

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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Drug Therapy Topics Supplement

A Drug Information Center / School of Pharmacy publication.
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CLINICAL PRACTICE

Antibiotic Prescribing for Cough and Related Symptoms

Each year, cough accounts for more than 30 million physician office visits. Of these visits, more than 10 million were made by otherwise healthy adults diagnosed with acute bronchitis; most of them received a prescription for an antibiotic, usually for a broad-spectrum macrolide or a quinolone.

Although acute cough in healthy adults is common and treatment costs \$50 to \$100 per episode, the evidence supporting the practice is limited. Until recently, it consisted of nine studies with only 750 patients. Collectively, these studies suggest a small benefit, with cough resolving about a half day sooner, balanced by an increased risk of antibiotic-related adverse effects. The small sample size, however, introduces much uncertainty [*JAMA* 2005;293:3062-64].

A recently reported study more than doubled the size of the database. The investigators enrolled 800 adults and children who presented with a cough and at least one symptom related to the lower respiratory tract (e.g., discolored sputum or shortness of breath). Patients were assigned to immediate treatment with 250 mg amoxicillin three times a day (or erythromycin, if allergic), no antibiotics, or an offer of delayed antibiotics if symptoms had not resolved after 10 days [*Ibid*, 3029-35].

The investigators found no significant difference in any of the primary outcomes—duration of moderately bad cough, duration of cough, and mean severity of symptoms—between patients receiving antibiotics and those receiving placebo. In addition to this remarkable finding, the study also provided information about the natural history of acute bronchitis. Patients had been symptomatic for an average of nine days before they presented for care and experienced cough for 12 more days after the physician visit.

The results suggest that patients with acute cough should be made to understand that the prescribing of an antibiotic is unlikely to provide benefit. Furthermore, they must be told that with or without an antibiotic, symptoms are likely to persist for three to four weeks.

Treatment of Gestational Diabetes Reduces Adverse Pregnancy Outcomes

Gestational diabetes mellitus, defined as carbohydrate intolerance beginning during pregnancy, is diagnosed in 3% to 7% of all pregnant women in the U.S. It poses serious risks to the offspring. Whether treatment reduces those risks is not known.

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CLINICAL PRACTICE (continued)

Treatment of Gestational Diabetes and Pregnancy Outcomes (continued)

To answer this important question, researchers in Australia assigned 1000 women between 24 and 34 weeks gestation who had gestational diabetes to receive dietary advice, blood glucose monitoring and insulin therapy as needed (the intervention group) or routine care [*N Engl J Med* 2005;352:2477-86]. Twenty percent of the women in the intervention group received insulin as compared with only 3% in the routine-care group.

The rate of serious perinatal complications was significantly lower among the infants of the women in the intervention group than among the infants of the women in the routine care group (1% vs. 4%). No perinatal deaths occurred among the infants of mothers in the intervention group, but there were five such deaths among infants born to women in the routine-care group.

Infants born to women receiving intensive therapy had lower birth weights than those born to women receiving routine care. This observation may be explained by the earlier gestational age at birth in this group, related to increased use of induction of labor. Low birth weight was probably the reason for the observation that more infants of women in the intervention group were admitted to the neonatal nursery than the infants of those in the routine care group (71% vs. 61%).

A related editorial notes, “This study provides critical evidence that identifying and treating gestational diabetes can substantially reduce the risk of adverse perinatal outcomes without...increasing the rate of cesarean delivery” [*Ibid*, 244-46].

Missed Contraceptive Pills: New Guidelines

Medical experts in the UK have issued a new guidance on how to advise women who have missed one or more doses of combined oral contraceptives. The new recommendations aim to simplify previous guidelines felt to be overcautious, confusing, and complex [*Lancet* 2005;365:1670-71].

The panel of experts reached consensus on: the importance of taking an active pill as soon as possible when pills are missed; the variable risk of pregnancy depending on not only how many pills are missed but also when the pills are missed; the considerable body of data for recommendations about missed pills from studies of women using pills containing 30-35 µg ethinyl estradiol; the limited information about missing pills containing 20 µg ethinyl estradiol; and the potentially higher risk of pregnancy upon missing low-dose estrogen pills compared with pills containing higher doses of estrogen.

The new rules are controversial because they state that no back-up contraception (e.g., condoms) or emergency contraception is needed until three or more pills containing 30-35 µg ethinyl estradiol have been forgotten or two or more pills containing 20 µg or less of ethinyl estradiol. One problem is that most women don't know if their OC contains ethinyl estradiol and even fewer know the dose of the estrogen in the product they are using.

The commentary in the *Lancet* praises the efforts of the panel in updating guidelines for missed combined OCs but stresses that “careful consideration must be taken when rules are relaxed in litigious societies.” The authors suggest one rule for all: action is to be taken after missing two pills for all doses of combined OC pills.

DRUG EVALUATION

Commonly Prescribed Drugs Are Ineffective for Agitation in People with Dementia

Neuropsychiatric symptoms are common in patients with Alzheimer's disease. They present major difficulties for caregivers, and accelerate nursing home placement. Antipsychotics have been widely prescribed but these agents appear to have only modest efficacy and present a plethora of adverse effects, including an

increased risk of stroke. Separately, preliminary evidence suggests that cholinesterase inhibitors may improve agitation. In truth, there is scant evidence to support the use of either class of drugs.

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Commonly Prescribed Drugs Ineffective for Agitation in Dementia (continued)

Thus, investigators in the UK designed a well-controlled short-term trial to determine the respective efficacy of the antipsychotic agent quetiapine (*Seroquel*) and the cholinesterase inhibitor rivastigmine (*Exelon*) in 93 patients with Alzheimer's disease, dementia, and clinically significant agitation. The researchers found that neither quetiapine nor rivastigmine are effective in the treatment of agitation in patients with dementia in institutional care. Furthermore, quetiapine, compared with placebo, is associated with significantly greater cognitive decline [*BMJ* 2005;330:874-79].

Relatedly, the FDA has asked manufacturers of atypical antipsychotics to add a black-box warning to labeling citing an increased risk of mortality associated with the use of these agents off-label to treat dementia-related behavioral disorders [*The Pink Sheet*, 18 April 2005]. The agency's request for a stringent warning was based on results from 17 placebo-controlled trials of *Zyprexa* (olanzapine), *Abilify* (aripiprazole), *Risperdal* (risperidone), and *Seroquel* (quetiapine). Most of the excess deaths were the result of cardiovascular events and infections.

Cancer and Cardiovascular Disease in Women: Aspirin and Vitamin E Provide Little Benefit

A new study indicates that low-dose aspirin taken by healthy female health care professionals has no effect in preventing invasive breast cancer, colorectal cancer, or cancer at any other site. However, aspirin may reduce the risk of lung cancer. Also noted in the trial was the absence of benefit in terms of cancer mortality, either overall or by site, except for lung cancer mortality [*JAMA* 2005;294:47-55]. These findings derive from the Women's Health Study, a long-term well-controlled trial evaluating the effects of aspirin (100 mg every other day) or vitamin E (600 IU every other day) in nearly 40,000 subjects.

The vitamin E arm of the study showed no effect on incidence or mortality for cancer overall or breast, lung, or colon cancer, or for overall mortality [*Ibid*, 56-65]. The study also showed no significant effect of vitamin E on major cardiovascular events, incidence of myocardial infarction, or stroke. On the other hand, vitamin E demonstrated a statistically significant 24% reduction in cardiovascular mortality. The authors of the report conclude: "These data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women" [*Ibid*].

Orlistat Improves Weight Management in Obese Adolescents but Carries Side Effects

The prevalence of overweight in adolescents is increasing worldwide. Treatment of obesity in youths presents an array of challenges. Behavioral therapy alone has had limited success and whether drug therapy improves on these results has not been studied. Orlistat (*Xenical*) is a gastrointestinal lipase inhibitor, which decreases intestinal fat absorption by up to 30%. It has been widely studied in adults and appears to be free of systemic effects. A recent report concerns a trial characterizing the safety and efficacy of orlistat plus diet, exercise, and behavioral therapy in treating obese adolescents [*JAMA* 2005;293:1873-83].

The investigators studied 539 obese adolescents (12–16 years old) over one year; each subject received a 120 mg dose of orlistat or placebo each day. They found that, on average, body mass index (BMI) decreased in both groups for up to week 12 and then stabilized with orlistat but increased beyond baseline with placebo. Among the participants taking orlistat, 26.5%

had a 5% or higher decrease in BMI as compared with 15.7% of the placebo group; 13.3% and 4.5%, respectively had a 10% or higher decrease. At the end of the study, body weight had increased by 0.53 kg in the orlistat group and 3.14 kg in the placebo group.

Adverse gastrointestinal events plagued many of the adolescents assigned to orlistat. Fifty percent of the subjects complained of oily stool; 20% or more reported flatus with discharge, fecal urgency, abdominal pain, oily evacuation, or oily spotting.

In summary, behavioral therapy combined with diet and exercise offers modest benefit to obese adolescents. When orlistat is added to the mix, additional weight gain is avoided and a small proportion of subjects achieve impressive weight loss. There is no evidence that orlistat alone offers a benefit that outweighs the disturbing GI side effects associated with the drug.

DRUG EVALUATION (continued)

Daclizumab Prevents Rejection after Cardiac Transplantation But the Price May Be Too High

A common immunosuppression protocol for cardiac transplantation includes cyclosporine, mycophenolate mofetil, and corticosteroids. This regimen, however, predisposes patients to infections, the leading cause of death in the first year after transplantation. Daclizumab (*Zenapax*), a humanized monoclonal antibody, functions as an immunosuppressant by antagonizing interleukin-2-mediated proliferation of T-cells. It has been shown to decrease the risk of rejection of organ transplants with no increased incidence of infection. On the basis of prior reports of decreased rejection rates, researchers conducted a well-controlled study designed to test the effect of daclizumab immunotherapy as prophylaxis against cardiac rejection [*N Engl J Med* 2004;352:2705-13].

The investigators randomly assigned 434 recipients of a first cardiac transplant treated with cyclosporine, mycophenolate, and corticosteroids to receive an intravenous dose of daclizumab (1.0 mg/kg body weight) or placebo within 12 hours after transplantation and four more doses over the next 50 days. The primary endpoint was a composite of moderate-to-severe cellular rejection, hemodynamically significant graft dysfunction, a second transplantation, or death.

By six months, 47.7% of patients in the placebo group had reached the primary endpoint as compared

with 35.6% of patients in the daclizumab group. The rate of rejection was also lower in the daclizumab group than in the placebo group (41.3% vs. 25.5%). Among patients reaching the primary endpoint, the median time to an event was three times longer in the daclizumab group than in the placebo group during the first six months (61 vs. 21 days) and even more at one-year (96 vs. 26 days).

At six months and at one year, mortality was higher in the daclizumab group than in the placebo group. Deaths from infections were more common in the daclizumab group than in the placebo group when they received concomitant cytolytic therapy, consisting of muromonab-CD3 and antithymocyte or antilymphocyte agents. Such therapy should be avoided when using daclizumab.

While the findings are provocative they are not definitive. The benefits of daclizumab are offset by disturbing mortality trends. Whether daclizumab is a better choice for the treatment of episodes of histologic rejection of cardiac grafts than is the current strategy of moderately increasing immunosuppressive therapy remains uncertain. The author of a related editorial observes: "I am certain that I would not be willing to trade even a small increase in the risk of death from infection for a reduction in the risk of histologic rejection" [*Ibid*, 2749-50].

Xigris Fails to Protect Against Sepsis in Children

Eli Lilly reported that it has stopped a pediatric clinical trial evaluating the effectiveness of *Xigris* (activated protein C) for treating severe sepsis because the controversial drug failed to show an improvement over placebo. The study also showed that *Xigris* resulted in more bleeding into the brain than did placebo. *Xigris* is currently approved to treat adults with severe cases of sepsis who are at high risk of death. Patient selection,

however, is challenging. The study enrolled about 400 patients; the primary outcome was the drug's ability to stop organ failure. Last month, the FDA issued a warning about *Xigris* based on two clinical trials in adults that found that patients who had had recent surgery and a single organ dysfunction were at increased risk of death when treated with the drug, as compared with those on placebo.

Chemotherapy Plus Tamoxifen Slashes Mortality Rate in Breast Cancer

For middle-aged women with hormone-sensitive breast cancer, six months of anthracycline-based chemotherapy (anthracycline combined with fluorouracil and cyclophosphamide) and five years of tamoxifen halves the long-term risk of death from the disease [*Lancet* 2005;365:1687-717].

The report derives from the Early Breast Cancer Trialists' Collaborative Group, established in 1984-85, a consortium of investigators that every five years has conducted a meta-analysis of clinical trials of women undergoing treatment for early breast

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Chemotherapy Plus Tamoxifen Slashes Breast Cancer Mortality (continued)

cancer. The most recent analysis includes data from 194 trials of adjuvant chemotherapy or hormone therapy that began in 1995; included were 144,939 women.

Of paramount importance was the finding that the effect of tamoxifen and chemotherapy on mortality is additive. Chemotherapy regimens based on anthracycline were more effective than combination therapy with cyclophosphamide, methotrexate, and fluorouracil.

The study suggests, in layman's terms, that a woman under 50 with a palpable tumor, but one not invading her lymph nodes, would have a 25% risk of dying of breast cancer in the next fifteen years if she had surgery but no drug therapy. Adding both chemotherapy and hormone treatment would decrease her risk to 11.6%. Older women also benefit, though not as much. The authors suggest that, with improvements in early diagnosis and new chemotherapeutic agents, women can look forward to even better outcomes in the future [*The New York Times on the Web*, 13 May 2005].

NEW DRUGS AND INDICATIONS

Heart Failure Treatment Approved for Blacks

Following the unanimous recommendation of an advisory panel, the FDA swiftly approved *BiDil* (isosorbide dinitrate/hydralazine) for the treatment of heart failure in self-identified blacks. The combination of these two shopworn drugs is indicated to improve survival, prolong time to hospitalization for heart failure, and improve patient-reported functional status, as an adjunct to current standard heart failure therapy. In a study of the medication, reported last year, 1,050 black patients with heart failure showed a 43% reduction in mortality and a 39% reduction in hospitalization for heart failure. Neither isosorbide dinitrate nor hydralazine alone is approved for heart failure. How the two drugs work together is not well understood [*MD Consult*, 27 June 2005].

The development of *BiDil* was prompted by previous trials that failed to demonstrate the efficacy of the combination in an unstratified heart failure population but showed a strong trend toward benefit in the African-American patients among them. Benefit was confirmed in the African-American Heart Failure Trial (A-HeFT). While acknowledging the apparent efficacy of *BiDil* in the target population, geneticists say that race should not be used as a substitute for genomic medicine because race is "a sociopolitical

construct" [*The New York Times on the Web*, 17 June 2005]. The limited approval of *BiDil* does not preclude the possibility that it may be useful for other populations, but as of yet there is insufficient evidence to support this premise.

The proposed price for *BiDil* is high, much higher than for any other treatment for heart failure. A great deal of money can be saved by prescribing generic isosorbide dinitrate and generic hydralazine separately and directing the patient to take them together.

Erbix Seeks Head and Neck Cancer Indication

The maker of *Erbix* (cetuximab) reports that it will submit an application seeking authorization to sell the monoclonal antibody as a treatment for head and neck cancer. *Erbix* was approved in early 2004 to treat colon cancer that is not responding to standard chemotherapy. Today, it is almost always used in combination with irinotecan. The company will ask the FDA to approve *Erbix* for use with radiation and as monotherapy for squamous cell carcinoma of the head and neck, a condition that affects about 40,000 Americans each year. Positive results from a Phase III trial prompted the submission [*The Wall Street Journal Online*, 20 June 2005].

DRUG SAFETY

***Sustiva* Not Safe during First Trimester**

In June, the FDA notified health care professionals that *Sustiva* (efavirenz), an antiretroviral agent indicated for the treatment of HIV infection, may cause fetal harm when administered during the first trimester to a pregnant woman, adding that pregnancy should be avoided in women receiving the drug. The warning was based on four cases of neural tube defects in infants born to women with first-trimester exposure. As a result of these reports, the pregnancy category for *Sustiva* has been changed from Category C (risk of fetal harm cannot

be ruled out) to Category D (positive evidence of fetal risk). *Sustiva* is a nonnucleoside reverse transcriptase inhibitor (NNRTI); it must be used in combination with a protease inhibitor and/or nucleoside RTIs. Women of childbearing potential should undergo pregnancy testing before initiation of treatment with *Sustiva*. If the drug is prescribed in early pregnancy, barrier contraception should always be used in combination with other contraceptive methods.

***Risperdal* May Promote Pituitary Tumors**

A comprehensive review of a database of adverse drug reactions discovered a higher incidence of benign tumors in the pituitary gland among patients taking *Risperdal* (risperidone) than among those taking other antipsychotic agents. *Risperdal* competes for market share with several other major

drugs in the so-called atypical antipsychotic class, including *Zyprexa*, *Seroquel*, and *Abilify*. Side-effects have a big impact on sales. *Zyprexa*'s market share has fallen over the past year over concerns about weight gain and diabetes [*The Wall Street Journal Online*, 17 June 2005].

Progressive Multifocal Leukoencephalopathy and Natalizumab

A recent issue of *The New England Journal of Medicine* [2005;353:362-68] carries reports describing three patients in whom progressive multifocal leukoencephalopathy (PML) developed during treatment with natalizumab (*Tysabri*), a humanized monoclonal antibody against α_4 integrins. The drug has shown remarkable benefits against multiple sclerosis.

The patients were among a few thousand participating in clinical trials of natalizumab for the treatment of multiple sclerosis or Crohn's disease. PML is a life-threatening opportunistic infection of the central nervous system; there is no specific treatment. It is caused by reactivation of a latent JC polyomavirus, which infects and destroys oligodendrocytes and leads to demyelination and neurologic dysfunction. The development of PML in this setting was totally unexpected [*Ibid*, 414-16].

A key question is: would it be possible to predict and prevent the occurrence of PML in patients re-

ceiving α_4 blockers? The authors of a companion editorial observe: "The prospective measurement of the JC viral load in plasma and the preemptive reduction of doses or interruption of treatment if JC virus DNA appears in the blood might actually prevent the development of PML in this setting." [*Ibid*]. The makers of *Tysabri*, the sale of which has been suspended, certainly hope that this turns out to be the case.

Another editorial on the subject states that the association seen between natalizumab therapy and the occurrence of PML seems clear, although the magnitude of the risk of PML per year of exposure is as yet unknown [*Ibid*, 417]. More data are required to better understand and possibly overcome the limitations posed by natalizumab. There is a pressing need for additional clinical trials focused on safety. Potential participants must carefully evaluate the substantial risks and benefits of natalizumab.