received the diagnosis of prostate cancer. The primary outcomes were the occurrence of any fracture and the occurrence of a fracture resulting in hospitalization [*N Engl J Med* 2005; 352:154-64].

The investigators reported that, among men who survived at least five years after diagnosis, 19.4% of those who received androgen-deprivation therapy had a fracture as compared with 12.6% of those who had not received androgen-deprivation therapies. Fractures resulting in hospitalization occurred in 5.19% and 2.37% of the patients, respectively. Further analysis suggested that there was a statistically significant relation between the number of doses of GnRH agonists received during the 12 months after diagnosis

and the subsequent risk of fracture. Androgen-deprivation-related fractures also increased with age. The number needed to harm for the occurrence of any fracture within 12 to 60 months after diagnosis was 74 for men 66-69 years old who received 1-4 doses of a GnRH agonist but fell to 12 for men 80 years or older who received nine or more doses.

Thus, androgen-deprivation therapy increases the risk of fractures by nearly 50% in men with prostate cancer. Physicians must monitor bone-mineral density closely in these patients and provide protection, as appropriate, to prevent bone loss. The authors of the report add, “Trials of therapies such as bisphosphonates to lower the risk of fracture are needed in patients for whom gonadotropin-releasing hormone agonists are clearly indicated.”

### COX-2 Inhibitor Increases Risk of GI Bleed for Patients on Warfarin

While COX-2 inhibitors may offer a degree of gastroprotection compared with nonselective NSAIDs, they do not appear to reduce the risk of warfarin-associated gastrointestinal hemorrhage [*Arch Intern Med* 2005; 165:159-160,189-92]. Investigators arrived at this conclusion based on an analysis of healthcare databases that identified 98,821 adults older than 66 years of age who were continuously prescribed warfarin over one year. Of these, 361 (0.3%) were admitted to a hospital for GI bleeding.

After adjustment for potentially confounding variables, the researchers determined that patients receiving warfarin who were hospitalized for GI bleeding were significantly more likely to have been treated with celecoxib, rofecoxib or a nonselective NSAID in the preceding 90 days. The odds ratios were 1.7, 2.4, and 1.9, respectively. The authors note, “While the concomitant use of warfarin with NSAIDs is a recognized risk factor for GI hemorrhage... our study is the first to examine the comparative safety of the COX-2 inhibitors... in patients receiving warfarin.” They warn, “Physicians and pharmacists who care for elderly patients taking warfarin should be aware of the potential risks of concomitant therapy with NSAIDs or COX-2 selective inhibitors.”