VOL. 4 • NO. 7 • JULY 2009

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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President Obama signed the Family Smoking Prevention and Tobacco Control Act in the Rose Garden of the White House.

Landmark Tobacco Law Gives FDA New Powers

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Public health advocates are applauding a new law that gives the Food and Drug Administration unprecedented authority to regulate the sale, marketing, and ingredients in tobacco products.

President Obama signed into law the Family Smoking Prevention and Tobacco Control Act (H.R. 1256) at a June 22 White House ceremony. The new law gives the FDA the power to regulate the levels of tar, nicotine, and other ingredients in tobacco products. While the law does not give the FDA the authority to ban tobacco products, it does give the agency broad authority to regulate labeling, packaging, and advertising of such products.

During a White House Rose Garden signing ceremony, President Obama said the law would "save lives and dollars" and would aid health reform efforts by reducing tobacco-related health care costs.

The law bans the use of cigarette additives or flavoring such as strawberry or grape that many public health advocates have said has been used by tobacco manufacturers to make smoking more appealing to minors. The law also prohibits tobacco companies from using descriptors such as "light" or "mild."

In addition, the bill calls on the FDA to consider fast-tracking the approval of new smoking cessation products.

The new law also aims to prevent youth smoking by placing restrictions on outdoor tobacco advertising within 1,000 feet of schools and playground, as well as sponsorships of entertainment and sporting events. Cigarette packs themselves will also be designed to deter smoking. Under the law, about half of the front and back of the package will be taken up by the warning label. Manufacturers can choose from a selection of warnings such as "WARNING: Smoking can kill you" or

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Results Mixed for Low-Dose CT Lung Cancer Screening

Trial compared CT with chest x-ray.

BY MARY JO M. DALES
Elsevier Global Medical News

ORLANDO — Low-dose CT screening was associated with twice the rate of false positives and more unneeded interventions, compared with chest x-ray screening, in a randomized trial of people at high risk for lung cancer.

But low-dose CT screens also detected twice as many lung cancers as did chest x-ray screens in the study, which was the feasibility trial for the ongoing randomized, controlled National Lung Screening Trial (NLST).

The findings should be considered only hypothesis generating, said Dr. Jennifer M. Croswell, who presented the results at the annual meeting of the American Society of Clinical Oncology. The NLST should provide definitive findings regarding the comparative utility of chest x-ray and low-dose CT scans as screens for early detection of lung cancer.

Until then, promotion of low-dose CT screening for early lung cancer detection should be reconsidered given the costs associated with the exams, the increased probability of unneeded interventions, and the anxiety associated with false-positive results, concluded Dr. Croswell of the National Cancer Institute.

James R. Marshall, Ph.D., who was the invited discussant of the study, concurred that low-dose CT scans have questionable cost benefit for addressing the larger health burdens of cigarette smoking.

But the results of the study do offer some reassurance that the immediate risk of lung cancer is low for those with a negative low-dose CT screen, said Dr. Marshall, chair of the department of cancer prevention

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INSIDE

Trial Shows Albuterol No Help in ALI

BY ROBERT FINN
Elsevier Global Medical News

SAN FRANCISCO — A placebo-controlled clinical trial of albuterol in acute lung injury was terminated after the first interim analysis when it became apparent that the beta-2 agonist was no better than placebo.

The Data and Safety Monitoring Board determined that patients given aerosolized albuterol experienced no improvement in ventilator-free days and no improvement in 60-day mortality, Dr. Michael A. Matthay, FCCP, reported at a meeting on critical care medicine sponsored by the University of California, San Francisco.

Dr. Matthay of UCSF said that there were good reasons to suspect that beta-2 agonist therapy would be beneficial in acute lung injury (ALI). In experimental models, the therapy increased the resolution of alveolar edema by promoting sodium and chloride transport. In animal studies, the therapy reduced lung vascular permeability. And researchers reported lower lung water in human ALI

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CT Detection Rate Higher

Screening • *from page 1*

and population sciences at Roswell Park Cancer Institute in Buffalo, N.Y. Furthermore, the burden of the additional interventions in the study was modest for the most part and, importantly, low-dose CT detected significantly more lung cancers than did chest x-rays.

The randomized study included more than 3,200 current or former smokers aged 55-74 years with 30 or more pack-years of smoking history. At enrollment, none of the participants had had a chest CT in the past 24 months or a history of lung cancer. A positive screen was a detection of any noncalcified nodule larger than 3 mm (T0 screen) or 4 mm or larger (T1 screen), or of another radiographic finding deemed suspicious for cancer. A false positive was a positive screen with a completed negative work-up or a follow-up of 1 year or more with no cancer diagnosis.

The cumulative false-positive rates after two annual exams were 34% with low-dose CT and 15% with chest x-ray. The only participant characteristic associated with false-positive results was older age in the low-dose CT group, with an odds ratio of 1.34 and a confidence interval of 1.04-1.73, Dr. Croswell reported.

For 1,610 people in the low-dose CT group, there were 38 true positives and 504 false-positive screens, and 2 false negatives for 1,066 negative screens. In the 1,580-person chest x-ray group, there were 16 true positives and 216 false-positive screens and 4 false negatives in 1,344 negative screens, Dr. Croswell reported.

Dr. Marshall said the finding of 40 cancers in the low-dose CT group and 20 in the chest x-ray group in this randomized trial is a "difference that is statistically significant" and needs an explanation.

The positive predictive value of low-dose CT comes out to about 5% and the positive predictive value of chest x-ray comes out to 7%, he said.

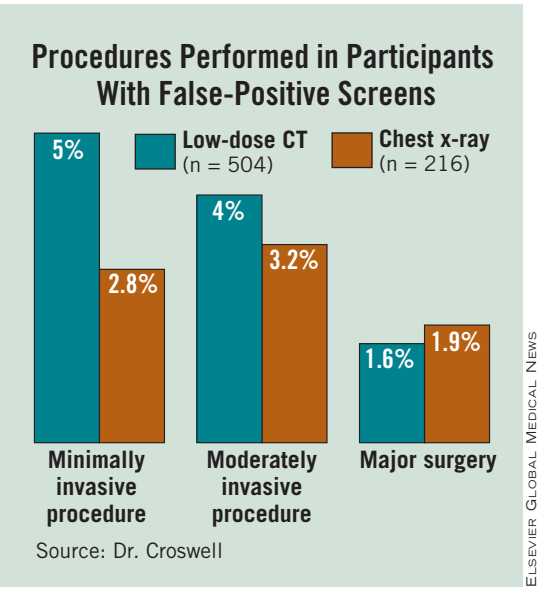
In the 504 patients with false positives in the low-dose CT group, 61% had at least one additional imaging exam and, overall, 6.6% had invasive procedures: 5% had a minimally invasive procedure (bronchoscopy), 4% had a moderately invasive procedure (lung or lymph node biopsy, mediastinoscopy or mediastinotomy, thoracentesis, or video-assisted thoracoscopic surgery), and 1.6% had a major surgical procedure (lung resection or thoracotomy). (Individual percentages add up to more than 6.6% because some patients had more than one invasive procedure.)

In the 216 patients with false positives in the chest x-ray group, 51% had at least one additional imaging exam and, overall, 4.2% had invasive procedures: 2.8% had a minimally invasive procedure, 3.2% had a moderately invasive procedure, and 1.9% had a major surgical procedure, Dr. Croswell reported. (See box.)

Yet Dr. Marshall considered the interventions to be "relatively modest burdens." In the low-dose CT group, 61% needed another imaging session and 29% were watched, for a "modest burden" rate of 90%. For those with false positives in the chest x-ray group, 51% had additional imaging and 45% were watched, for a "modest burden" rate of 96%.

According to the data, no mortality reduction advantage has yet been demonstrated for low-dose CT scans in a randomized, controlled trial, he said.

Dr. Croswell and Dr. Marshall had no relevant financial relationships to disclose in regard to the study. ■



Dr. Philip Marcus, MPH, FCCP, comments: *We see, once again, that there are many "false positives" detected as a result of CT scan screening. These false positives represent scans and inflammatory lesions that cannot easily be discriminated from lung cancer given their small size. Therefore, we are left with the realization that there does not seem to be an effective screening procedure for lung cancer. Further efforts should be directed at preventing smoking and promoting smoking cessation.*

New Labeling For Leukotriene Inhibitors

BY LORINDA BULLOCK
Elsevier Global Medical News

The Food and Drug Administration on June 12 called on manufacturers of leukotriene inhibitors to include safety precautions on their drug's labeling, because of reports of neuropsychiatric events in patients taking these drugs.

The FDA said the reported neuropsychiatric events included cases of agitation, aggression, anxiety, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal ideation and behavior, and tremor in patients using montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo, Zyflo CR).

Manufacturers of these drugs were asked to submit all available clinical trial data for these products for the safety review that concluded in April.

In its review, the FDA found that some reports included clinical details consistent with a drug-induced effect.

According to an FDA update from May, most of the reports of neuropsychiatric events were associated with montelukast.

The FDA advises that patients and health care providers be aware of the potential for neuropsychiatric events with these drugs used to treat asthma and symptoms of allergic rhinitis. The agency also suggests that physicians discontinue treatment if patients develop neuropsychiatric symptoms. ■

Information is available at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079523.htm.

IN THIS ISSUE

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

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Drug May Slow Deterioration From Pulmonary Fibrosis

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Results of two phase III studies of pirfenidone, an oral antifibrotic and anti-inflammatory agent, have shown that the drug could slow the deterioration of lung capacity in patients with idiopathic pulmonary fibrosis.

The 72-week-long trials, known as CAPACITY 1 and CAPACITY 2, enrolled 779 patients at 110 sites in 11 countries.

"The findings of the CAPACITY trials, coupled with the results of the phase II and phase III studies in Japan and the urgent unmet medical need, suggest that pirfenidone may provide a meaningful clinical benefit in patients with IPF," trial cochair Dr. Paul Noble, FCCP, said during a late-breaker abstract session at an international conference of the American Thoracic Society.

Manufactured by InterMune Inc., pirfenidone is currently approved in Japan for the treatment of IPF. InterMune expects to submit a New Drug Application for the agent to the Food and Drug Administration in the summer of 2009.

Patients were eligible for the studies if they had a diagnosis of pulmonary fibrosis confirmed by CT scan or by biopsy and if they had a forced vital capacity (FVC) that was 50% of predicted value or greater and a diffusing capacity of the lung for carbon monoxide that was 35% of predicted value or greater.

The 344 patients in CAPACITY 1 were randomized to receive pirfenidone 2,403 mg/day or placebo for 72 weeks, while the 435 patients in CAPACITY 2 were randomized to receive either pirfenidone 2,403 mg/day, pirfenidone 1,197 mg/day, or placebo for 72 weeks. The primary end point was change in percent predicted FVC from baseline to week 72.

The mean age of patients in CAPACITY 1 was 68 years, while the mean age of CAPACITY 2 patients was 67 years, said Dr. Noble, professor of medicine and chief of pulmonary, allergy, and critical care medicine at Duke University, Durham, N.C.

In CAPACITY 2, patients in the treatment group achieved a significant reduction in change in percent predicted FVC at week 72, compared with placebo (–6.49% vs. –9.55%, respectively), and an increase in progression-free survival time (hazard ratio of 0.64). The treatment group also demonstrated a favorable effect on change in FVC category ($P = .001$).

In CAPACITY 1, there was no significant mean change in percent predicted FVC at week 72 between the treatment and placebo groups (–6.49% vs. –7.23%, respectively), but there was evidence of a treatment benefit at each assessment through week 48. "CAPACITY 1 did not achieve statistical significance on the primary end point," Dr. Noble said. "However, results were generally consistent with and supportive of CAPACITY 2."

According to a prepared statement from InterMune, a pooled analysis of categorical FVC change from the two studies "showed that 30% fewer patients experienced a 10% or greater decrease in FVC at week 72 in the pirfenidone group than in the placebo group. This magnitude of decline is considered clinically meaningful, as a 10% decline in percent predicted FVC has been shown in multiple studies to be an independent predictor of mortality in patients with IPF. In addition, 40% more patients in the pirfenidone group did not experience a decline in percent predicted FVC at week 72 versus baseline compared to those who received placebo."

PATIENTS TREATED WITH PIRFENIDONE ACHIEVED A SIGNIFICANT INCREASE IN PROGRESSION-FREE SURVIVAL TIME (HAZARD RATIO OF 0.64).

At the meeting, Dr. Noble reported that the pattern of adverse events in both trials was generally comparable to those observed in previous clinical studies of pirfenidone.

The most common adverse events in the pirfenidone group compared with placebo were nausea (35% vs. 18% in CAPACITY 2, and 38% vs. 16% in CAPACITY 1), rash (31% vs. 10%, and 34% vs. 13%), fatigue (28% vs. 21%, and 33% vs. 20%), diarrhea (25% vs. 17%, and 33% vs. 21%), dyspepsia (17% vs. 9%, and 21% vs. 6%), and dizziness (19% vs. 10%, and 18% vs. 10%).

The researchers also analyzed the incidence of patients who died during the treatment period, which was defined as the time between receiving the first dose of study treatment and 28 days after receiving the last dose.

In CAPACITY 1, 5% of the pirfenidone group died during the treatment period, compared with 9% of the placebo group. In CAPACITY 2, 6% of pirfenidone patients died during the treatment period, compared with 8% of placebo patients.

The studies were funded by InterMune. Dr. Noble disclosed that he has served as a consultant, steering committee member, or cochair of a steering committee for InterMune, Actelion Pharmaceuticals Ltd., Boehringer Ingelheim GmbH, and Novartis. ■

Law Toughens Smoking Regs

Tobacco • *from page 1*

"WARNING: Cigarettes cause cancer."

"The passing of legislation to regulate tobacco in the United States has been long overdue," said Dr. James A. L. Mathers, Jr., FCCP, president of the American College of Chest Physicians. "We are honored to have played a role in this historical occasion through our consistent advocacy efforts and close collaboration with congressional leaders and organizations that support tobacco prevention."

The law's new types of restrictions will help chip away at some of the ways tobacco companies have successfully created an aura of "cool" around smoking, said Danny McGoldrick, vice president for research at the Campaign for Tobacco-Free Kids.

Other physician groups also hailed enactment of the new law. "The new law represents an important break from the past, as it signifies broad acceptance that nicotine is a drug harmful to people's health," Dr. J. James Rohack, president of the American Medical Association, said in a statement.

"To now have this kind of statement coming out in terms of control of tobacco products is a huge shot in the arm for the health of America," said Dr. Ted Epperly, president of the American Academy of Family Physicians. Dr. Epperly said he hopes the attention from the new law will spur physicians to make it routine to ask patients about smoking and follow up with advice on quitting.

For those physicians who think they don't have the time, Dr. Epperly pointed out that it doesn't have to be the physician who asks about smoking, it can also be a nurse or medical assistant. He also advised physicians to be patient about seeing results from patients. "I've had multiple patients that aren't ready yet to stop smoking. But I always remind them, 'I'm here for you if and when you decide [to quit],' " Dr. Epperly said.

One of the ways the FDA will be able to use its new authority to assist in smoking cessation is by regulating the ingredients in tobacco products. But finding the best way to do that may take some time, said Erika Sward, director of national advocacy for the American Lung Association.

For example, under the law the FDA is gaining the authority to reduce the amount of nicotine in cigarettes, but scientists don't yet know if that would only lead people to compensate by smoking more, she said.

Aside from the concrete elements of the law, Ms. Sward said she hopes the law will also help people understand that tobacco addiction is powerful and that most people can't quit "cold turkey."

It's important for physicians to talk to patients repeatedly about the need to quit smoking, she said. ■

Albuterol Disappoints in ALTA

ALI • *from page 1*

patients treated intravenously with salbutamol in a clinical trial.

The ALTA (Albuterol for the Treatment of ALI) trial was designed with aerosolized albuterol, because observational studies suggested that therapeutic levels of albuterol could be achieved in the pulmonary edema fluid of ALI patients. The drug does not simply deposit in the airways.

To be included in the trial, patients had to have a P/F (arterial oxygen pressure to fraction of inspired oxygen ratio, or PaO_2 to FIO_2 ratio) less than 300 mm Hg, bilateral infiltrates, and no clinical evidence of left atrial hypertension. The patients had to be receiving positive pressure ventilation via endotracheal tube.

Patients were excluded if they had moderate to severe liver disease, moderate to severe chronic obstructive pulmonary disease, chronic or acute need for beta-agonists, or acute myocardial infarction within 30 days.

Patients were given aerosolized albuterol at a dose of 5 mg/2.5 mL or 2.5 mL of normal saline every 4 hours until day 10 or until 24 hours following extubation. The dose of albuterol was reduced to 2.5 mg/2.5 mL if the patient experienced tachycardia or arrhythmia.

At the time the DSMB terminated the trial, 282 patients had been enrolled. There were no significant differences between albuterol and placebo groups on any baseline demographic or laboratory measurement, including Acute Physiology and Chronic Health Evaluation (APACHE III) score, number of organ failures, tidal volume, type of primary lung injury, electrolytes, blood pressure, and central venous pressure.

The investigators were able to determine that plasma albuterol levels were in the expected range in virtually all of the patients in whom they were measured.

The study's primary outcome was the number of ventilator-free days within 28 days after admission. Patients receiving albuterol had a mean of 14.5 ventilator-free days, compared with 16.5 days for the control patients. A secondary outcome was 60-day mortality, which was 23% among the patients taking albuterol and 17.7% among the control patients. Neither difference was statistically significant.

Dr. Matthay, who was the principal investigator of the ALTA trial, suggested three possible reasons that albuterol did not perform as expected. It could be that the alveolar epithelium may have been too injured to respond to beta-agonist therapy. The aerosol route could have delivered inadequate levels of albuterol to the injured alveoli. Or, conservative fluid management and lower tidal volume ventilation might have reduced lung injury and lung water to the extent that any additional fluid clearance with albuterol therapy had no beneficial effect.

Dr. Matthay had no conflicts of interest to disclose. The ALTA study was supported by the National Heart, Lung, and Blood Institute. ■

New Drug Class May Curb Multidrug-Resistant TB

BY MARY ANN MOON
Elsevier Global Medical News

The investigational diarylquinoline TMC207 proved to be effective and safe in a phase II clinical trial of 47 patients with multidrug-resistant tuberculosis.

"Demonstration of antituberculosis activity in patients with multidrug-resistant TB paves the way for larger-scale trials of first-line antituberculosis combination therapy for patients with drug-susceptible TB," said Dr. Andreas H. Diacon of the University of Stellenbosch, Tygerberg (South Africa), and his associates (N. Engl. J. Med. 2009;360: 2397-405).

Just as important, the drug's safety and efficacy findings demonstrate that inhibiting mycobacterial ATP synthase offers a new direction for antituberculosis therapy, the researchers said.

The multicenter trial, sponsored by Tibotec BVBA Pharmaceuticals, involved patients aged 18-57 years with newly diagnosed pulmonary TB that was resistant to isoniazid and rifampin. Most of the patients were men (74%), were black (55%), and were HIV negative (87%).

A total of 23 subjects were randomly assigned in a double-blind fashion to active treatment with TMC207 for 8 weeks, and 24 patients were randomized to placebo for 8 weeks. In addition, all patients received standard background therapy with kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone.

After 8 weeks, all patients continued on the background regimen and were followed for another 96 weeks.

RATES OF CONVERSION FROM A POSITIVE TO A NEGATIVE SPUTUM CULTURE AFTER 8 WEEKS WERE 48% WITH THE ACTIVE DRUG, COMPARED WITH 9% WITH PLACEBO.

Compared with placebo, adding TMC207 to standard background therapy yielded faster conversion to a negative sputum culture. Rates of conversion from a positive to a negative culture after 8 weeks were 48% with the active drug (10 of 21 patients), compared with 9% with placebo (2 of 23 patients).

"Treatment responses were similar for all trial centers and across all strata of lung cavitation," Dr. Diacon and his colleagues said.

TMC207 significantly increased the proportion of patients who had negative sputum cultures both halfway through the course of treatment and at the conclusion of treatment. Rates of negative cultures were 77% with TMC207 and 57% with placebo at 4 weeks, and were 84% and 68%, respectively, at 8 weeks.

No patients discontinued treatment early because of adverse events. "Overall side-effect profiles were similar in the two treatment groups, with nausea, unilateral deafness, arthralgia, hemoptysis, hyperuricemia, pain in the extremities, rash, and chest pain being the most common adverse events associated with treatment," the investigators noted.

Of those side effects, only nausea occurred in significantly more patients who were receiving active therapy (26%) than placebo (4%).

The development of TMC207 "represents an important advance in the chemotherapy of tuberculosis," said Clifton E. Barry III, Ph.D., of the National Institute of Allergy and Infectious Diseases, in an editorial comment accompanying the report.

"The diarylquinolines are a new class of drugs that increase the therapeutic options for patients who have multidrug-resistant or extensively drug-resistant tuberculosis, for whom treatment options are often sparse, largely ineffective, and often highly toxic," he noted (N. Engl. J. Med. 2009;360:2466-7).

The "very encouraging" clinical trial results also were important because "one of the largest barriers to the development of new drugs for tuberculosis is the paucity of targets that, when their function is inhibited by drugs, have a positive therapeutic effect in patients," Dr. Barry said.

Efforts are already under way to create other drugs that target ATP synthase, he added. ■

Smoking Cessation Drugs Receive Boxed Warning

BY JEFF EVANS
Elsevier Global Medical News

Accumulating reports of serious neuropsychiatric symptoms associated with the smoking cessation medications varenicline and bupropion have prompted the Food and Drug Administration to require new boxed warnings for the drugs.

The warnings, which went into effect July 1, highlight symptoms that include changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and suicide.

The manufacturers also were required to revise the plain-language medication guides that come with the drugs.

The requirements affect the drugs specifically indicated for smoking cessation—Chantix (varenicline), manufactured by Pfizer Inc., and Zyban (bupropion), manufactured by GlaxoSmithKline—as well as the generic and branded formulations of bupropion (Wellbutrin, Aplenzin) that already carry a boxed warning about the risk of suicidal thinking and behavior in the treatment of psychiatric disorders.

The FDA previously informed the public about the possibility of serious neuropsychiatric symptoms with varenicline in November 2007, and issued a health advisory in February 2008 about new warnings and precautions in the drug's labeling about the risk of such symptoms.

However, the new cases involving Zyban took the agency by "surprise," Dr. Curtis Rosebraugh, director of the Office of Drug Evaluation II at the FDA's Center for Drug Evaluation and Research, said in a press telebriefing.

Dr. Rosebraugh said that symptoms "have occurred in patients with and without a history of psychiatric illness. They tend to occur shortly after starting the medication and usually end when the medication is stopped, although we do have some reports of people who continue to have symptoms after stopping the medication and, in a few cases, [patients began] experiencing problems after the medication was stopped."

Through adverse-event spontaneous reporting systems, the agency has received reports of 98 completed suicides involving varenicline and 14 involving bupropion, as well as reports of 188 suicide attempts with varenicline and 17 with bupropion, Dr. Rosebraugh said. However, some of the cases may be duplicates because the FDA has not "been through every one of the individual reports to see if there are repeat reports," he said.

Dr. Rosebraugh noted that it has been difficult to evaluate the cases "because people who stop smoking without using medications can have similar symptoms due to nicotine withdrawal, such as depression, anxiety, irritability, restlessness, and sleep disturbances." Yet some of the cases of adverse events have occurred when people continued smoking while on the medications.

The difference in the number of reported cases of suicide and suicide attempts with Chantix in comparison to Zyban probably reflects the greater market penetration of Chantix and previous media reports of changes in behavior with it, Dr. Rosebraugh indicated.

The FDA also is requiring the manufacturers to conduct a clinical trial to determine the incidence of these symptoms in smokers with and without a history of mental health disorders.

Despite the new warnings, Dr. Rosebraugh said "varenicline and Zyban are effective smoking cessation aids. The possible risk of serious adverse events occurring should always be weighed against the significant health benefits of quitting smoking." ■

Women More Susceptible to Effects of Smoking

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Women are more susceptible to the lung-damaging effects of smoking, compared with men, according to the results of a large case-control study.

The gender effect seemed to be most pronounced when the level of smoking exposure was low and decreased in magnitude with an increasing number of pack-years, lead investigator Dr. Dawn L. DeMeo reported in a poster session at an international conference of the American Thoracic Society.

She and her associates evaluated data from a case-control study performed at Haukeland University Hospital in Bergen, Norway, between 2003 and 2005 that involved 583 men and 371 women with chronic pulmonary obstructive disease (COPD).

To be eligible for the trial, participants had to be white, at least 40 years of age, and current or ex-smokers with a history of 2.5 pack-years or more; and they had

The gender effect seemed to be most pronounced when the level of smoking exposure was low.

DR. DEMEO

to have no severe alpha-1 antitrypsin deficiency, reported Dr. DeMeo of Harvard Medical School and the Channing Laboratory, Boston, and her colleagues.

The researchers observed no differences between men and women with respect to lung function and COPD severity, but the women were younger (a mean of 64 vs. 66 years) and had smoked significantly less than men (a mean of 24 vs. 32 pack-years).

Dr. DeMeo and her associates then restricted the analysis to two subgroups: an early-onset group of 316 patients who were younger than age 60 at the time of the study and a lower-exposure group of 241 patients with a smoking history of fewer than 20 pack-years. Analysis of these subgroups revealed that women had a later smoking onset and fewer pack-years than men.

Women also had a more severe reduction of forced expiratory volume in 1 second for lower levels of smoking exposure, but after 25-30 pack-years the curves for males and females converged and showed a similar dose-response relationship. "There seems to be a female predominance for the lung-damaging effects of cigarette smoke, but it seems to be most pronounced when the cigarette smoke exposure is on the lower end," said Dr. DeMeo in an interview.

Reasons for the gender differences remain unclear, but could be related to the fact that women have smaller lungs than men. "That likely doesn't explain all of the potential impact here," she commented. "There have been hormonal arguments cited and also social constructs associated with gender differences. Perhaps women are underreporting [their cigarette smoking]. One of the goals of our research group at the Channing Laboratory is to address what may be going on from genetic and epigenetic points of views. More research is needed." Dr. DeMeo is also with Brigham and Women's Hospital's lung transplantation program and the COPD center at the Center for Chest Diseases.

She acknowledged certain limitations of the study, including its retrospective design and the fact that it was conducted only in Norwegian whites.

The study received funding from the Research Council of Norway, GlaxoSmithKline, and the Foundation for Respiratory Research at Haukeland University Hospital. Dr. DeMeo was supported by a grant from the National Institutes of Health and an award from the Doris Duke Charitable Foundation. ■

Dr. Philip Marcus, MPH, FCCP, comments: *This study emphasizes that there is no such thing as a "safe" amount of cigarette smoking, and this applies particularly to women. The results here duplicate those from prior studies, and the attitudes of young women need to be addressed as to the attractiveness and safety of "light" smoking. National statistics show more COPD diagnosed in women than men, and increased COPD mortality in women.*

Drug Duo Helped Reduce Bronchiolitis Burden

BY MARY ANN MOON
Elsevier Global Medical News

The combination of oral dexamethasone and nebulized epinephrine appeared to reduce hospital admission, hasten discharge from the emergency department, and decrease the duration of symptoms in infants with bronchiolitis, according to a report in the New England Journal of Medicine.

The researchers compared each of the drugs alone and in combination against placebo in a study of 800 infants aged 6 weeks to 1 year who presented to the ED with a first episode of bronchiolitis and signs of upper respiratory infection.

Hospitalizations for the disorder have almost doubled over the past 10-15 years in the United States and Canada, and treatment is controversial.

"Bronchodilators and corticosteroids are widely used but not routinely recommended," said Dr. Amy C. Plint of Children's Hospital of Eastern Ontario, Ottawa, and her associates.

They conducted a randomized, double-blind, clinical trial at eight Canadian pediatric emergency departments. The patients had scores of 4-15 on the respiratory distress assessment index.

The primary outcome—hospital admission within 7 days of the ED visit—occurred in only 17% of the infants who received combined dexamethasone and epinephrine, compared with 24% of those who received epinephrine only, 26% of those who received dexamethasone only, and 26% of those who received placebo only. That represents a relative risk reduction of 35% with the combined therapy, the investigators said (N. Engl. J. Med. 2009;360:2079-89).

The benefit of dexamethasone plus epinephrine was evident within 3 days of presentation, and it was not affected by the duration or severity of the illness, whether or not the patient proved to have respiratory syncytial virus, or whether or not the patient had a history of atopy.

"We also found an apparent benefit from the combined therapy on our secondary outcomes: Infants in this group were discharged earlier from medical care and resumed quiet breathing and normal feeding sooner than did those in the placebo group," Dr. Plint and her colleagues said. "In contrast, neither dexamethasone alone nor epinephrine alone had any effect on these outcomes."

There were no serious short-term adverse events related to treatment. However, "we do not have findings from long-term follow-up to establish whether our study treatments caused adrenal suppression, arrest of somatic growth, or neurodevelopmental delay," as has been suggested by some researchers.

"Given the unexpected synergy we found between epinephrine and dexamethasone, and the lack of any apparent benefit when either drug is used alone, our results should be considered exploratory," Dr. Plint and her associates noted. "Confirmation of our findings by a study powered specifically to compare combined epinephrine and dexamethasone therapy with placebo is needed," they added.

In an editorial comment accompanying the report, Dr. Urs Frey of the University Hospital of Bern (Switzerland) and Dr. Erika von Mutius of University Children's Hospital, Munich, said that the effect size of the treatment benefit was small.

"Given [that] 11 infants would have to be treated to prevent one hospital admission, it does not seem practical to apply [this] treatment, especially considering the potential effects of high-dose corticosteroids on brain and lung development in such young children," they noted (N. Engl. J. Med. 2009;360:2130-1).

Instead, "it is essential during the first episode [of bronchiolitis in a preschooler] to provide supportive care—including supplemental oxygen, hydration, nutrition, and short-term bronchodilation—[but] the key intervention is close follow-up," they said.

Dr. Frey reported receiving a travel grant from GlaxoSmithKline PLC and research support from VoluSense AS. Dr. von Mutius reported receiving consulting fees from GlaxoSmithKline, UCB SA, and ProtectImmun GmbH, lecture fees from Novartis and Alk-Scherax-Abelló Arzneimittel GmbH, and grant support from Airsonett AB. Dr. von Mutius also was named as an inventor on a pending patent for protection from allergies and inflammatory disorders. ■

Sleep Apnea May Hinder Glycemic Control in Diabetics

BY SUSAN LONDON
Elsevier Global Medical News

SEATTLE — Treating obstructive sleep apnea in patients with type 2 diabetes could improve glycemic control as much as using common antidiabetic drugs, according to the results of an observational study.

The study of 54 patients with type 2 diabetes indicated that blood glucose levels may be harder to control in cases of untreated OSA, Dr. Renee Simon Aronsohn reported at the annual meeting of the Associated Professional Sleep Societies.

Results showed that mean glycosylated hemoglobin (HbA_{1c}) rose significantly from 6.5% in patients without OSA to 8.7% in those with severe OSA, she said.

The higher HbA_{1c} values also were significantly related to the number of episodes of oxygen desaturation of 3% or more during REM sleep.

In published reports, the prevalence of polysomnography-proven OSA in type 2 diabetes has ranged from 58% to 86%. "Despite this strikingly high prevalence

'Our findings suggest that untreated OSA may ... increase the need for more intensive pharmacotherapy.'

DR. ARONSOHN

of disease in patients with type 2 diabetes, the impact of OSA on glucose control in this patient population" has remained unknown, said Dr. Aronsohn, an endocrinology fellow at the University of Chicago.

She and her colleagues enrolled 54 patients seen in outpatient clinics during 2000-2008 who had physician-diagnosed type 2 diabetes and were on stable doses of medication for diabetes and comorbidities. A total of 29 patients (54%) were women, and 29 (54%) were black.

Participants completed a diabetes and quality of life survey, performed wrist actigraphy monitoring for 5 days at home, underwent overnight laboratory polysomnography, and had a glycosylated hemoglobin measurement.

On the basis of their apnea-hypopnea index, patients were classified as having no OSA (index less than 5), mild OSA (5-14), moderate OSA (15-29), or severe OSA (30 or greater).

Overall, 76% of the patients had OSA, which was classified as mild in 35%, moderate in 26%, and severe in 15%. Compared with their counterparts without OSA, patients with OSA, on average, were older (60 years vs. 53 years), had a higher body mass index (35 kg/m^2 vs. 29 kg/m^2), and had a greater prevalence of diabetic complications (68% vs. 23%). The patients with OSA also had less total sleep time on polysomnography (6.3 hours vs. 7.2 hours), poorer sleep efficiency (81% vs. 90%), and less time spent in REM sleep (20% vs. 27%).

In a multivariate analysis that adjusted for potential confounders (age, gender, race, body mass index, insulin use, duration of diabetes, and total sleep time), mean HbA_{1c} increased significantly across OSA categories, with values of 6.5%, 7.5%. 7.8%, and 8.7% among patients with no, mild, moderate, and severe OSA, respectively.

"It's important to note that the magnitude of the effect sizes we see here are comparable to—if not exceeding—those seen with widely used pharmacologic agents," Dr. Aronsohn commented.

Two other measures of OSA severity were significantly and positively associated with log-transformed HbA_{1c} values: the number of obstructive events in REM sleep (beta coefficient 0.0750), and the number of oxygen desaturations of 3% or greater during REM sleep (beta coefficient 0.0638).

Giving a clinical example, she noted that a 100% increase in the number of obstructive events during REM sleep, from the median of 35 to 70 events per night, would result in a predicted increase in median HbA_{1c} from 7.2% to 7.7%. "This again is a clinically significant change in hemoglobin A_{1c} value," she pointed out.

"Our findings suggest that untreated OSA may worsen glucose control and increase the need for more intensive pharmacotherapy," Dr. Aronsohn said.

Dr. Aronsohn reported that she had no conflicts of interest. ■

Erlotinib Boosted Progression-Free Survival in NSCLC

Mean survival among patients was 22.4 weeks with erlotinib vs. 16.0 weeks with placebo.

BY PATRICE WENDLING
Elsevier Global Medical News

ORLANDO — Maintenance therapy with oral erlotinib significantly improves progression-free survival in patients with non–small cell lung cancer without progression after first-line platinum-based chemotherapy, according to data from the phase III SATURN trial.

In an intent-to-treat analysis in 884 patients, progression-free survival that was confirmed by independent review was significantly prolonged with erlotinib (Tarceva), compared with placebo (hazard ratio, 0.71; *P* less than .0001). The median was 12.3 weeks with erlotinib vs. 11.1 weeks with placebo; the mean was 22.4 weeks vs. 16.0 weeks.

The study also met its coprimary end point: significantly improving progression-free survival in patients with epidermal growth factor receptor (EGFR)–tumors (HR, 0.69; *P* less than .0001), principal investigator Dr. Federico Cappuzzo reported at the annual meeting of the American Society of Clinical Oncology.

As expected from earlier erlotinib trials, progression-free survival was particularly improved in females (HR, 0.56), Asians (HR, 0.58), and never smokers (HR, 0.56). Significant benefits were seen irrespective of adenocarcinoma (HR, 0.60) or squamous cell histology (HR, 0.76).

Study discussant Dr. Nasser Hanna of Indiana University in Indianapolis noted that patients with EGFR wild-type tumors, who make up about 90% of the NSCLC patients whom oncologists see,

had a small gain in progression-free survival (HR, 0.78; $P = .018$), whereas the 10% of patients who harbor EGFR mutations had a substantial gain in progression-free survival (HR, 0.10; P less than .0001).

"The benefits are disproportionately large for patients with EGFR mutations," he said.

Although overall survival data are not expected until later this year, OSI Pharmaceuticals Inc. (which comarkets erlotinib with Roche Holding AG) is already touting to shareholders on its Web site that the "10-fold improvement in [progression-free survival] for EGFR mutants in SATURN is almost certain to translate into a survival benefit."

Dr. Hanna noted that only 16% of patients in the placebo arm ever received an EGFR tyrosine kinase inhibitor, which could have implications for overall survival outcomes. In addition, there was no signal for an overall survival benefit when 150 mg/day of erlotinib was given after six cycles of platinum chemotherapy plus gemcitabine in a smaller, randomized phase II trial reported at ASCO last year (J. Clin. Oncol. 2008 [May 20 suppl.] abstract 8031).

"The question is, could survival benefits be preserved if erlotinib were delayed, allowing patients time for treatment breaks," he said.

In the SATURN (Sequential Tarceva in Unresectable NSCLC) trial, 889 patients who did not progress after four cycles of first-line platinum-based doublet chemotherapy were randomized to 150 mg/day of erlotinib or placebo. Their median age was 60 years, three-fourths of them were male, about 55% were current smokers, and about 40% had squamous cell histology.

The response rate, including complete and partial responses, was 12% with erlotinib vs. 5% with placebo ($P = .0006$), reported Dr. Cappuzzo of Istituto Clinico Humanitas IRCCS, Rozzano, Italy. Stable disease was not significantly different between erlotinib (48.6%) and placebo (45.4%). Disease control rate lasting 12 weeks or more was 41% with erlotinib and 27.4% with placebo (P less than .0001).

More adverse events, mainly rash and diarrhea, occurred with erlotinib than placebo. Study withdrawal due to adverse events was 5% for erlotinib and 2% for placebo.

The investigators reported no deterioration in quality of life between erlotinib and placebo, although presumably there was no enhancement either, Dr. Hanna said.

Regulatory applications for Tarceva as first-line maintenance therapy in NSCLC have been submitted by OSI in the United States and by Roche in Europe. OSI officials expect that Tarceva could gain U.S. approval in this setting by mid-January 2010, representing "an estimated potential opportunity in the [U.S. of more than] $0.5 billion."

Erlotinib is currently indicated for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, and for first-line treatment of locally advanced, unresected, or metastatic pancreatic cancer in combination with gemcitabine.

Dr. Cappuzzo has provided consultation and attended advisory boards for the study sponsor, F. Hoffman–La Roche Ltd., and has received honoraria from Eli Lilly & Co., AstraZeneca, and Boehringer-Ingelheim GmbH. ■

FYI

Contractual Agreements Guide

The American Medical Association and the American Association of Preferred Provider Organizations have partnered to develop the "Provider Contracting Toolkit" to help physicians, preferred provider networks, and payers better understand contractual agreements. The guide can be accessed online at www.ama-assn.org or www.aappo.org.

Communicating With Elder Patients

The National Institute on Aging has released a new booklet about communicating with older patients. "Talking with Your Older Patient: A Clinician's Handbook" offers practical techniques for diagnosis, promoting treatment adherence, and making effective use of a clinician's time. To download the booklet, visit www.nia.nih.gov/healthinformation/publications/clinicianhb.

AMA Opens ePrescribing Center

The American Medical Association has launched its online ePrescribing Learning Center. The new Web site provides physicians with the tools they need to make informed decisions about electronic prescribing. For further information and to access AMA's ePrescribing Learning Center, contact the AMA at www.ama-assn.org/go/eprescribing.

NetWorks

Treating CA-MRSA Pneumonia; Sleep Disorders in Chronic Illness

Chest Infections

Community-Associated MRSA Pneumonia: A Real Concern

Staphylococcus aureus (SA) is one of the most important pathogens associated with health-care-acquired infections and, recently, an important community-acquired pathogen in the United States and worldwide.

Severe and life-threatening infections by community-associated methicillin-resistant SA (CA-MRSA) have been described, including severe skin and soft tissue infections (*eg*, necrotizing fasciitis), septic thrombophlebitis, and severe pneumonia.

Severe CA-MRSA pneumonia usually presents with severe and rapid progression of symptoms (usually less than 3 days), including hemoptysis, high fever, leukopenia, septic shock, and destructive lung disease.

Several risk factors have been identified, including viral infections (*eg*, influenza), participation in contact-sports, living in crowded conditions (*eg*, prisons), sexual contact between men, injection drug abuse, perinatal transmission, and recent health-care contact.

The classic patient with CA-MRSA pneumonia is a previously healthy young individual with a recent influenza-like illness. High death rates are associated with influenza coinfection and development of ARDS and septic shock.

The severity of the disease is implicated with the presence of the Panton-Valentine leukocidin (PVL) toxin. This virulent factor causes tissue necrosis and leukocyte destruction. Pneumonia due to PVL-positive CA-MRSA is often associated with severe forms of disease.

The initiation of appropriate antibiotic therapy is critical in order to improve outcomes. However, treatment trials data for CA-MRSA pneumonia are lacking, and we rely on extrapolating therapeutic strategies from other MRSA infections.

Recommended antibiotics for patients with CA-MRSA pneumonia include vancomycin and linezolid. CA-MRSA is usually resistant to antibiotics often used for community-acquired pneumonia, such as beta-lactams, fluoroquinolones, clindamycin, and macrolides. CA-MRSA can be susceptible to clindamycin, but inducible resistant strains to clindamycin can occur.

In conclusion, we need to be mindful to identify patients with pneumonia at risk for CA-MRSA and to institute prompt diagnostic and effective therapeutic interventions to improve patient outcomes.

Dr. Marcos Restrepo, FCCP
Steering Committee Member

Home Care

Canadian Thoracic Society; Home Mechanical Ventilation Guidelines

The Canadian Thoracic Society is developing Home Mechanical Ventilation (HMV) Guidelines in order to better inform the practice of HMV, to encourage governments to recognize its value, and to help educate consumers about appropriate care options in order to understand risk and avoid hospitalization.

There is rapid development of home-based technologies, previously only available in hospitals and ICUs. Considering the benefit of noninvasive airway management and the costs of health care in institutions, the need for expertise in HMV is both desirable and critical. Home management of respiratory failure is associated with both improved quality of life and reduced health-related costs.

However, a good understanding of the initiation and maintenance of HMV is severely lacking in the medical community.

There is little recognition of the substantial number of patients who are at risk of predictable respiratory failure and limited introduction of preventive strategies. There is a failure to recognize the safety of HMV, an over-reliance on formal polysomnography, and a lack of recognition of state-supported ventilator equipment pools.

Representatives from almost every province in Canada have contributed to this guideline. It is informed by an extensive database of English literature and follows the recent ACCP publication on the grading of evidence (Guyatt G, et al. *Chest* 2006; 129; 174). The document takes a diagnosis-based approach to recommendations for the management of adults. Section topics include: ALS, muscular dystrophy, MS, spinal cord injury, central hypoventilation, obesity hypoventilation syndrome, COPD, kyphoscoliosis, and myotonic dystrophy, as well as specific sections on airway clearance, transition home, and ethics in HMV.

It is anticipated that this guideline will assist in the provision of a high standard of proactive and cost-effective management of patients with respiratory failure. It will provide a comprehensive reference for physicians, allied health-care providers, caregivers, and patients in the art and science of HMV.

Dr. Doug McKim, FCCP; and
Dr. Jeremy Road

Interstitial and Diffuse Lung Disease

Clinical Advances in Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis (LAM) is a multisystem disorder affecting primarily women, characterized by cystic lung destruction, lymphatic abnormalities (chylous effusions, thoracoabdominal lymphangioleiomyomas) and abdominal tumors (angiomyolipomas) resulting from the proliferation of abnormal-appearing smooth muscle-like LAM cells.

Patients with LAM present with dyspnea, pneumothorax, chylous effusions, or intraabdominal hemorrhage caused by angiomyolipomas. CT scans show characteristic thin-walled cysts throughout the lungs. Pulmonary function abnormalities include airflow obstruction, decreased lung diffusion capacity, and desaturation with exertion.

Progressive respiratory failure from cystic lung destruction can require lung transplantation; 10-year survival with LAM has been estimated at 90%.

LAM occurs in approximately one-third of women with tuberous sclerosis complex (TSC), an autosomal dominant disorder, and in patients with no evidence of TSC (sporadic LAM). In both situations, LAM cells have mutations of the TSC tumor suppressor genes *TSC1* or *TSC2*, the protein products of which regulate key cellular pathways involving the mammalian target of rapamycin (mTOR), which govern cell size, proliferation, and viability.

Since LAM is a disease of women and may worsen during pregnancy or following the administration of estrogen, antiestrogen therapy has been employed, although objective evidence of its efficacy is lacking.

A drug that appears promising in LAM treatment is sirolimus, an inhibitor of mTOR. Data from the recently concluded Cincinnati Angiomyolipoma Sirolimus Trial (CAST) showed that sirolimus decreased the size of angiomyolipomas by as much as 53% after 1 year of therapy, but in some patients, tumor size increased after discontinuing the drug. Of note, lung function appeared to improve with sirolimus therapy.

An ongoing trial (MILES trial), based in Cincinnati (Francis X. McCormack, PI), is evaluating the efficacy of sirolimus in preventing decline in lung function.

Another trial based in Nottingham, UK (Simon Johnson, PI), will assess the effect of doxycycline, a bacteriostatic antibiotic with antimatrix metalloproteinase and antiangiogenic activity, in LAM.

Dr. Joel Moss

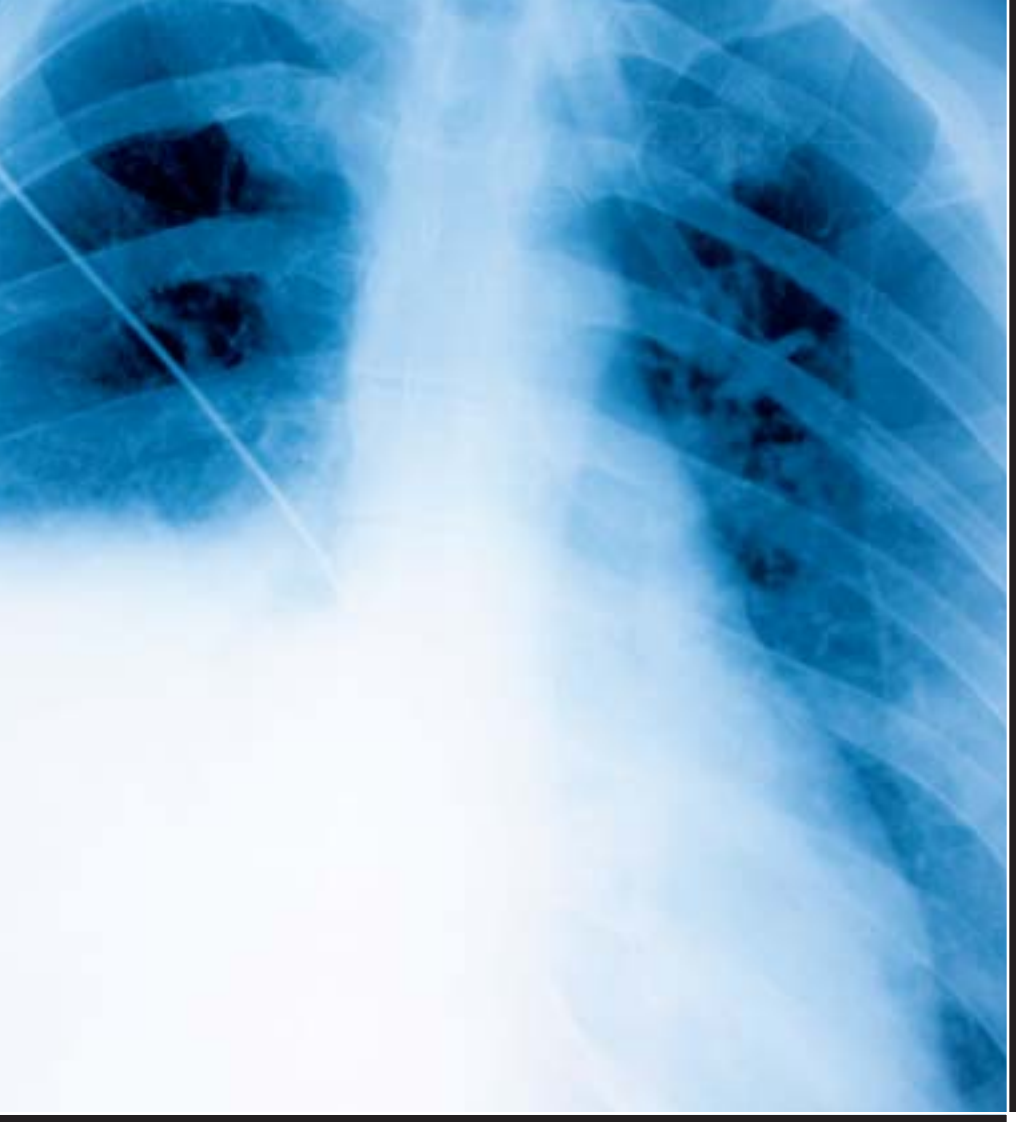
Sleep Medicine and Palliative and End-of-Life Care

Sleep at the End of Life

Persons with chronic progressive illnesses, such as COPD, end stage lung cancer, and HIV infection, among others, have a poor quality of life. It has also been long appreciated that a number of sleep disorders, including insomnia, restless legs syndrome, and sleep-related breathing disorders, can negatively impact quality of life.

Fatigue and difficulty sleeping are frequent complaints among patients with chronic diseases; however, they are often overlooked by the medical provider. Appropriate recognition and treatment of sleep disorders may improve patient quality of life, particularly when cure of the disease is no longer an option. There are published guidelines on the management of pain, depression, anxiety, nutrition, oxygen therapy, and hydration for terminally ill patients. Despite being a major problem for some dying patients, the issues related to the proper management of insomnia, drowsiness, restless legs, obstructive sleep apnea, sun downing, and parasomnias have not been explored. Among the several ongoing projects of the Sleep Medicine and Palliative and End-of-Life Care NetWorks is the development of a consensus statement on the management of sleep and sleep disorders at the end of life. This project is headed by Drs. Laura Herpel (Sleep Medicine NetWork) and Dee Ford, FCCP (Palliative and End-of-Life Care NetWork), and it will be the first to clarify these issues and, hopefully, provide medical providers with the necessary tools to manage these conditions.

Dr. Teofilo-Lee Chiong, FCCP
Sleep Medicine NetWork Chair



SERIOUS INFECTION

SERIOUS RESULTS

ZYVOX—proven efficacy in nosocomial pneumonia, due to known or suspected MRSA[1-3*]

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

IV/Oral

ZYVOX®

(linezolid)

SMART BUG. SMART DRUG.™

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH, for the Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980-992. **3.** Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent page.

ZYVOX® linezolid injection, tablets and for oral suspension Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (**see PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]). **Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis**, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone. **WARNINGS Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer 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. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.** In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections**. ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated. **PRECAUTIONS General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).** Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions *Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **ADVERSE REACTIONS Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^3/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^3/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^3/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^3/mm^3) 12.9 and 13.4; WBC (x 10^3/mm^3) 12.4 and 10.3 and neutrophils (x 10^3/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a^ >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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SLEEP STRATEGIES

Obstructive Sleep Apnea and Cognitive Dysfunction

Dr. James Parish, FCCP
Section Editor,
Sleep Strategies

Cognitive impairment is well recognized in individuals with sleep deprivation and excessive sleepiness. It is also well known that patients with obstructive sleep apnea (OSA) frequently present with excessive daytime sleepiness. It makes intuitive sense, then, to postulate that patients with OSA who are excessively sleepy may have cognitive impairment. The goals for this brief review are to identify the potential mechanisms, tests used, and epidemiologic studies, and identify the effects of CPAP and other treatments on cognitive impairment in patients with OSA.

OSA is characterized by repetitive upper airway obstructions that are accompanied by brief arousal and/or intermittent nocturnal oxygen desaturations. These events can lead to sleep fragmentation and chronic sleep deprivation with resultant daytime sleepiness and potential cognitive impairment.

Sleep deprivation studies in healthy volunteers have demonstrated an association between sleep loss and impaired cognitive function that primarily affects the neurocognitive domains of executive function, working memory, and other higher cognitive functions involved in decision making. Similar changes can occur in individuals with sleep apnea with sleep fragmentation and chronic sleep deprivation. These effects, however, are not uniformly seen in all, and some individuals may be affected more than others, thus suggesting individual vulnerability to the effects of sleep loss (Durmer and Dinges. *Semin Neurol* 2005; 25:117).

The distinction between daytime sleepiness and cognitive impairment is an important one. The assessment of daytime sleepiness includes subjective tests, like the Epworth sleepiness scale (ESS) and Stanford sleepiness scale (SSS), as well as objective tests like the multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT). The Epworth sleepiness scale is the most commonly used test in clinical practice.

Cognitive function, on the other hand, can be assessed with a battery of tests, each designed to measure deficits in one or more different domains of cognition. The Psychomotor Vigilance Task (PVT) measures attention and visual and audio motor skills (Dinges et al. *Sleep* 1997; 20:267); the Wisconsin Card Sorting Test (WCST) measures attention, working memory, and visual processing (Greeve et al. *Arch Clin Neuropsychol* 2005; 20:355); and the simple reaction time (SRT) measures alertness and vigilance. All these tests are designed for use in the research setting and are not easily adaptable for everyday clinical use.

Neuroimaging studies have been employed to assess the effects of OSA on brain structure and function. Magnetic resonance spectroscopy (MRS) studies suggest an atrophic hippocampus in patients with OSA as compared with control subjects; neurochemical evidence suggests white matter impairment in OSA, particularly in the region of the frontal lobes. Functional magnetic resonance imaging (f MRI) studies in OSA, as compared with control subjects, demonstrate lack of activation in the region of dorsolateral prefrontal cortex with increased activation in other parts of the cortex (Zimmerman et al. *J Clin Sleep Med* 2006; 2:461).

It is generally accepted that cognitive impairment is seen in patients with OSA; however, the association between OSA and cognitive impairment has not been consistently demonstrated in all studies. In the Sleep Heart Health Study of 1,700 subjects, cognitive scores were similar between patients with mild to moderate OSA and the control group. Additionally, cognitive functional scores did not correlate with respiratory disturbance index (RDI) (Boland et al. *J Sleep Res* 2002; 11: 265). Similarly, a study in 718 Japanese-American elderly men found no difference in cognitive function between patients with and without OSA (Foley et al. *Sleep* 2003; 26:596).

On the other hand, several studies have demonstrated a link between OSA and cognitive impairment. In a cross-sectional study of 100 patients with sleep apnea, a small but significant association was found between the severity of OSA as judged by nocturnal hypoxemia or RDI and various cognitive measures as compared with healthy control subjects. In contrast, sleepiness correlated negatively with vigilance (Adams et al. *Am J Respir Crit Care Med* 2001; 163:1626).

A metaanalytic review was conducted in 25 eligible studies that included 1,092 untreated OSA subjects and 899 healthy control subjects. This analysis showed that the effects of OSA on cognition were primarily found in the area of vigilance, executive function, and fine motor coordination. The effects on memory function were mixed, and intelligence and basic verbal and visual-perceptual abilities were unaffected. This suggests that clinicians should focus on assessment of changes in vigilance, executive function, and motor coordination (Beebe et al. *Sleep* 2003; 26:298).

Another cross-sectional study of 100 subjects with OSA found an association between nighttime hypoxemia

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Making a Difference Awards Dinner

Saturday, October 31, 2009
Manchester Grand Hyatt San Diego
One Market Place
San Diego, CA

The CHEST Foundation's 11th Annual Making a Difference Awards Dinner will begin a weeklong celebration of the ACCP's 75th anniversary. Festivities at this year's dinner include an ACCP historical display, a fun and interactive ACCP History Trivia Game, and recognition of ACCP members' pro bono service, with the presentation of the D. Robert McCaffree, MD, Master FCCP Humanitarian Awards for members' winning projects. Please join your ACCP colleagues and friends for the open reception from 7:00 PM to 7:45 PM, and dinner and ceremonies from 8:00 PM to 10:30 PM. Due to the close proximity of the Manchester Grand Hyatt San Diego hotel to other CHEST meeting hotels, transportation will not be provided this year. Sponsors, to date, are: AstraZeneca, LP; Boehringer Ingelheim Pharmaceuticals, Inc.; and Merck & Co., Inc.

THE CHEST FOUNDATION

Making a Difference Society members at the $1,000 level have two complimentary tickets available, upon request. Annual donors at the $500 level have one complimentary ticket available, upon request. Make reservations online at www.chestfoundation.org. Contact Teri Ruiz for more information at truiz@chestnet.org. ■

Continued from previous page

and visuoconstructional abilities, processing speed, and mental flexibility. Poor sleep quality was linked with decreased processing speed, while high levels of subjective sleepiness showed greater impairment of executive functioning. This suggests differential effects of sleep quality, hypoxemia, and subjective sleepiness on neurocognitive impairment in patients with sleep apnea (Naismith et al. *J Clin Exp Neuropsychol* 2004; 26:43).

The use of nasal CPAP in a diverse group of patients with OSA has demonstrated definite benefit in reducing subjective and objective sleepiness, with greater benefit noted in patients with more severe sleep apnea and sleepiness (Patel et al. *Arch Intern Med* 2003; 163:565). The duration of nightly use of CPAP in patients with OSA also correlates with improved outcomes. Differential effects of improvements in subjective sleepiness (ESS), objective sleepiness (MSLT) and daytime functioning were noted at 4, 6, and 7.5 h, respectively, of nightly use of CPAP. Additionally, individual susceptibility to the effects of sleep loss and interindividual differences in response to CPAP treatment was also recognized in this study (Weaver et al. *Sleep* 2007; 30:711). However, the benefits of CPAP use on cognition have not been well established.

The use of CPAP when compared with subtherapeutic CPAP showed improvement in cognitive function, but this was statistically not significant (Henke et al. *Am J Respir Crit Care Med* 2001; 163: 911). In another study of 16 patients with severe OSA, utilizing functional MRI, the use of CPAP for 8 weeks found no significant improvement in behavioral performance despite improvement in subjective sleepiness. This study also demonstrated reduced working memory speed and lack of prefrontal lobe activation, even after treatment with CPAP. This suggests that improvements in sleepiness with CPAP treatment may not necessarily lead to improved cognitive dysfunction (Thomas et al. *J Appl Physiol* 2005; 98: 2226).

On the positive side, the use of CPAP in 23 OSA patients for 15 days resulted in partial improvement in cognitive function as compared with baseline. Extending CPAP treatment up to 4 months did not result in additional benefit (Ferini-Strambi et al. *Brain Res Bull* 2003; 61:87). More recently, in a study of 56 patients with OSA, the group of patients that used CPAP for a median of 4 h or more showed better performance in working memory as compared with the group with less than 4 h (Felver-Gant et al. *J Clin Sleep Med* 2007; 3:589).

The use of a stimulant, such as modafinil, may be considered in patients with OSA who continue to have residual daytime sleepiness despite adequate compliance with CPAP, sufficient sleep, and good sleep hygiene. The use of modafinil, 400 mg/day, in one study showed a trend toward cognitive improvement in vigilance that was statistically not significant as compared with the control group (Kingshott et al. *Am J Respir Crit Care Med* 2001; 163: 918).

In patients with OSA who are being assessed for sleepiness and possible cognitive impairment, it is important to consider other diagnoses that may be contributing to these symptoms. Some of these include narcolepsy, shift-work sleep disorder (SWSD), poor sleep hygiene, insufficient sleep, and circadian rhythm disorders. The presence of any one or more of these conditions can have a significant impact on treatment outcomes and should be considered in the differential diagnosis when planning comprehensive treatment strategies.

In summary, OSA is a common disease that typically presents with symptoms of excessive sleepiness and potential cognitive impairment. Excessive sleepiness responds more readily to CPAP treatment than cognitive impairment. Neurostructural changes in the prefrontal cortex may explain cognitive dysfunction and resistance to CPAP treatment. Pharmacotherapy may be considered in cases of excessive sleepiness unresponsive to optimum CPAP therapy and may improve vigilance. ■

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Low Molecular Weight Heparins: Update on Follow-On "Generic" Compounds (Part 1)

Proceedings of a November 2008 ACCP Roundtable

This roundtable was supported by sanofi-aventis.

Should Clinical Trials Be Required for Approval of Follow-on ("Generic") Low-Molecular-Weight Heparins?

Clinicians and patients depend on low-molecular-weight heparins (LMWHs) for safe and effective venous thromboembolism (VTE) prophylaxis and treatment of established thromboembolic disease. The first LMWHs were approved for use in the early 1990s. Others have followed, as have pentasaccharide agents developed by synthesis of the active anticoagulant portion of the LMWH molecule.

LMWHs will soon begin to lose their patent protection as branded drugs. This will open the way to development of "generic" LMWHs. In the case of chemical drugs, this is a routine matter. In the case of LMWHs, it is not a routine matter. Characterization of the chemistry, pharmacokinetics, and pharmacodynamics of these drugs is complex. They are of biologic origin, and their pharmacologic (anticoagulant) activity is associated with only a portion of the molecular structure. Physiologic effects, if any, of the other segments of the LMWH molecule are not well understood. Each LMWH has a unique structure and efficacy/safety profile. The LMWHs are not therapeutically interchangeable, and it has been necessary to conduct clinical trials for each of these agents to prove efficacy and safety.

Those "generic" versions of branded LMWHs are already being developed and submitted to the US Food and Drug Administration (FDA) for approval. Many issues regarding efficacy, safety, cost, and regulatory oversight are raised by the expectation of "generic" LMWH development and submission for FDA approval. (This is not just expected, but has already happened. The manufacturer of Lovenox has filed suit as early as 2003 to prevent marketing of a so-called generic variety.) A harbinger of such issues is how such drugs are to be identified for regulatory purposes. In the U.S. States, the generic versions of LMWHs and certain other drugs of biologic origin are to be termed "follow-on" drugs to branded reference drugs. In the European Union, the European Medicines Agency has adopted the term "biosimilar" to identify such compounds.

THE OUTSTANDING QUESTION IS WHETHER LMWH FOLLOW-ON DRUGS WILL BE AS RELIABLY SAFE AND EFFECTIVE AS THEIR REFERENCE BRANDED DRUGS.

The outstanding question is whether LMWH follow-on drugs will be as reliably safe and effective as their reference branded drugs. How can efficacy and safety be ensured? The American College of Chest Physicians convened a roundtable discussion in November 2008 with an expert panel to review this question and discuss it with a panel of clinicians who use LMWHs in daily practice. This article (Part 1) summarizes the presentations of the meeting. Part II will appear in the August 2009 issue of *CHEST Physician* and will summarize the discussion and reactions of the roundtable participants. The meeting followed up a March 2008 roundtable on *Low-Molecular-Weight Heparins: Patient Safety and Clinical Data Requirements for Follow-on "Generic" Biologic Compounds,* which was published as a supplement to *CHEST Physician* in September 2008 and included a full list of references. To view the proceedings of the March 2008 Roundtable and the list of references, see the *CHEST Physician* September 2008 Supplement at www.chestnet.org/downloads/about/chestPhysician/Sept08supplement.pdf.

The Question

Should follow-on ("generic") versions of LMWH branded drugs be (1) approved following the current FDA process for approving generic chemical drugs; or (2) should each LMWH follow-on drug be required to begin the approval process with a New Drug Application and follow the new-drug approval process including clinical trials; or (3) should one or more clinical trials be required

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for each LMWH follow-on drug?

If clinical trials are required, what criteria should be established? Should trials be conducted for both prophylaxis and therapy? Should they be conducted for each prophylactic indication? What should clinical trials assess?

LMWH Defined

Low-molecular-weight heparins (LMWH) are derived from unfractionated heparin (UFH), and, therefore, are of biologic origin. UFH is most commonly derived from porcine intestine, and LMWH is derived from UFH. The LMWHs are smaller molecules than UFH with Factors Xa and IIa as antithrombotic targets.

Several LMWH drugs have been approved for clinical use in preventing VTE and preventing and treating thromboembolic disease. Each LMWH drug is derived from UFH by a unique, proprietary manufacturing process of chemical or enzymatic depolymerization. The manufacturing process differs for each LMWH molecule so that each LMWH is unique or only slightly different from other LMWH preparations.

A conundrum of UFH/LMWH pharmacodynamics is that only a fraction of the molecular structure has anticoagulant activity. The larger portion of the molecule may have other physiologic activities that are not completely understood but may, to some extent, be immunogenic and contribute to the development of heparin-induced thrombocytopenia (HIT).

Each LMWH manufacturing process affects the molecular structure differently. The effect of this is that the LMWHs have clinical profiles that render them therapeutically noninterchangeable. Noninterchangeability may be related to anticoagulant or to nonanticoagulant effects. An example of the latter is renal clearance in the presence of renal impairment—a matter of concern with a drug that is cleared primarily by renal excretion but an issue for which little data are available from clinical trials. Anticoagulant indications for LMWHs overlap but are not interchangeable for prophylaxis and treatment of thromboembolic disease.

Efficacy/Safety Issues

Therapeutic Interchange and Substitution

Many chemical drugs of the same class are interchangeable on the basis of therapeutic equivalence and adverse effects. The angiotensin-converting enzyme (ACE) inhibitors are an example: a hospital formulary need not have all of the available ACE inhibitors in stock because they are interchangeable. The same is *not* true of drugs of biologic origin, such as the LMWHs. They are not interchangeable, and drug substitution should not be permitted.

Generic Substitution

Substitution of a lower-cost generic chemical drug for a branded drug is generally accepted by physicians and patients. Physicians often specify the generic drug on a prescription or indicate that generic substitution is permitted. The chemistry of both the branded drug and generic drug is identical. The FDA approval process for generic chemical drugs bases approval of a generic on the principle that identical chemistry is equivalent to identical therapeutic effect and side effects. The LMWH drugs are known to differ in their chemistries.

Interchange/Substitution Potential for Adverse Event

Any time one drug is substituted for another, problems may arise. These may occur with chemical drugs where therapeutic equivalency is assumed but where efficacy and/or safety may not be equivalent in critically ill patients or in patients with multiple risk factors for adverse events. Pharmacokinetics, for example, may be substantially different in critically ill patients compared with those who are not as ill. In addition, milligram for milligram equivalence is often unclear.

Health-care Systems Issues

Issues regarding drugs including LMWHs at the level of the hospital or health-care system include the following:

- Interchangeability within drugs of the same class for the same indications;
- Cost advantage with therapeutic interchange;
- Equivalence of lower-cost generic drugs with their reference branded drugs;
- Adequate evidence to support each therapeutic indication;
- Assurance that a generic drug will have the same therapeutic effect as the branded drug, with no different side effects; and,
- Ability to accurately identify adverse events as drug side effects.

Watch for Part 2 of this article, summarizing the discussion and reactions of the Roundtable participants, in the August 2009 issue of CHEST Physician.

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This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, FCCP
Editor in Chief, CHEST

- **Idiopathic Pulmonary Fibrosis and Emphysema: Decreased Survival Associated With Severe Pulmonary Arterial Hypertension.** *By Dr. M. Mejia, et al.*
- **Association of the Metabolic Syndrome With Pulmonary Venous Hypertension.** *By Dr. I. M. Robbins, et al.*
- **Effects of Neuromuscular Electrical Stimulation of Muscles of Ambulation in Patients With Chronic Heart Failure or COPD: A Systematic Review of the English-Language Literature.** *By M. J. H. Sillen et al.*

Special Feature

- **The New Lung Cancer Staging System.** *By Dr. F. C. Detterbeck, FCCP, et al.*

Commentary

- **The Role of Conflict of Interest in Reporting of Scientific Information.** *By Dr. R. S. Irwin, FCCP*

Medical Writing Tip of the Month

- **Reporting "Basic Results" in ClinicalTrials.gov.** *By Dr. T. Tse, et al.*

www.chestjournal.org

Breaking News: CHEST*'s Impact Factor has risen to 5.154 and its ranking went up from 6th to 4th. Watch for more details in the next issue of* CHEST Physician.

Five Student Teams Tackle Global Tobacco Control

The CHEST Foundation and the Kellogg Graduate School of Management 2nd Annual Case Competition

BY DR. JOHN C. ALEXANDER, JR., FCCP, PRESIDENT, THE CHEST FOUNDATION; AND MARILYN LEDERER, EXECUTIVE DIRECTOR, THE CHEST FOUNDATION

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From left to right: Professor David Dranove; Siddhartha Vaidyanathan; and Dr. John C. Alexander, Jr., FCCP; along with members of the winning team: Susan Bortz '10, Wendy Yip, Zsolt Abonyi '09, and Scott Shurtliff '09.

Background on the Case Competition

In 2007, The CHEST Foundation, the philanthropic arm of the American College of Chest Physicians (ACCP), and the Social Enterprise at Kellogg (SEEK) Program initiated a case competition designed to respond to public health issues through the creation of sustainable business solutions.

Taking as its impetus an asthma epidemic estimated to affect 630,000 Chicagoans each year, the competition challenged five student teams from Kellogg, the Feinberg School of Medicine, and the University of Chicago to devise entrepreneurial solutions that would alleviate asthma, including those undiagnosed or untreated cases often found among the city's poorer communities.

The case competition organization process was very robust. It featured securing mentors—medical, community, and research experts—for each team. An illustrious group of judges from the business, government, and philanthropic sectors was recruited to provide guidance for the student teams, as well as interact with them about future career goals. A highlight for the students was the involvement of former US Surgeon General Dr. C. Everett Koop, FCCP(Hon), who served as both a judge and the keynote speaker for the culminating dinner. Information about the competition was disseminated following the selection of the two winning teams.

Two teams—Open Mic.Health and Home Clean Home—advanced to the contest's final round. The Home Clean Home team impressed judges with a business plan designed to attack key asthma triggers in the home. Through an effort to educate people about these triggers, and also help them reduce exposure in the home, the team developed a hybrid for-profit and nonprofit business model. The for-profit arm would raise revenue through a residential cleaning service that specialized in eliminating indoor asthma triggers, while the nonprofit organization would use these funds to drive a community-based "train the trainers" asthma education program.

The runner-up, Open Mic.Health, developed a DVD-driven media tool designed to engage and educate patients about asthma. The device, which featured YouTube-like videos created by community members, would be placed in clinics to reach the target audience. Visitors to the clinic would be likely to share with friends and neighbors the insights gleaned from the educational programming, thereby increasing knowledge about asthma in the community and helping change attitudes about the disease and its management.

Postcompetition, both teams are pursuing venture capital for the implementation of their projects. Both teams had an opportunity to present their projects to 200 members of asthma coalitions at a symposium that ACCP hosted in Philadelphia, PA, as part of its annual scientific meeting. As an outgrowth of that meeting, the teams were able to pursue funding leads. In addition, Home Clean Home has been working on a corporate structure and pursuing intellectual property rights. Open Mic.Health team members are pilot testing its program concept in two hospitals in Chicago.

The 2009 Case Competition

Building on the success of the first competition, The CHEST Foundation and the Carol and Larry Levy Social Entrepreneurship Lab at Kellogg, led by Professor Timothy Feddersen, focused the second case competition on global tobacco control in the developing world.

CHEST Foundation Trustees Mr. Robert Barnett III and Dr. D. Robert McCaffree, Master FCCP, participated in the competition as judges for the final case presentations. Dr. John C. Alexander, Jr., FCCP, and Dr. Allen I. Goldberg, Master FCCP, served as mentors to teams developing a case. Dr. Kalpalatha K. Guntupalli, FCCP, ACCP President-Elect, was a guest lecturer in Professor Joel Shalowitz's class and served as a resource. ACCP member Dr. Janet Han served as a resource based in China. Noted tobacco control expert Dr. Judith MacKay also served as a resource to the students. Professor David Dranove, a noted health-care expert, rounded out the team from Kellogg. Dean Dipak C. Jain continued to support the competition and lend suggestions on how to implement the winning cases in India and China.

Thirteen teams participated in the competition. The teams consisted of at least one full-time MBA student from Kellogg and graduate students representing other disciplines, including journalism and engineering. Eight teams submitted cases dealing with solutions to tobacco control in China and India. A team of judges reviewed the eight cases and decided upon two teams to present to a distinguished panel of judges on May 12, 2009. The two teams are Team Pulmo and Novo Aer. The panel of judges, in addition to CHEST Foundation Trustees, included Professor David Dranove, who served as Chair of the judging panel; Kenneth D. Hooten, a partner in Concentric Equity Partners; Gary MacDougal, an entrepreneur and author of Make a Difference; William Parra, MS, Chief Operating Officer, CDC, Bloomberg Initiative To Reduce Tobacco Use; and Michael Sachs, Chairman and CEO of Sg2, a health-care data provider.

The Winning Teams

Siddhartha Vaidyanathan is having trouble quitting smoking. In his home country of India, cigarettes are available for less than a nickel, and there are few health warnings about the risks of smoking.

As a result, "You think, oh, it's just one cigarette," said Vaidyanathan, a graduate student at Northwestern's Medill School of Journalism.

Drawing upon his personal experience, Vaidyanathan partnered with three Kellogg students and one student from the McCormick School of Engineering to develop a plan for combating smoking in the Third World. Dubbed "Team Pulmo," the students won first prize in the final round of the case competition.

Team Pulmo produced a tobacco control program that would work through India's national railway system. The system provides health insurance to employees, who often work there for a lifetime.

"The program would cost an estimated $60,000 per 1,000 quitters but would save $160,000 in health costs and, ultimately, thousands of lives," said Kellogg student Zsolt Abonyi '09, who brought the team together. Other team members included Scott Shurtliff '09, Susan Bortz '10, and McCormick student Wendy Yip.

"We wanted to do something with prevention. But we just couldn't find a way to turn it into a business idea," Abonyi said. Cessation seemed to provide a stronger entrepreneurial hook, he added, and the railway system seemed to be the right starting point. Other nationalized industries, such as oil and steel, could come next. For its winning plan, Team Pulmo received a $15,000 prize.

The second-place team, Novo Aer, offered a plan to reduce smoking in China and focused on pregnant women and their husbands. The team—which included Kellogg doctoral student Bingxiao Wu; McCormick students Lide Zhang, Jingsi Xie, Gali Baler, and Jieyi Long; and Medill student Minfei Chen—received a $5,000 prize.

David Dranove, the Walter J. McNerney Professor of Health Industry Management and a final-round judge, said the judging panel had a difficult time choosing the winner. The panel admired Novo Aer's focus on a key target segment with long-term importance, as well as Pulmo's breadth and "potential to hit the ground running," Dranove said.

"These were both terrific proposals," he added.

Kellogg Dean Dipak Jain noted that the CHEST competition furthers the Kellogg School's goal of educating leaders who make lasting and significant contributions to the world.

"The focus on this school cannot just be on advancing shareholder value," Jain said. "We should be meeting problems with a social cost. Students should contribute to society. They need to go beyond their personal success. Business schools should go beyond business. We want to produce leaders who are going to make an impact of significance."

Dr. Alexander and the Board of Trustees of The CHEST Foundation believe that this unique partnership between a medical society foundation and a business school can serve as a model for other partnerships to form around the country.

For more information about the Kellogg/CHEST Foundation collaboration, visit the Foundation's Web site at www.chestfoundation.org. ■

Pulmonary Conference in Turkey Is a Success

The interactive conference was attended by almost 200 pulmonologists from all regions of Turkey.

BY DR. SUHAIL RAOOF, FCCP

The potential to recruit international members is limitless. For example, there are approximately 50,000 thoracic physicians in China alone. Thus, when I received an invitation from Dr. Günseli Kilinç, FCCP, Past Chair of the International Regents, to present at the annual Pulmonary Conference (organized by Cerrahpasa Istanbul University), I immediately consented. Dr. David Naidich, FCCP, and I offered to present a full day course in Chest Radiology for the Pulmonologist.

This interactive conference, attended by almost 200 pulmonologists from all regions of Turkey, was held in Istanbul on March 13, 2009.

Interspersed between the lectures, two separate presentations discussing the benefits of ACCP's e-membership, the educational value of attending annual meetings, and the utility of practice guidelines for the busy practitioner were delivered.

At a separate ACCP booth, flyers printed in Turkish describing CHEST 2009-2011, educational calendars, product catalogs, and description of The CHEST Foundation 2009 Awards Program were distributed to the participants during registration. In particular, the local organizers of the course, Dr. Sema Umut and Dr. Kilinç spoke several times about the ACCP.

UTILIZE EVERY OPPORTUNITY TO PARTICIPATE IN MEDICAL CONFERENCES, ESPECIALLY IN REGIONS OF GROWTH.

The participants were encouraged to send their cases to the CHEST 2009 Clinical Case Puzzlers forum. This would allow them to become part of the faculty of the annual meeting and may also facilitate in the procurement of a visa to come to the United States. Finally, Dr. Can Ozturk, FCCP, ACCP Regent from Turkey, compiled a list of 110 participating physicians who provided their e-mail addresses.

ACCP will correspond with them on a regular basis.

The experiences we gained from this meeting were invaluable. These include the following:

1. Utilize every opportunity to participate in medical conferences, especially in the five regions of potential international growth (China, Brazil, Mediterranean Belt, Indian subcontinent, and Middle East). Members of the College who are from these regions should be encouraged to garner support for such conferences.

2. The international Regents of the College should be encouraged to organize or facilitate in the organization of such conferences. Participants relate to their compatriots more than to visiting guests. Thus, the international Regents should be requested to speak about the College at these meetings.

3. If possible, staff members from the College should go to some of these conferences. They should try to enroll participants as e-members and collect contact information of attendees.

4. It is important that the efforts of the College be directed toward the local physicians, convincing them of the value of attending the CHEST meeting.

5. Active members of the College, such as Drs. Kilinç and Ozturk, can mobilize opinion amongst their peers in their areas of influence, and their efforts for the College are greatly appreciated.

These members should be encouraged to continue on the various committees/networks/international committees of the College, even after they have completed their terms.

Both Dr. Naidich and I enjoyed the educational experience and received as much from the audience as we gave to them. ■

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