VOL. 8 • NO. 11 • NOVEMBER 2013

CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

PATRICE WENDLING/IMNG MEDICAL MEDIA

At CHEST 2013, Dr. Srihari Veeraraghavan described myths surrounding hookah smoking and what physicians can do in the face of its growing popularity. Visit chestphysician.org for the video. Story on page 6.

Procalcitonin proves useful for taming antibiotic resistance

Biomarker can help tailor CAP therapy.

BY WHITNEY McKNIGHT
IMNG Medical News

Despite some controversy over its efficacy, the biomarker procalcitonin does have a legitimate role to play in helping determine the duration of antibiotic therapy in community-acquired infections, according to a presenter at the annual meeting of the American College of Chest Physicians.

Procalcitonin is a biomarker of inflammation that, like C-reactive protein, is seen at higher levels in patients with bacterial infections. How statistically significant a difference it will make in curbing antibiotic use in a hospital and helping to stratify risk "depends on what your baseline [of antibiotic use] is," said Dr. Richard Wunderink, FCCP, of Northwestern University, Chicago.

Dr. Wunderink cited two meta-analyses, including a Cochrane Database systematic review of patient-level data, that showed "highly statistically significant differences" in the duration of antibiotic therapy when procalcitonin was measured. In the study, 898 out of 999 patients with community-acquired pneumonia were given antibiotics and had their procalcitonin levels mea-

See **Procalcitonin** • *page 2*

CT says it all: Quit smoking, cut heart risk

BY NASEEM S. MILLER
IMNG Medical News

AMSTERDAM – A prospective analysis of CT angiography of more than 13,000 patients bears some good news and some bad news for patients who have quit smoking, and yet another warning for those who continue to smoke.

Current smokers had nearly a twofold increase in risk of major adverse cardiac events (MACE), compared with those who had quit and those who had never smoked. However, they – along with past smokers – still had a significantly higher prevalence, extent, and severity of coronary artery disease (CAD), compared with individuals who never smoked.

The unpublished study, which is from the CONFIRM Registry, was presented by Dr. James K. Min of Weill Cornell Medical College, New York, and New York-Presbyterian Hospital, at the annual congress of the European Society of Cardiology.

Researchers evaluated the extent and severity of CAD, as well as the risk of MACE, for active smokers, past

See **Smoking** • *page 18*

Know your mid-level provider risk

BY ALICIA GALLEGOS
IMNG Medical News

A patient called his doctors' office complaining of postsurgical pain. The practice's physician assistant recommended increased pain medication, but failed to alert the on-call physician regarding the contact. The patient later sued the PA and the supervising physician after he was diagnosed with compartment syndrome.

But which physician was named in the lawsuit? Not the surgeon. Not the on-call physician. An orthopedist who was out of town during the incident was named as defendant.

The out-of-town orthopedist "was the supervising physician on record," explained Dr. Alan Lembitz, a

See **Practice** • *page 25*

INSIDE

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Flu vaccine linked to lower cardiovascular risk

BY MARY ANN MOON
IMNG Medical News

Use of the flu vaccine was consistently associated with a lower risk of adverse cardiovascular events in a meta-analysis of the worldwide medical literature, according to a report in JAMA.

The risk reduction was greatest among people at highest cardiovascular risk, said Dr. Jacob A. Udell of Women's College Hospital, University of Toronto, and his associates. The finding that a simple, annual injection may prevent scores of cardiovascular deaths, hospitalizations, MIs, strokes, and cases of heart failure, urgent coronary revascularization, and unstable angina also is of "considerable clinical and health policy importance, given the profound underuse of vaccination among the general public and the potential impact this preventive strategy may have on high-risk patients," the investigators said (JAMA 2013;310:1711-20).

The researchers performed a meta-analysis of 12 randomized clinical trials in which influenza vaccination was compared against either placebo or standard care, and in which cardiovascular outcomes during the year following vaccination were reported.

Five of the 12 trials were considered to be of high quality and the remainder were of low or uncertain quality. The meta-analysis included 6,469 participants (mean age: 67 years) who had varying degrees of CV risk.

The overall rate of the primary end point, a composite of all major adverse cardiovascular events, was 2.9% among recipients of the influenza vaccine (95 of 3,238 patients). This was significantly lower than the 4.7% rate (151 of 3,231 patients) among controls. The number needed to treat to prevent a single major adverse CV event was 58.

In a subgroup analysis involving patients with coronary artery disease, influenza vaccination was even more protective. For example, the rate of major adverse CV events was 10.25% among vaccinated patients with a history of recent acute coronary syndrome, vs. 23.1% among controls. The number needed to treat to prevent one CV event in this subset was 8.

The Canadian Institutes for Health Research and the Canadian Foundation for Women's Health supported the study. Dr. Udell reported no financial conflicts; his associates reported industry ties.

IN THIS ISSUE

Taming antibiotic resistance

Procalcitonin *from page 1*

sured; the control group (n = 1,028) was also given antibiotics but did not have procalcitonin levels measured (Cochrane Database Syst. Rev. 2012 Sept. 12;9:CD007498 [doi: 10.1002/14651858.CD007498.pub2]).

The group measured for elevated procalcitonin as a way of determining the course of antibiotic therapy had an average exposure to antibiotics of 6 days, compared with an average exposure of 10 days in the control group.

"It does shorten the course of therapy," said Dr. Wunderink. However, he added, there has been an effort over the past decade in the United States to reduce overall antibiotic therapy as a way to combat antibacterial resistance, so the difference is less than it might be in European countries.

Also important to consider, said Dr. Wunderink, is the ongoing inflammatory response in some patients. "There is a point at which the cytokines response starts to drive the procalcitonin more than the bacteria do … so at some point, it switches from being a marker of uncontrolled bacterial infection to a marker of uncontrolled inflammation," Dr. Wunderink said.

Another issue, he said, is that physicians "need to be comfortable withholding antibiotics in patients with community-acquired pneumonia," since some patients will not have notably elevated procalcitonin levels, regardless of infection. "It may be that procalcitonin can tell you enough about etiology that you can treat for atypicals, but it's still to be proven," said Dr. Wunderink.

When there is diagnostic uncertainty, as in a patient who has underlying heart failure and symptoms that may or may not be pneumonia, Dr. Wunderink said that short-course antibiotic therapy, such as 5-7 days, is appropriate.

"But I am not sure that procalcitonin actually decreases that duration of therapy," he said. "It may support the idea of narrower-spectrum atypical antibiotic therapy, but the greatest benefit is in discontinuing the therapy in patients with diagnostic uncertainty."

Dr. Wunderink disclosed that he has received investigator grants from bioMérieux.

Scan the code to watch a video interview at chestphysician.org.

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, a Frontline Medical Communications Inc. company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Please see Brief Summary of Prescribing Information, including ***BOXED WARNING*** *for embryo-fetal toxicity, on adjacent pages.*

ACTELION

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macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see *Warnings and Precautions (OPSUMIT REMS Program)*].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity),* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (Females and Males of Reproductive Potential)*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions (Clinical Trial Experience)*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242)	Placebo (N=249)
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see *Clinical Pharmacology (Pharmacokinetics)*].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

OPSUMIT® (macitentan)

Drug Interactions

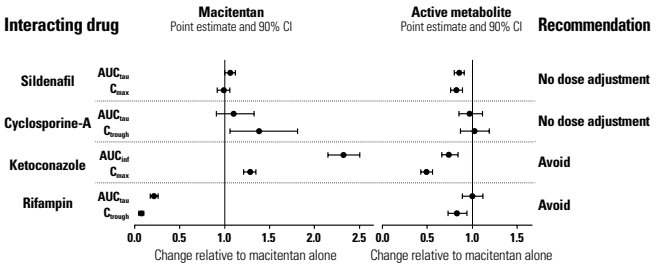
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see *Drug Interactions (Strong CYP3A4 Inhibitors)*].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
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South San Francisco, CA 94080, USA

ACT20131018

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.

ACTELION

With hookah bars, new smoking trend wafts in

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Despite a national downturn in cigarette smoking, a growing number of young Americans are turning to hookah bars to smoke tobacco, a study has shown.

The trend is driven by the social nature of hookah bars and myths about the safety of smoking hookah, also called shisha, narghile, hubble-bubble, and goza, Dr. Srihari Veeraraghavan reported at the annual meeting of the American College of Chest Physicians.

For the first time, a large study showed hookah smoking had eclipsed cigarette smoking for both ever use (46.4% vs. 42.1%) and past-year use (28.4% vs. 19.6%) among 1,203 University of Florida students (BMC Public Health 2013;13:302).

More than a third of current cigarette smokers used hookah, but equally worrisome, 29% of current hookah smokers reported never having smoked a cigarette.

"We've made impressive strides in the last 40-50 years by reducing smoking in this country," he said in an interview. "And the concern is that students use hookah in their universities, and when they get out in their real life, they're going to go back to cigarettes because it's as addictive, if not more [so], than cigarettes."

Patrice Wendling/IMNG Medical Media

"In one hookah session, smokers may inhale the equivalent of 100 cigarettes," Dr. Srihari Veeraraghavan of Emory University reported.

Myths surrounding hookah/shisha smoking are that it is less addictive, less harmful, and contains less nicotine than conventional cigarettes, said Dr. Veeraraghavan of Emory University in Atlanta.

He highlighted a widely publicized 1997 New York Times article quoting one hookah smoker as saying cigarettes are for "nervous," "competitive" people, but that narghile smoking "teaches you patience and tolerance, and gives you an appreciation of good company."

Some smokers also believe the water in the pipe filters out toxins and that adding molasses or fruit to flavor the tobacco imparts a health benefit.

"Hookah smoking leads to cigarette smoking, and cigarette smokers planning to quit take up hookah thinking that it's better," Dr. Veeraraghavan said.

Though data in humans are limited, a study found similar peak nicotine concentrations after smoking one cigarette vs. smoking a hookah for a maximum of 45 minutes, but that hookah smoking was associated with greater carbon monoxide levels and 1.7 times the exposure to nicotine (Am. J. Prev. Med. 2009;37:518-23).

A typical hookah session lasts about an hour and may involve 200 puffs. Thus, "in one hookah session, smokers may inhale the equivalent of 100 cigarettes," he said.

This is particularly concerning in light of the recent Canadian Youth Smoking Survey showing that hookah use increased 6% from 2006 through 2010 among kids, grades 9 through 12 (Prev. Chronic Dis. 2013 May 9;10E73). Once again, current cigarette smokers were more likely to use hookahs, but marijuana and alcohol use also predicted hookah use.

Dr. Veeraraghavan suggested that alternative forms of smoking such as hookahs, e-cigarettes, and marijuana should be included in all smoking surveys and that additional research is needed to elucidate the effects on pulmonary function and overall health. Better regulatory mechanisms are also needed, as laws are unclear about hookah smoking in restaurants and other public venues.

Finally, physicians should begin asking patients of all ages about their hookah use since younger adult smokers are less likely to visit the office, but parents will go home and talk to their kids – young or older – about the health risks posed by hookah smoking, he said.

For physicians unaware or uncertain about the emerging popularity of hookah smoking, Dr. Veeraraghavan concluded by showing a slide listing no fewer than 50 hookah bars all in the Chicago area, many not far from CHEST 2013.

Dr. Veeraraghavan reported having no relevant financial disclosures.

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Community docs can tackle hypersensitivity pneumonitis

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – Community physicians can feel comfortable diagnosing and treating hypersensitivity pneumonitis, according to a panel of pulmonary experts.

"It's not always necessary to refer patients to academic centers where the specialists are," said Dr. Karen Patterson, who moderated the panel at the annual meeting of the American College of Chest Physicians.

"That's not always easy for patients, since those centers are often far away from where they live."

The key to accurate diagnosis is taking a thorough clinical history. Sometimes, that means asking family members the same questions asked of the patient, since not everyone recalls the same information, said Dr. Patterson of the Penn Lung Center at the University of Pennsylvania, Philadelphia.

Hypersensitivity pneumonitis is antigen driven, and lymphocytosis is a hallmark, Dr. Patterson said.

The allergens associated with the condition typically come from birds, but apparently not from chickens, according to panelist Dr. Kevin Brown of National Jewish Health in Denver.

Other antigens to ask about include bird products such as down bedding as well as mold and various industrial antigens.

Pulmonary and systemic symptoms can vary in intensity with each patient, Dr. Patterson said. When classifying the disease, it is important to distinguish between fibrotic and nonfibrotic disease. "Fibrotic disease is difficult to diagnose, and is associated with [poorer] outcomes," she said.

Patients present with dyspnea, hypoxemia, and cough as well as systemic manifestations such as fever, myalgia, weight loss, and fatigue.

CT findings are usually more thorough than radiography, said Dr. Patterson, who added that biopsy is necessary on rare occasions.

"Be sure to get all three lobes of the affected lung"; otherwise there will not be enough information to accurately assess the disease, she added.

Patrice Wendling and Terry Rudd/IMNG Medical Media

Dr. Karen Patterson gives specific tips on taking an accurate occupational and exposure history, what to request in a biopsy, treatment options and more. Watch a video at chestphysician.org.

"Antigen avoidance is the best management of hypersensitivity pneumonitis," according to Dr. Mary Strek of the University of Chicago. "Patients do best when you've accurately identified the antigen, and then removed it, although this is not always easy."

Treatment includes corticosteroids, and in some cases, immunosuppressive therapies.

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Expert: Mobility helps thwart ICU-acquired weakness

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – A culture change that allows mechanically ventilated critically ill patients to have more mobility correlates with better outcomes.

"Physicians should consider how respiratory therapies for critically ill patients in the intensive care unit impact patient mobility," Dr. Gregory A. Schmidt, FCCP, said at the annual meeting of the American College of Chest Physicians. Dr. Schmidt was the moderator of a plenary session titled "Liberating the Critically Ill."

"The past 30 years have shown us that many things that we thought were helpful and protective and nurturing of our patients in fact were not," said Dr. Schmidt, professor of internal medicine – pulmonary, critical care, and occupational medicine at the University of Iowa, Iowa City.

Physicians should not keep patients so deeply sedated that it is impossible for them to participate in moving their muscles. 'You need to animate your patients.'

Current therapies result in greater levels of diaphragmatic dysfunction and peripheral muscle weakness, two primary causes of longer lengths of stay and overall worse outcomes in critically ill ICU patients, according to Dr. Schmidt.

Several studies he cited indicate that there is a correlation between the length of time a patient is mechanically ventilated, and at what level, and prognosis.

Although there are a number of aspects of diaphragmatic dysfunction attributable to how the body responds to critical illness regardless of therapies used, there are even more factors directly related to care protocols for the critically ill that can result in ICU-acquired weakness, said Dr. Schmidt.

"Ventilation and critical illness cause impaired force generation and atrophy, and this happens acutely and progressively," said Dr. Schmidt. "Diaphragm dysfunction is associated with impeding liberation from the ventilator, and it predicts death."

The dysfunction can be ameliorated with active contraction, said Dr. Schmidt, who presented data indicating that the more independent a patient's respiration, the less atrophy the patient experiences.

Because the phrenic nerve impulse is not implicated but peripheral muscle weakness is, Dr. Schmidt suggested that engaging these muscles improves outcomes, including shortening time to extubation and length of stay.

"Similar to the diaphragm, contraction lessens dysfunction," said Dr. Schmidt, who cited data on how electrical stimulation of the muscles preserved muscle mass, as well as how early physical therapy and occupational therapy increased independent function of patients at discharge.

Continued on page 9

Details of dyspnea should drive choice of therapy

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – Taking a personalized approach to treating dyspnea will result in better outcomes, and will make choosing between surgical and the increasing number of nonsurgical techniques an easier process, according to Dr. Frank Sciurba, a presenter at the annual meeting of the American College of Chest Physicians.

In a talk that reviewed current and trial surgical and bronchoscopic treatments of dyspnea in chronic obstructive pulmonary disease, Dr. Sciurba said, "Just treating diseases that are now naively classified as COPD or [interstitial lung disease] is not enough. We can instead look at variations within those diseases that may or may not be responsive to different therapies."

For example, because data from the VENT (Impact of Heterogeneity on Outcome Following Endobronchial Valves) trial showed that fissure integrity (collateral tracts) significantly influenced target and adjacent lobe volume changes, Dr. Sciurba said that medical device manufacturers have begun to develop technologies that are more specific to the patient.

Straight nitinol coils (PneumRx), which are placed bronchoscopically, are implanted in stages, and according to collateral tracts. "The concept is to target the most affected areas of the lung, allowing regional expansion of the least affected lung. It's not dependent on just lobar re-expansion," said Dr. Sciurba, director of the emphysema research center at the University of Pittsburgh Medical Center.

Straight nitinol coils are planted 'to target the most affected areas of the lung, allowing regional expansion of the least affected lung. It's not dependent on just lobar re-expansion.'

Pilot trial data for this technique published in CHEST earlier this year showed that patients ($n = 56$) had a 17.5% improvement in forced expiratory volume in 1 second (FEV_1), a greater than 10% drop in residual volume, and clinically meaningful improvements in 6-minute walk distances at more than a 28% improvement from baseline; in addition, 73% had a greater than 25-meter improvement at 6 months post treatment.

The hydrogel foam, AeriSeal (Aeris) is another bronchoscopic technique currently undergoing a small (n = 20) pilot trial. After fibrinogen was eliminated from the sealant, this polymeric lung volume reduction technology was cleared by the Food and Drug Administration for testing in humans.

The sealant is administered into specific subsegments of the lungs, where the foam adheres to the surrounding tissues; air and water in the foam are reabsorbed when collapse occurs, with durable absorption in atelectasis.

Continued on following page

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The results will soon be published, although Dr. Sciurba said that at this point, "the mechanical benefits seem to exceed the symptomatic benefits," but that a trial in a larger population would produce more definitive results.

Other factors to consider include "understanding the pulmonary physiologic interaction in lung volume reduction, and how that translates downstream, and the importance of linking the mechanical intervention with pulmonary rehab.

Expanding the 'tool chest'

In determining whether bronchoscopic solutions can achieve the same benefits of surgical ones, while also minimizing adverse effects, Dr. Sciurba said, the FDA is beginning to take a more personalized view when approving trials, which he hopes will increase the "tool chest" available to physicians.

Clinical trials going forward may need to consider selection criteria such as interlobar collaterals, regional emphysema heterogeneity, and the degree of hyperinflation, as well as the most relevant outcomes when determining adverse events, Dr. Sciurba said.

Whether therapies are reversible also will be relevant in the future, and will have an effect on future criteria for lung volume reduction surgery and transplant candidacy.

"If we actually look in a little more detail and start to classify these patients both on physiologic and clinical patterns, and as we evolve, on genetic patterns and molecular patterns, we will isolate groups of patients who are home run responders from those in whom certain therapies may not be cost effective."

Dr. Sciurba disclosed that he has received support from AstraZeneca, GlaxoSmithKline, Pfizer, and other companies, as well as a grant monies from the National Institutes of Health and the University of Pittsburgh.

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Continued from page 7

The key to improving outcomes, said Dr. Schmidt, is to change our current culture and "liberate our patients." It is a cultural change that requires changing the view that current therapies are always "nurturing and helpful."

It also means physicians should not keep patients so deeply sedated that it is impossible for them to participate in moving their muscles. "You need to animate your patients," said Dr. Schmidt, adding that it's important to avoid keeping patients completely passive and to set ventilators accordingly.

Patients should be seen as active participants in their recovery and supported with a culture that empowers respiration therapists to do their job.

"You need to find champions with an attitude that this is absolutely essential to do," he advised.

Noting that liberating patients can result in setbacks, Dr. Schmidt said there are many cultural barriers to this move, including "blame and criticisms and 'you shouldn't have done this.' "

Without a champion for this mindset and the dedicated resources for it, "this will fail," he concluded.

Dr. Schmidt reported having no conflicts of interest.

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High-dose flu vaccine beats regular dose in seniors

BY MICHELE G. SULLIVAN
IMNG Medical News

A high-dose influenza vaccine for elderly patients provided 24% more protection against the disease than did the standard-dose vaccine in a randomized postlicensure study.

Switching seniors to the higher-dose formulation could prevent as many as five cases of flu per 1,000 people aged 65 years and older each year, Dr. David Greenberg said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP).

Fluzone High-Dose vaccine (Sanofi Pasteur) is a trivalent, inactivated, split-virus influenza vaccine that contains 16 mcg of hemagglutinin per dose of each included strain (aH1N1, B, and aH3N2). This is four times

more antigen than in the standard Fluzone (15 mcg/dose). The high-dose formulation was developed to induce better antibody responses in adults aged 65 years or older.

"Older adults represent about 13% of the U.S. population, but account for 63% of the hospitalizations for influenza-like illness, and more than 80% of influenza-related deaths," Dr. Greenberg said.

The Food and Drug Administration approved the high-dose vaccine on its accelerated approval pathway in late 2009. A prelicensure phase III study was conducted in 3,600 elderly adults. The high-dose vaccine stimulated significantly more protective antibody responses against all three strains than did the corresponding regular-dose vaccine; the high-dose vaccine met the FDA superiority requirement for both A strains. The response was stable across age, sex, and the presence of comorbid conditions.

"Last year, however, only an estimated 19% of vaccinated seniors got the high-dose vaccine, largely because policy groups and providers have been waiting for the results of this postlicensure trial," Dr. Greenberg said. He reported these results at the meeting in Atlanta.

The postlicensure study comprised more than 32,000 persons aged 65 years and older. They were enrolled at 126 sites in the United States and Canada. The trial spanned two flu seasons (2011-2012 and 2012-2013). Participants were randomized to either one dose of the high concentration vaccine or one dose of the regular vaccine.

Over both seasons, the high-dose vaccine was an average of 24% more effective in preventing influenza-like illness from types A and B combined than the regular-dose vaccine.

The high-dose vaccine stimulated significantly more protective antibody responses against all three strains than did the corresponding regular-dose vaccine.

That benefit was more pronounced in older subjects, Dr. Greenberg said. Among those aged 65-74 years, the relative efficacy was almost 20%; among those aged 75 years and older, the relative efficacy was 32%. The benefit held whether the illness was defined as lab confirmed (24%) or culture confirmed (23%).

The high-dose vaccine significantly reduced the risk of pneumonia associated with laboratory-confirmed influenza by up to 53%. The risk of cardiorespiratory illness within 30 days of flu onset dropped by almost 30%, while the risk of flu-related 30-day hospital admissions fell by about 40%.

Safety outcomes were good when compared with the regular-dose vaccine, Dr. Greenberg said. Serious adverse events occurred in 8% of the high dose group and 9% of the regular-dose group.

Sanofi Pasteur will continue to analyze the study data, Dr. Greenberg said. The company intends to submit a Clinical Study Report to FDA's Center for Biologics Evaluation and Research by the first quarter of next year. Sanofi will also seek a revision of the prescribing information supporting the vaccine's clinical superiority to the regular-dose vaccine.

Dr. Greenberg is the senior director of U.S. scientific and medical affairs for Sanofi Pasteur.

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Esmolol stabilizes heart rate in septic shock

BY JENNIE SMITH
IMNG Medical News

The short-acting, intravenous beta-blocker esmolol has been shown to reduce and stabilize heart rates without adverse effects in patients with severe septic shock, a new phase II study has found.

In an open-label study that randomized 154 patients with septic shock and a heart rate of 95 or higher to standard care or titrated esmolol, the beta-blocker was associated with successful reductions in heart rate to between 80 and 94 beats per minute over a 96-hour period: a median of –28 BPM for the esmolol group compared with –6 for controls (*P* less than .001).

For their research, Dr. Andrea Morelli of the University of Rome La Sapienza and colleagues recruited from the hospital's intensive care unit patients with septic shock and a heart rate of 95 BPM or above (JAMA 2013;310:1683-91).

Patients with lower heart rates or with previous beta-blocker use were excluded. Subjects in both groups required norepinephrine to maintain a mean arterial pressure of 65 mm Hg or higher. The primary outcome measure was heart rate stabilization at between 80 and 94 BPM.

The esmolol group, which received a median continuous infusion of 100 mg/hr during the treatment period, also saw improved stroke work index and left ventricular stroke work, which investigators suspected was a result of improved diastolic filling. Esmolol treatment was associated with maintenance of mean arterial pressure and reduced need for norepinephrine. It was not associated with higher hepatic, renal, or myocardial injury compared with controls. Importantly, mortality at 28 days was considerably and significantly lower in the esmolol group than in controls: 49.4% vs. 80.5%. Each group comprised 77 patients.

In an editorial, Dr. Michael R. Pinsky of the department of critical care at the University of Pittsburgh called the findings "consistent with selective blockage of beta-adrenergic hyperactivity causing improved myocardial performance and decreased metabolic demand without compromising peripheral vascular function." Nonetheless, he cautioned clinicians against applying these results to all patients in septic shock (JAMA 2013;310:1677-8). "The reasons for this caution involve the limitations of this study and limitations in the current understanding of how beta-blocker therapy can cause such effects."

The esmolol group, which received a median continuous infusion of 100 mg/hr during treatment, also saw improved stroke work index and left ventricular stroke work.

Dr. Morelli and colleagues acknowledged several limitations of their study. One was its single-center, open-label design. (As Dr. Pinsky noted in his editorial, a blinded study would be almost impossible to carry out because heart rate titration would be difficult to mask.) The results should be replicated in a larger, multicenter trial, the researchers wrote. They noted that they had used "an arbitrary predefined heart rate threshold rather than an individualized approach titrated to specific myocardial characteristics or other biomarkers." Finally, the researchers allowed that the unexpectedly large mortality difference seen in the study could have been the result of confounding.

The study was funded by the University of Rome La Sapienza. Dr. Morelli disclosed honoraria from Baxter, the manufacturer of esmolol. A coauthor, Dr. Mervyn Singer, reported ties with Baxter. Dr. Pinsky did not report any disclosures relevant to his editorial.

Crystalloid, colloid solutions equal in hypovolemic shock

BY JENNIE SMITH
IMNG Medical News

Critically ill patients with hypovolemic shock had the same rate of survival when resuscitated with crystalloid as with colloid solutions, a large randomized controlled trial has found.

In a randomized, international multicenter trial lasting 9 years and enrolling nearly 3,000 patients, 28-day mortality did not differ significantly between those treated with colloid solutions, such as gelatins, hydroxyethyl starches, or albumin, and those treated with crystalloid solutions, such as salines. Mortality at 90 days was found to be somewhat better for colloids than crystalloids, though investigators cautioned that the 90-day finding would require further study.

The question of whether to resuscitate patients with hypovolemic shock with colloids or crystalloids has long been controversial, and many large randomized trials have attempted, over the past decade, to define any differences in mortality and other outcomes between the two classes of fluid therapies.

The study, published in JAMA (doi:10.1001/jama2013.280502), supports previous studies in that no significant mortality differences were found at 28 days. Unlike some earlier studies, which showed adverse renal outcomes associated with colloid use (JAMA 2013;309:678-88), this study did not find a difference in renal outcomes.

For their research, Dr. Djillali Annane, of the University of Versailles, in Garches, France, and colleagues at 57 intensive care units in France, Belgium, Tunisia, and Canada, recruited 2,857 patients with hypovolemic shock over a 9-year period ending in 2012. Of these 1,414 were randomized to colloids and 1,443 to crystalloids. At 28 days the colloids group had 359 deaths (25.4%) and the crystalloids group, 390 (27%). At 90 days the colloids group had 434 deaths (30.7%) and the crystalloids group, 493 (34.2%).

Unlike some earlier studies, which showed adverse renal outcomes associated with colloid use, this study did not find a difference in renal outcomes.

Dr. Annane and colleagues called the 90-day mortality findings surprising. However, "given the null findings at 28 days and the fact that the confidence limit approaches 1, the finding of improved mortality with colloids should be considered exploratory until replicated in a study focusing on this outcome," the investigators wrote.

Colloid use did show other improved outcomes compared with crystalloid use. Patients on colloids had significantly more days alive without mechanical ventilation within 7 days, and more days without vasopressor therapy within 7 days.

Renal outcomes were similar, with 156 patients (11%) in the colloids group requiring renal replacement therapy compared with 181 patients (12.5%) in the crystalloids group.

The fact that the study did not find a higher rate of renal effects associated with colloids, the investigators said, could be due to the trial's exclusion of patients with severe chronic renal failure, the total dose of starches never exceeding doses recommended by regulatory agencies in the study countries, or the majority of the crystalloids patients receiving chloride-rich normal saline, which might increase the risk of kidney injuries compared with a chloride-restricted fluid therapy.

Dr. Annane and colleagues noted the study's long recruitment period and open-label design as weaknesses.

In an editorial accompanying Dr. Annane and colleagues' study, Dr. Christopher W. Seymour and Dr. Derek C. Angus, of the University of Pittsburgh, questioned the two-fluid-classes design of the trial, which, they argued, might not have been ideal to settle the question of ideal fluid therapies in hypovolemic shock. Rather, they wrote, "there are a number of complexities, including the type of shock requiring resuscitation, the resuscitation targets, and the use of adjunctive vasoactive therapies."

In addition, they wrote, "any given fluid choice could have both beneficial and harmful effects, with trade-offs that vary depending on the other complexities listed above. Thus, perhaps the most important message from the latest round of trials is that simply performing larger two-group trials with greater rigor will not bring the field to consensus. Instead, alternative study designs should be considered, perhaps with multiple study interventions and use of adaptive trial design methods."

Two of the 22 coinvestigators reported financial ties to industry. Dr. Seymour disclosed receiving institutional grants from the American Heart Association, the Society of Critical Care Medicine, and the MedicOne Foundation. The study was funded by the French Ministry of Health.

Alprazolam plus melatonin boosts preop anxiolysis

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Adding melatonin to alprazolam significantly decreased preoperative anxiety, compared with either medication alone or with placebo, in a randomized, double-blind trial of 80 patients.

Adult patients undergoing laparoscopic cholecystectomy who reported a preoperative anxiety level of at least 3 cm on a 10-cm visual analog scale (VAS) had average anxiety scores of 5 cm before being randomized to preoperative medication with alprazolam 0.5 mg, melatonin 3 mg, both drugs, or placebo (with 20 patients in each group).

After 1 hour spent in a quiet room following the premedication, VAS scores had fallen by an average of 3 cm in the two-drug group, significantly more than average 2-cm reductions with either drug alone, or a 1-cm decline on placebo, Dr. Krishna Pokharel and her associates reported.

Adding melatonin did not seem to worsen the sedative or amnesiac effects of alprazolam, she reported in a poster presentation at the annual meeting of the American Society of Anesthesiologists.

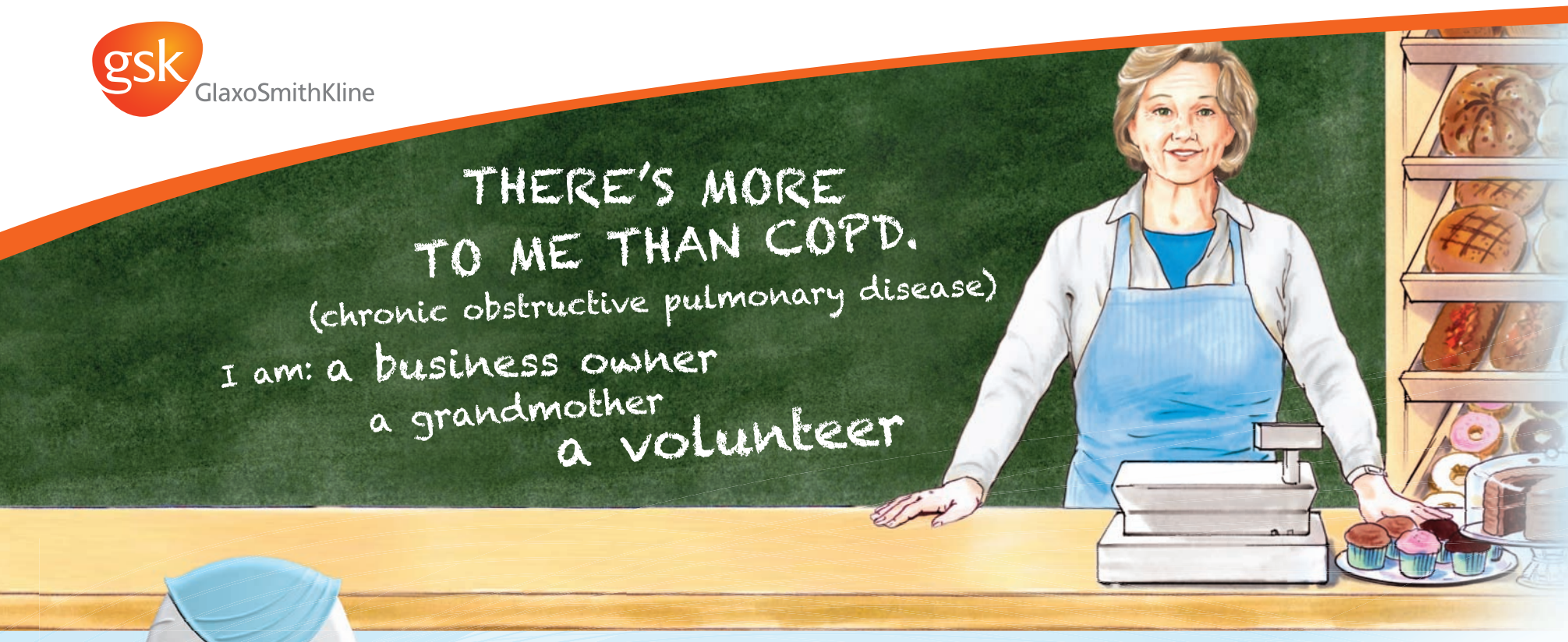
In the past, some of her patients who had been premedicated with a benzodiazepine before general anesthesia and surgery sometimes became aroused during the procedure, perhaps because benzodiazepines suppress endogenous melatonin levels, Dr. Pokharel said. She hypothesized that adding melatonin might help, and the study results have convinced her institution to routinely add melatonin to alprazolam for surgical premedication in anxious patients, said Dr. Pokharel of B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

Patients were shown different pictures during assessments of anxiety and sedation at various time points before surgery. At 24 hours after surgery, 10 patients on alprazolam plus melatonin could recall the picture they saw 1 hour after taking the presurgical medication, compared with 9 patients on alprazolam alone, 18 patients on melatonin alone, and 16 patients on placebo, the poster reported.

In other results, average scores on a 5-point scale for sedation at 1 hour were 0.5 with melatonin, 1 for each group using alprazolam, and 0 with placebo, among other secondary outcomes. At 24 hours after surgery, five patients in the two-drug group could not remember being transferred to the OR, compared with four patients on alprazolam, one patient on melatonin, and none of the patients on placebo.

All groups scored 2 on a 3-point scale for orientation 1 hour after taking the premedication. The amount of propofol needed to achieve a loss of response to verbal commands at the time of general anesthesia induction averaged 66 mg in the alprazolam plus melatonin group, 59 mg after alprazolam alone, 79 mg after melatonin alone, and 76 mg on placebo.

No patients developed serious adverse events. Dr. Pokharel reported having no financial disclosures.



BREO ELLIPTA

The only once-daily ICS/LABA (inhaled corticosteroid/long-acting beta$_2$-agonist) for the maintenance treatment of COPD.

Indications

- BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.
- BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for BREO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABAs), such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol.**
- **The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO ELLIPTA. Advise patients to rinse the mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO ELLIPTA. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO ELLIPTA 100/25 mcg (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and FF/VI 200/25 mcg (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO ELLIPTA at the approved strength (100/25 mcg) and in 7 subjects receiving FF/VI 200/25 mcg (<1% for each treatment group).
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.

BREO ELLIPTA. One inhalation. Once daily.

THE ONLY ONCE-DAILY ICS/LABA FOR THE MAINTENANCE TREATMENT OF COPD

- Approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD
- Approved to reduce COPD exacerbations in patients with a history of exacerbations
- Not approved for the relief of acute bronchospasm or for the treatment of asthma
- Delivered in the ELLIPTA inhaler

Important Safety Information for BREO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO ELLIPTA.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO ELLIPTA slowly.
- Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO ELLIPTA may need to be discontinued. BREO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO ELLIPTA (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).
- In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects treated with BREO ELLIPTA in two 1-year studies included COPD, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with reversible obstructive airways disease.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate exposure may increase in these patients. Monitor for systemic corticosteroid effects.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO ELLIPTA on the following pages.

BREO ELLIPTA was developed in collaboration with Theravance

BREO™ ELLIPTA™
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

BREO™ ELLIPTA™
(fluticasone furoate and vilanterol inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including vilanterol, an active ingredient in BREO ELLIPTA *[see Warnings and Precautions (5.1)]*.

The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE
BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA. A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO ELLIPTA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO ELLIPTA has been conducted. The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.
5.2 Deterioration of Disease and Acute Episodes BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD. The initiation of BREO ELLIPTA in this setting is not appropriate. BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of BREO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Local Effects of Inhaled Corticosteroids In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but at times therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
5.5 Pneumonia An increase in the incidence of pneumonia has been observed in subjects with COPD receiving the fluticasone furoate/vilanterol combination, including BREO ELLIPTA 100 mcg/25 mcg, in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 6% [48 of 820 subjects]; 100 mcg/25 mcg: 6% [51 of 806 subjects]; or 200 mcg/25 mcg: 7% [55 of 811 subjects]) than in subjects receiving vilanterol 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving fluticasone furoate/vilanterol 100 mcg/25 mcg and in 7 subjects receiving fluticasone furoate/vilanterol 200 mcg/25 mcg (less than 1% for each treatment group).
5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
5.7 Transferring Patients From Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO ELLIPTA may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amount of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe COPD exacerbation. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO ELLIPTA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, and depression) despite maintenance or even improvement of respiratory function.
5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic dose of BREO ELLIPTA. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD symptoms should be considered.
5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.11 Hypersensitivity Reactions Hypersensitivity reactions may occur after administration of BREO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not take BREO ELLIPTA *[see Contraindications (4)]*.
5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher systemic exposure than seen in patients with COPD) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPTA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered. In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2% [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 818 subjects]).
5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those receiving vilanterol 25 mcg alone (1% [9 of 818 subjects]).
5.15 Coexisting Conditions BREO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In 4 clinical trials of 6- and 12-month duration evaluating BREO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warnings and Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Increased risk for decrease in bone mineral density *[see Warnings and Precautions (5.13)]*.
6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical program for BREO ELLIPTA included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects have received at least 1 dose of BREO ELLIPTA 100 mcg/25 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6-month and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with BREO ELLIPTA in Table 1 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 1,224 and n = 1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were Caucasian. They had a mean age of 62 years and an average smoking history of 44 pack

years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 1. Adverse Reactions With ≥3% Incidence and More Common Than Placebo With BREO ELLIPTA in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Event	BREO ELLIPTA 100 mcg/25 mcg (n = 410) %	Vilanterol 25 mcg (n = 408) %	Fluticasone Furoate 100 mcg (n = 410) %	Placebo (n = 412) %
Infections and infestations				
Nasopharyngitis	9	10	8	8
Upper respiratory tract infection	7	5	4	3
Oropharyngeal candidiasis[a]	5	2	3	2
Nervous system disorders				
Headache	7	9	7	5

[a]Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal.

12-Month Trials: Long-term safety data is based on two 12-month trials (Trials 3 and 4; n = 1,633 and n = 1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were Caucasian. They had a mean age of 64 years and an average smoking history of 46 pack years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, or vilanterol 25 mcg. In addition to the events shown in Table 1, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO ELLIPTA (N = 806) for 12 months included COPD, back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, are both substrates of CYP3A4. Concomitant administration of the potent CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants Vilanterol, like other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO ELLIPTA, but may produce severe bronchospasm in patients with reversible obstructive airways disease. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO ELLIPTA in pregnant women. Corticosteroids and $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal studies are not always predictive of human response, BREO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO ELLIPTA. *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 9 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at approximately 9 and 2 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 3 times the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day). *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).
Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO ELLIPTA during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO ELLIPTA by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO ELLIPTA for COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for BREO ELLIPTA. BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO ELLIPTA.

10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol. Treatment of overdosage consists of discontinuation of BREO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BREO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with BREO ELLIPTA; however, studies are available for the individual components, fluticasone furoate and vilanterol, as described below.
Fluticasone Furoate: Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m^2 basis). Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats. No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on a mcg/m^2 basis).
Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 530 times the MRHDID in adults on an AUC basis). In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID in adults on an AUC basis). These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay. No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,000 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use)

17.1 Asthma-Related Death Patients should be informed that LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma.

17.2 Not for Acute Symptoms BREO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with a rescue inhaler such as albuterol. The physician should provide the patient with such medicine and instruct the patient in how it should be used. Patients should be instructed to notify their physicians immediately if they experience any of the following: Symptoms get worse; Need for more inhalations than usual of their rescue inhaler; Significant decrease in lung function as outlined by the physician. Patients should not stop therapy with BREO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting $Beta_2$-Agonists When patients are prescribed BREO ELLIPTA, other medicines containing a LABA should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO ELLIPTA, but at times therapy with BREO ELLIPTA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth without swallowing after inhalation is advised to help reduce the risk of thrush.
Pneumonia: Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia and should be instructed to contact their healthcare providers if they develop symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing problems).
Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.
Hypercorticism and Adrenal Suppression: Patients should be advised that BREO ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids.
Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.
Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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Revised 05/2013 BRE:1BRS

CT says it all

Smoking *from page 1*

smokers, and nonsmokers undergoing coronary CT angiography.

Of the 13,372 patients without known CAD who underwent CT, 21% were current smokers, 24% were past smokers who had quit more than 3 months prior to the CT, and 55% were nonsmokers.

The average age of the patients was 56 years, and half were men. Patients were followed up for 2 years, and MACE occurred in 279 cases (2.1%).

Analysis showed that current and past smokers had a 50% or greater risk of obstructive CAD than did nonsmokers. One-vessel disease was present in 11.1% of nonsmokers, compared with 16.6% and 16.2% of current and past smokers, respectively. The frequency of two-vessel disease was 4.8% among nonsmokers, compared with 7.3% and 7.8%, respectively, in current and past smokers; while the frequency of three-vessel disease in the three groups was 2.3%, 5.1%, and 5%, respectively.

In addition, current smokers had a significantly higher risk of MACE than did nonsmokers, but past smokers did not. Even after matched-cohort analysis, the relationship remained the same, and current smoking was still significantly associated with MACE risk, although past smoking was not.

Dr. Min and Dr. Verheugt reported having no disclosures.

Cessation benefits flow into old age

BY NASEEM S. MILLER
IMNG Medical News

NASEEM S. MILLER/IMNG MEDICAL MEDIA

Dr. Freek Verheugt and Dr. Eva Prescott discuss several studies about the benefits of quitting smoking. Watch the video at chestphysician.org.

AMSTERDAM – Older men who continued to smoke in their 70s were 50% more likely to die from cancer, cardiovascular disease, and respiratory disease, compared with those who never smoked. They were also less likely to survive to age 85, according to findings from a British survey.

"The real message is that risk remains big for smokers at any age, and the evidence regarding benefits of quitting smoking persists even into old age," said Jonathan Emberson, Ph.D., a senior statistician at the University of Oxford (England), who presented the study at the annual congress of the European Society of Cardiology.

The results were from a prospective study of more than 7,000 surviving men who were initially recruited between 1967 and 1970 in the Whitehall study. The men were surveyed again in 1997-1998, when their mean age was 77 years. Follow-up information was obtained on cause-specific mortality through 2012.

At the resurvey in 1997-1998, 13% were current smokers and smoked a median of 9 cigarettes a day; 58% were former smokers, with median time of 25 years since quitting; and 23% said they never smoked. The remaining 5% said they were never-smokers in the resurvey, but not in the initial survey in 1967-1970, and were handled as a separate category, the researchers noted.

During the median follow-up of 15 years, there were 4,965 deaths, 2,063 of which resulted from cardiovascular disease, 1,167 from cancer, 802 from respiratory disease, and 933 from other causes. Comparing the 984 smokers with 1,625 never-smokers showed that current smokers had a 50% increase in annual mortality. Their odds of death from vascular causes increased by nearly one-third, and from nonvascular causes by nearly two-thirds.

Meanwhile, a comparison between 4,091 ex-smokers and 1,625 never-smokers showed that ex-smokers had a 15% increase in annual mortality, mainly because of cancer (hazard ratio, 1.24) and respiratory disease (HR, 1.58). Also, their risk varied considerably depending on the number of years since they had quit smoking. Men who had quit within the past 25 years had a 22% higher mortality than never-smokers, but men who had quit 25 or more years ago had no significant excess risk (HR, 1.05). Men who had quit smoking within the past 10 years had a 44% increase in all-cause mortality, vs. never-smokers.

Dr. Emberson had no disclosures. The U.K. Medical Research Council, the British Heart Foundation, and Cancer Research UK funded the study.

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VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: These two studies add to the body of evidence underscoring the health benefits of not smoking. The prospective analysis of CT angiography demonstrated a significantly lower risk of major adverse cardiac events in nonsmokers. Even those who were former smokers had a lower risk compared with current smokers. The other, a long-term prospective study demonstrated the effect of never smoking on longevity. Individuals who had never smoked not only lived longer, but had better quality of life than current smokers who had a lower odds of surviving to age 85 years. While never smoking is great from a health perspective, smoking cessation at any age is still beneficial.

Nintedanib boosts NSCLC survival as second-line agent

BY SARA FREEMAN
IMNG Medical News

AMSTERDAM – Both progression-free and overall survival were improved by the addition of nintedanib to standard chemotherapy with docetaxel in the second-line treatment of non–small cell lung cancer in a randomized phase III trial presented at the European Cancer Congress 2013.

Results of the LUME-Lung 1 trial showed progression-free survival of 3.5 months in patients treated with nintedanib plus docetaxel versus 2.7 months for those treated with placebo plus docetaxel (hazard ratio = 0.85; $P = .007$) at a data cutoff of February 2013.

SARA FREEMAN/IMNG MEDICAL MEDIA

With adenocarcinoma, overall survival improved, said Dr. Anders Mellemgaard.

"To date, no targeted agent had been shown to prolong overall survival when combined with second-line chemotherapy," said Dr. Anders Mellemgaard of Herlev University Hospital, Copenhagen.

Overall survival was a median of 10.1 months with combination treatment and 9.1 months with docetaxel alone (HR, 0.94). The overall survival results were significantly better in patients with adenocarcinoma (12.6 months vs. 10.3 months; HR, 0.83) and in those adenocarcinoma patients treated within 9 months of the completion of first-line therapy (10.9 vs. 7.9 months, HR, 0.75).

"Patients with advanced non–small cell lung cancer who have first-line chemotherapy will progress at one point or another," Dr. Mellemgaard said at the multidisciplinary European cancer congresses. Docetaxel is a standard of care for second-line treatment of NSCLC, even though the effects of such treatment are rather modest. Nintedanib is an oral angiokinase inhibitor that blocks the receptors for vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptor.

The LUME-Lung 1 trial comprised 1,314 patients with stage IIIB/IV or recurrent non–small cell lung cancer. Subjects were randomized to treatment with docetaxel at 75 mg/m^2 on day 1 of a 21-day cycle; 655 patients were randomized to nintedanib 200 mg, and 659 patients were given placebo twice daily on days 2-21. Monotherapy with nintedanib was allowed after four or more cycles of combination therapy.

"Patients with adenocarcinoma histology had significantly improved overall survival with nintedanib," Dr. Mellemgaard said. An exploratory analysis is looking at patients with

Continued on following page

Immunotherapy induces striking responses in NSCLC

BY SARA FREEMAN
IMNG Medical News

AMSTERDAM – Almost a quarter of patients with advanced and heavily pretreated lung cancer responded to treatment with the novel immunotherapy MPDL3280A in an ongoing phase I study.

The objective response rate was 23% in 53 patients with non–small cell lung cancer (NSCLC) evaluated for clinical activity, with 17% of patients achieving stable disease for 24 weeks or longer, and a progression-free survival rate of 45%. The best responses were seen in patients with the highest expression of the targeted protein, PD-L1; current or past smokers seemed to gain the greatest benefit from the novel immunotherapy.

MPDL3280A was well tolerated by the 85 patients with NSCLC who were evaluated for safety, which was the main aim of the early clinical study.

"Most adverse events seen in the trial were grade 1 or 2 and did not require intervention," Dr. Jean-Charles Soria said at the European Cancer Congress 2013.

Dr. Soria, director of the Institut Gustave Roussy's integrated cancer research center in Villejuif, France, noted that were no dose-limiting toxicities with doses of up to 20 mg/kg, and no cases of grade 3-5 pneumonitis. There was, however, a single, severe grade 3-4 adverse event in a patient with large-cell neuroendocrine NSCLC, and one death due to cardiac arrest in a patient with sinus thrombosis and a large tumor mass invading the heart at baseline.

Dr. Soria explained that MPDL3280A inhibits PD-L1 in such a way that it leaves some immune homeostatic functions intact, which could potentially prevent the development of autoimmunity.

The phase I trial he presented included patients with nonsquamous (76%) and squamous (24%) histology who were treated with an intravenous (10, 15, or 20 mg/kg) infusion of MPDL3280A every 3 weeks for up to 1 year. The patients' median age was 60 years; 56% were male. Most (81%) were current or former smokers, and more than half (55%) of the patients had received three or more systemic regimens. Almost all (95%) patients had metastases involving the central nervous system, and 60% had EGFR wild-type.

Objective response rates (ORRs) were 21% and 27%, respectively, in patients with nonsquamous and squamous histology. Interestingly, the ORR increased with PD-L1 expression, which was determined using immunohistochemistry (IHC), suggesting this might be a potential biomarker for response. The ORR was 83% when 10% or more of the tumor cells were positive for PD-L1 (IHC 3), 46% when 5% or more of the tumor cells were PD-L1 positive (IHC 2 and 3), and 31% when 1% or more of tumor cells were PD-L1 positive (IHC 1/2/3). The respective rates of progressive disease by IHC status were 17%, 23%, and 38%.

TERRY RUDD/IMNG MEDICAL MEDIA

'I used to belong to the 'immuno-skeptical world of oncology' says Dr. Jean-Charles Soria, who reported at European Cancer Congress 2013 that MPDL3280A is a 'game changer' for patients with pretreated lung cancer. Watch a video at chestphysician.org.


SARA FREEMAN/IMNG MEDICAL MEDIA

The agent's activity in former smokers is key, said Dr. Paul Baas.

Responses to the investigational drug were "outstandingly" durable, and all but one of the 12 patients who had responded to the drug continued to respond at the time of the data cutoff, Dr. Soria said. The longest duration of treatment response seen at this time point was 84 weeks, he added.

As it had been recently suggested that there might be a relationship between the mutational tumor load and the immunogenicity of the tumor (Clin. Cancer Res. 2012;18:6580-7), Dr. Soria and his associates decided to determine if there was any difference in the response to MPDL3280A according to patients' smoking status. The results were striking: ORRs in smokers versus never-smokers were 26% and 10%, respectively.

"It is very good to now have something for patients who were former smokers," said Dr. Paul Baas of the Netherlands Cancer Institute, Amsterdam. "It works in adenocarcinoma and squamous cell carcinomas, and I think the importance of this [study] is that [MPDL3280A] is already very active in phase I."

Roche is now pushing ahead with its clinical development program for MPDL3280A in a larger population of patients with NSCLC to see if the novel immunotherapeutic fulfills this early promise.

Phase II studies of MPDL3280A in patients with NSCLC (NCT01846416 and NCT01903993) have already been initiated, and further studies are planned. The investigational drug is also being tested in combination with vemurafenib (Zelboraf) in the treatment of BRAFV600-mutation positive melanoma (NCT01656642), in combination with bevacizumab (Avastin) in patients with advanced solid tumors (NCT01633970), and as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies (NCT01375842).

Genentech, a member of the Roche Group, supported the study. Dr. Soria received research funds and advised the company. Dr. Baas received research grants from Pfizer and Roche and advised MSD and Verastem.

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: The PD-L1/PD-1 ligand complex is a natural suppressive pathway used by cells to inhibit IL-2 production and T-cell proliferation, so that inflammation is kept under control. However, some remarkably clever cancers including renal cell, ovarian, and non–small cell lung cancer exploit this pathway by up-regulating PD-L1 to evade and hide from the host's immune system. The monoclonal antibody MPDL3280A blocks PD-L1 and exposes the cancer to the host's activated immune system – the activated "killer" (cytotoxic) T cells.

This phase I clinical trial has remarkable and exciting results using this minimally toxic anti-PD-L1 agent in patients with highly chemoresistant stage IV lung cancer, with nearly one-quarter achieving an objective, durable response and a progression-free survival in 45%.

This novel immunotherapy approach to systemic treatment of lung cancer is regarded by thoracic oncologists as a potential breakthrough in treatment, and it may soon become the preferred first-line, well-tolerated therapy for this very large group of metastatic lung cancer patients who express high levels of PD-L1.

Continued from previous page

adenocarcinoma and progressive disease, as the best response to first-line treatment showed a 3.5-month survival gain by using the targeted therapy (HR, 0.62).

Diarrhea was the most common adverse effect in the combination arm (any grade 43.3% vs. 24.6% in the control group; 6.3% vs. 3.6% for grade 3 or higher). Other adverse effects were elevated alkaline phosphatase (any grade 37.8% vs. 9.3%; grade 3 or higher 11.6% vs. 0.9%) and fatigue (any grade 30.9% vs. 29.4%; grade 3 or higher 4.7% vs. 4.2%).

"This toxicity was manageable by dose reductions and supportive care," Dr. Mellemgaard observed.

Dr. Mellemgaard is a member of an advisory board for Boehringer Ingelheim, which funded the study.

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PROLASTIN-C, Alpha$_1$-Proteinase Inhibitor (Human) is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$-antitrypsin deficiency).

The effect of augmentation therapy with any alpha$_1$-proteinase inhibitor (alpha$_1$-PI) on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials. PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe alpha$_1$-PI deficiency has not been established.

PROLASTIN-C may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. PROLASTIN-C is contraindicated in patients with antibodies against IgA.

The most common drug related adverse reactions during clinical trials in ≥1% of subjects were chills, malaise, headache, rash, hot flush, and pruritus. The most serious adverse reaction observed during clinical studies with PROLASTIN-C was an abdominal and extremity rash in one subject.

PROLASTIN-C is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of PROLASTIN-C full Prescribing Information on adjacent page.

References: 1. Data on file, Grifols. **2.** Campos MA, Alazemi S, Zhang G, Wanner A, Sandhaus RA. Effects of a disease management program in individuals with alpha-1 antitrypsin deficiency. *COPD*. 2009;6:31-40.

GRIFOLS

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PROLASTIN®-C
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROLASTIN®-C (Alpha$_1$-Proteinase Inhibitor [Human]) safely and effectively. See full prescribing information for PROLASTIN-C.

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----------INDICATIONS AND USAGE ----------

PROLASTIN-C is an alpha$_1$-proteinase inhibitor that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$-antitrypsin deficiency). The effect of augmentation therapy with any alpha$_1$-proteinase inhibitor (Alpha$_1$-PI) on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials. PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe Alpha$_1$-PI deficiency has not been established.

----------CONTRAINDICATIONS ----------

IgA deficient patients with antibodies against IgA.

---------WARNINGS AND PRECAUTIONS -------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

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The most common drug related adverse reactions during clinical trials in ≥ 1% of subjects were chills, malaise, headache, rash, hot flush, and pruritus.

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Four-variable score predicts acute kidney injury

BY DOUG BRUNK
IMNG Medical News

DENVER – A four-variable risk score predicted acute kidney injury with high specificity in patients receiving vancomycin, results from a single-center study demonstrated.

During a poster session at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Joseph J. Carreno, Pharm.D., discussed findings from a study that set out to identify patients at high risk for AKI during vancomycin therapy.

"Vancomycin has been the standard therapy for infections with methicillin-resistant *Staphylococcus aureus*," Dr. Carreno of Albany (N.Y.) College of Pharmacy and Health Sciences and his associates wrote in their abstract.

In a study conducted during his infectious disease pharmacy fellowship at Henry Ford Hospital, Detroit, the researchers reviewed the records of 112 adults (mean age, 58 years; 54% male) who were prescribed IV vancomycin for an infection between January 2011 and January 2012.

Four risk factors were evaluated: receiving at least 4 g of daily vancomycin or having a body weight of at least 110 kg; a history of renal dysfunction; concurrent use of IV vasopressors; and use of concurrent nephrotoxins. Most (84) had fewer than two risk factors, while the rest had two or more.

The results showed that the prevalence of AKI was 46%. In analysis adjusted for the other three risk factors, the odds for the development of AKI was greatest in patients on vasopressors (odds ratio, 5.92), followed by those with a history of AKI or chronic kidney disease (OR, 2.99), those on high-dose vancomycin or with a body weight of at least 110 kg (OR, 1.68), and those on nephrotoxins (OR, 1.07).

In all, 68% of patients with at least two risk factors at baseline developed AKI, versus 38% of those with fewer than two ($P = .01$).

The sensitivity and specificity of the model were 78% and 33%, respectively, among patients with at least one risk factor, and 37% and 85% in those with at least two risk factors.

Dr. Carreno said he had no relevant financial disclosures.

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VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments:

This is an interesting and easy-to-use tool that has the potential for predicting the development of acute renal failure in patients receiving vancomycin.

The results are interesting, but the retrospective study is small, and the predictive value is moderate. The risk factors in the scoring system are all known to be associated with AKI during vancomycin therapy, and there is value in quantifying the association.

Steroids may ease antibiotics-related *C. difficile* risk

BY DOUG BRUNK
IMNG Medical News

DENVER – Use of systemic corticosteroids during antibiotic treatment for respiratory infections may reduce the incidence of *Clostridium difficile*–associated diarrhea, a single-center study demonstrated.

"Using steroids may not predispose people to having *C. diff.*, as previously thought," Amy Wojciechowski, Pharm.D., said in an interview during a poster session at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Dr. Wojciechowski, along with Kari Mergenhagen, Pharm.D., and their associates at the VA Western New York Healthcare System, Buffalo, set out to determine the incidence of *Clostridium difficile*–associated diarrhea (CDAD) in patients treated in the hospital with antibiotics for a chronic obstructive pulmonary disease (COPD) exacerbation or community-acquired pneumonia. The investigators evaluated baseline characteristics and risk factors that affect the incidence of CDAD.

The study population comprised 532 veterans (mean age, 76 years; 99% male) who were hospitalized between March 2006 and July 2012 and were treated with moxifloxacin or with ceftriaxone plus azithromycin. CDAD was defined as diarrhea with positive PCR assay or toxin assay for *C. difficile* within 30 days of antibiotic treatment.

The researchers found that CDAD occurred in 11 patients, for an incidence rate of 2.07%.

Variables associated with a lower risk of CDAD were diagnosis of COPD ($P = .01$) and use of corticosteroids during antibiotics treatment ($P = .0035$). There was no difference in the incidence of CDAD between patients treated with moxifloxacin and those treated with ceftriaxone plus azithromycin.

After the researchers controlled for COPD, the use of corticosteroids remained linked to a decreased risk of developing CDAD (odds ratio, 0.12).

Dr. Wojciechowski, an infectious diseases pharmacy resident, and Dr. Mergenhagen, a clinical infectious diseases pharmacist, said that they had no relevant conflicts of interest to disclose.

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VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: Be careful about jumping to many conclusions regarding the beneficial effects of corticosteroids preventing *Clostridium difficile*–associated diarrhea. These associations derived from retrospective studies should be assessed in randomized controlled trials before specific recommendations are translated into clinical practice.

Mid-level providers may add risks

Practice *from page 1*

family physician and chief medical officer for COPIC, a Colorado-based medical liability insurer. "The liability and supervision goes to the doctor who is registered with the medical board."

The vignette goes far to illustrate the type of legal cases that are becoming more common with the increased use of mid-level providers, Dr. Lembitz said.

Supervising physicians must have good rapport with the mid-level providers.

MR. INDEST

A report from national medical liability insurer the Doctors Company quantifies the situation.

The report examined claims between 2001 and 2010 involving nurse practitioners and physician assistants compiled by the PIAA Data Sharing Project, a claims database operated by PIAA, a national trade association that represents medical liability insurers. (PIAA was formerly known as Physician Insurers Association of America.)

Of 1,180 closed claims involving physician assistants (PAs) and nurse practitioners (NPs), the payments were made on behalf of mid-level providers by the supervising physician's policy or that of the practice's professional association. Family medicine was the most common specialty associated with claims against mid-level providers.

The average defense payment paid on behalf of NPs was $309,405,

Mid-levels may claim no fault because 'the physician did not appropriately supervise.'

DR. SZALADOS

while the average defense payment made on behalf of PAs was $321,991, the report said.

With federal incentives aimed at more collaborative care and declining physician reimbursement, the growing demand for physician extenders is inevitable, said George F. Indest III, president of the Health Law Firm, headquartered in Altamonte Springs, Fla.

"With the increased role of [mid-level providers], there will no doubt be some increase in liability placed on physicians who are their supervisors," Mr. Indest said.

Mr. Indest stressed that when used effectively, mid-level providers improve quality of care, fill gaps in medical care coverage, and provide needed treatment for underserved populations. The key is that "supervising physicians must have good rapport with the [mid-level providers] they supervise and keep open channels of communication with them at all times."

Common liability theories

Frequent legal claims faced by physicians supervising mid-level providers include vicarious liability, agency, and failure to supervise.

Vicarious liability assigns liability to a person who did not cause the alleged negligence but who had a legal relationship with the negligent party.

Physicians can be disciplined by state medical boards for poor patient outcomes caused by other professionals.

MR. SAXTON

Agency is used to link the negligent acts of one party to another because the two are said to have an agent-principal relationship. In such cases, plaintiffs claim the agent was authorized to act on behalf of the principal.

Failure to supervise is a growing allegation by plaintiffs and by mid-level providers, said Dr. James Szalados, an anesthesiologist and medical liability defense attorney based in New York.

"Inadequate supervision is becoming a bigger issue because mid-levels are using that as a defense," he said. They claim no fault because "the physician did not appropriately supervise."

Physicians also can be disciplined by state medical boards for poor patient outcomes caused by other professionals, according to James W. Saxton, chair of the health care litigation and risk management group at Stevens & Lee, headquartered in Reading, Pa. Most states have supervision requirements that address the oversight of mid-level providers. Running afoul of such rules means state scrutiny.

Boards "take ensuring quality very seriously," Mr. Saxton said. "If you're a physician supervisor and you don't have a system in place to make sure you are appropriately supervising your [mid-level provider] and that provider is [operating] outside their scope of practice, the state board can do an investigation of the doctor."

Reducing risk

Knowing your state's supervision requirements is key to reducing legal dangers and defending potential claims, according to Frank B. O'Neil, senior vice president and chief communications officer for ProAssurance, a national medical liability insurer. Some states allow a broader scope of practice for mid-level providers, while others outline specific intervals that physicians must attend to a patient.

"The bottom line is whenever a physician is employing a [mid-level provider], there are general rules about their duties and supervision laid out by state boards and other regulatory authorities," he said. "It's imperative to know those regulations and comply with them."

Improving communication among team members is also essential, according to Dr. Hardeep Singh, chief of the health policy and quality and informatics program at the Houston VA Center for Innovations in Quality, Effectiveness, and Safety.

Dr. Singh was the lead author of a study last August in Health Affairs that examined causes of diagnostic delays. Top reasons included poor teamwork, miscommunication, and lack of care coordination (Health Aff. 2013;32:1368-75).

"People underestimate the importance of responsibility diffusion," he said. "We really need to be clear on who's going to follow-up."

Physicians must also alert the state and their insurer of any changes to their supervision status, whether it's overseeing more providers or no longer supervising, Mr. O'Neil said. He added that if a physician fails to inform a carrier of a change, the doctor may not be covered against certain claims.

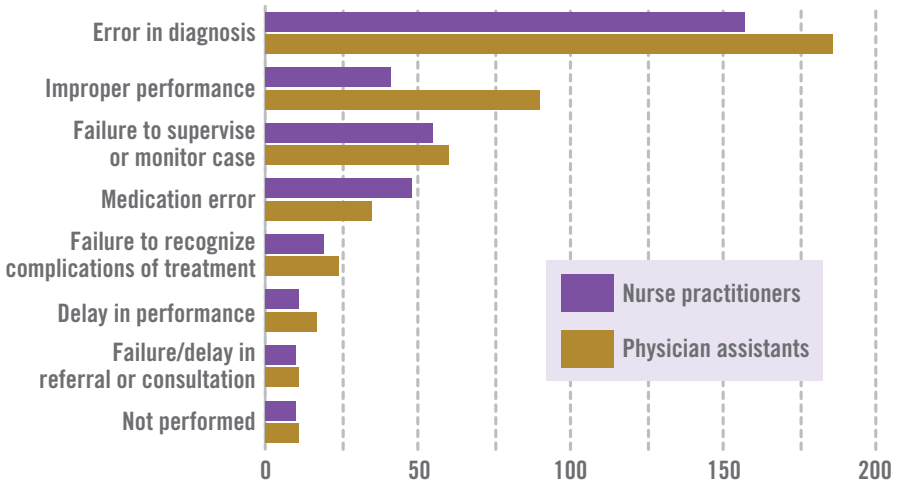
It's imperative to know your state's regulations and comply with them.

MR. O'NEIL

Considering risk management steps early reduces malpractice dangers and ensures health care teams operate successfully, Mr. Indest said.

"After the mishap occurs, [it] may be too late to prevent fault … just as with any accident or error," he said. "Being proactive and taking measures to prevent liability ahead of time is much more effective."

Number of closed claims involving mid-level practitioners



Note: Based on data compiled by the PIAA for 1,180 closed claims from 2001 to 2010.
Source: The Doctors Company
IMNG Medical Media

VIEW ON THE NEWS

Dr. Burt Lesnick, FCCP, comments: As use of extenders increases, physicians need to understand their supervisory obligations and liabilities with regard to their PAs and NPs.

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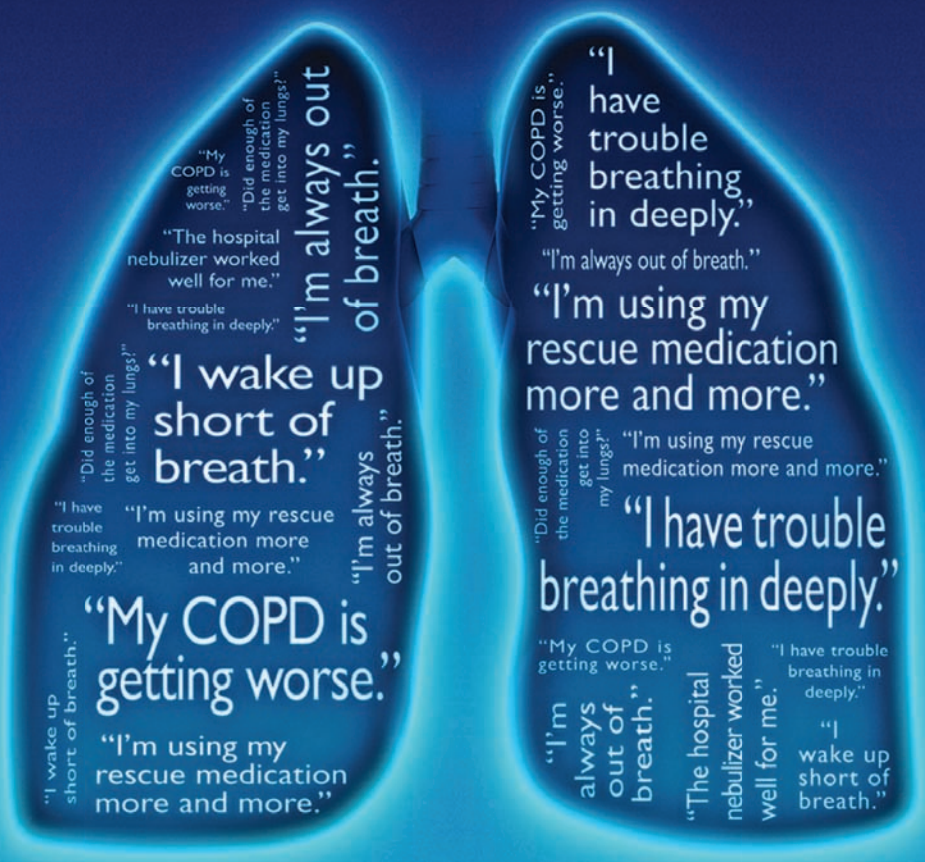

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Please see Important Safety Information and brief summary of Prescribing Information on adjacent pages.

*A randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group study in 351 moderate to severe COPD patients evaluating the efficacy and safety of PERFOROMIST (20 mcg/2 mL BID) vs placebo over 12 weeks.

†Two randomized, double-blind, placebo-controlled, parallel-group studies (n=130, n=155) evaluating the efficacy and safety of PERFOROMIST/Spiriva vs placebo/Spiriva over 6 weeks.

COPD=chronic obstructive pulmonary disease. LABA=long-acting beta$_2$-agonist. BID=twice-daily dosing.

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- It is not indicated to treat asthma. The safety and effectiveness of PERFOROMIST Inhalation Solution in asthma has not been established.

Important Safety Information

PERFOROMIST Inhalation Solution like other LABAs is contraindicated in patients with asthma without use of a long term asthma control medication.

PERFOROMIST Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. PERFOROMIST Inhalation Solution should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

As with other inhaled beta$_2$-agonists, PERFOROMIST Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, PERFOROMIST Inhalation Solution should be discontinued immediately and alternative therapy instituted.

PERFOROMIST Inhalation Solution should not be used more often, at higher doses than recommended, or in conjunction with other inhaled, long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

PERFOROMIST Inhalation Solution should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

PERFOROMIST Inhalation Solution, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms.

PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta agonist medications may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Immediate hypersensitivity reactions may occur after administration of PERFOROMIST Inhalation Solution, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

PERFOROMIST Inhalation Solution, as with other beta$_2$-agonists, should be used with extreme caution in patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents.

Beta-blockers and formoterol fumarate may inhibit the effect of each other when administered concurrently. Therefore, patients with COPD should not normally be treated with beta-blockers except under certain circumstances e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD.

Concomitant treatment with Xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists. The EKG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, so caution is advised in the co-administration.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on adjacent pages.

References: 1. Perforomist® (formoterol fumarate) Inhalation Solution Prescribing Information. Mylan Specialty L.P.; 2013. **2.** Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005;127(1):335-371. **3.** Gross NJ, Nelson HS, Lapidus RJ, et al; for the Formoterol Study Group. Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients. *Respir Med.* 2008;102(2):189-197. **4.** Tashkin DP, Littner M, Andrews CP, et al. Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: a placebo-controlled trial. *Respir Med.* 2008;102(4):479-487. **5.** Hanania NA, Boota A, Kerwin E, et al. Efficacy and safety of nebulized formoterol as add-on therapy in COPD patients receiving maintenance tiotropium bromide: results from a 6-week, randomized, placebo-controlled, clinical trial. *Drugs.* 2009;69(9):1205-1216. **6.** Brovana® (arformoterol tartrate) Inhalation Solution Prescribing Information. Sunovion Pharmaceuticals Inc.; 2012.

PERFOROMIST®
(formoterol fumarate) Inhalation Solution

BRIEF SUMMARY
Please see package insert for full Prescribing Information.

WARNING: ASTHMA-RELATED DEATH

Long-acting $beta_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting $beta_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication *[see CONTRAINDICATION, WARNINGS AND PRECAUTIONS].*

INDICATIONS AND USAGE

Maintenance Treatment of COPD

PERFOROMIST (formoterol fumarate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Important Limitations of Use

PERFOROMIST Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease *[see WARNINGS AND PRECAUTIONS].*

PERFOROMIST Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of PERFOROMIST Inhalation Solution in asthma have not been established.

DOSAGE AND ADMINISTRATION

The recommended dose of PERFOROMIST (formoterol fumarate) Inhalation Solution is one 20 mcg unit-dose vial administered twice daily (morning and evening) by nebulization. A total daily dose greater than 40 mcg is not recommended.

PERFOROMIST Inhalation Solution should be administered by the orally inhaled route via a standard jet nebulizer connected to an air compressor. The safety and efficacy of PERFOROMIST Inhalation Solution have been established in clinical trials when administered using the PARI-LC Plus® nebulizer (with a facemask or mouthpiece) and the PRONEB® Ultra compressor. The safety and efficacy of PERFOROMIST Inhalation Solution delivered from non-compressor based nebulizer systems have not been established.

PERFOROMIST Inhalation Solution should always be stored in the foil pouch, and only removed IMMEDIATELY BEFORE USE. Contents of any partially used container should be discarded.

If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

The drug compatibility (physical and chemical), efficacy, and safety of PERFOROMIST Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

DOSAGE FORMS AND STRENGTHS

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as a sterile solution for nebulization in low-density polyethylene unit-dose vials. Each vial contains formoterol fumarate dihydrate, USP equivalent to 20 mcg/2 mL of formoterol fumarate.

CONTRAINDICATIONS

All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. [*see WARNINGS and PRECAUTIONS*].

WARNINGS AND PRECAUTIONS

Asthma-Related Deaths *[See BOXED WARNING]*

Data from a large placebo-controlled study in asthma patients showed that long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting $beta_2$-adrenergic agonists.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the long-acting $beta_2$-adrenergic agonists, including PERFOROMIST Inhalation Solution. No study adequate to determine whether the rate of asthma related death is increased in patients treated with PERFOROMIST Inhalation Solution has been conducted. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. [*see CONTRAINDICATIONS*].

Clinical studies with formoterol fumarate administered as a dry powder inhaler suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Deterioration of Disease and Acute Episodes

PERFOROMIST Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. PERFOROMIST Inhalation Solution has not been studied in patients with acutely deteriorating COPD. The use of PERFOROMIST Inhalation Solution in this setting is inappropriate.

PERFOROMIST Inhalation Solution should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. PERFOROMIST Inhalation Solution has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

When beginning PERFOROMIST Inhalation Solution, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing PERFOROMIST Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient how it should be used. Increasing inhaled $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If PERFOROMIST Inhalation Solution no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting $beta_2$-agonist becomes less effective or the patient needs more inhalation of short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of PERFOROMIST Inhalation Solution beyond the recommended 20 mcg twice daily dose is not appropriate in this situation.

Excessive Use and Use with Other Long-Acting $Beta_2$-Agonists

As with other inhaled $beta_2$-adrenergic drugs, PERFOROMIST Inhalation Solution should not be used more often, at higher doses than recommended, or in conjunction with other medications containing long-acting $beta_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Paradoxical Bronchospasm

As with other inhaled $beta_2$-agonists, PERFOROMIST Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, PERFOROMIST Inhalation Solution should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

PERFOROMIST Inhalation Solution, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, PERFOROMIST Inhalation Solution may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

Clinically significant changes in serum potassium and blood glucose were infrequent during clinical studies with long-term administration of PERFOROMIST Inhalation Solution at the recommended dose.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of PERFOROMIST Inhalation Solution, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

ADVERSE REACTIONS

Long acting $beta_2$-adrenergic agonists such as formoterol increase the risk of asthma-related death *[See BOXED WARNING and WARNINGS AND PRECAUTIONS].*

$Beta_2$-Agonist Adverse Reaction Profile

Adverse reactions to PERFOROMIST Inhalation Solution are expected to be similar in nature to other $beta_2$-adrenergic receptor agonists including: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, malaise, insomnia, hypokalemia, hyperglycemia, and metabolic acidosis.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with COPD

Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was greater than or equal to 2% in the PERFOROMIST Inhalation Solution group and where the rate in the PERFOROMIST Inhalation Solution group exceeded the rate in the placebo group. In this trial, the frequency of patients experiencing cardiovascular adverse events was 4.1% for PERFOROMIST Inhalation Solution and 4.4% for placebo. There were no frequently occurring specific cardiovascular adverse events for PERFOROMIST Inhalation Solution (frequency greater than or equal to 1% and greater than placebo). The rate of COPD exacerbations was 4.1% for PERFOROMIST Inhalation Solution and 7.9% for placebo.

TABLE 1

Number of patients with adverse reactions in the 12-week multiple-dose controlled clinical trial

Adverse Reaction	PERFOROMIST Inhalation Solution 20 mcg		Placebo	
	n	(%)	n	(%)
Total Patients	123	(100)	114	(100)
Diarrhea	6	(4.9)	4	(3.5)
Nausea	6	(4.9)	3	(2.6)
Nasopharyngitis	4	(3.3)	2	(1.8)
Dry Mouth	4	(3.3)	2	(1.8)
Vomiting	3	(2.4)	2	(1.8)
Dizziness	3	(2.4)	1	(0.9)
Insomnia	3	(2.4)	0	0

Patients treated with PERFOROMIST Inhalation Solution 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events above the number expected based on the medical condition and age of the patients.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of PERFOROMIST Inhalation Solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylactic reactions, urticaria, angioedema (presenting as face, lip, tongue, eye, pharyngeal, or mouth edema), rash, and bronchospasm

DRUG INTERACTIONS

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol may be potentiated *[see WARNINGS AND PRECAUTIONS]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists *[see WARNINGS AND PRECAUTIONS]*.

Non-potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

Formoterol, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-blockers

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. However, formoterol fumarate was found to be teratogenic in rats and rabbits in other testing laboratories. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 40 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 1200 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg. Because there are no adequate and well-controlled studies in pregnant women, PERFOROMIST Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women should be advised to contact their physician if they become pregnant while taking PERFOROMIST Inhalation Solution.

Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of PERFOROMIST Inhalation Solution during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, PERFOROMIST Inhalation Solution should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if PERFOROMIST Inhalation Solution is administered to nursing women. There are no well-controlled human studies of the use of PERFOROMIST Inhalation Solution in nursing mothers.

Women should be advised to contact their physician if they are nursing while taking PERFOROMIST Inhalation Solution.

Pediatric Use

PERFOROMIST Inhalation Solution is not indicated for use in children. The safety and effectiveness of PERFOROMIST Inhalation Solution in pediatric patients have not been established. The pharmacokinetics of formoterol fumarate has not been studied in pediatric patients.

Geriatric Use

Of the 586 subjects who received PERFOROMIST Inhalation Solution in clinical studies, 284 were 65 years and over, while 89 were 75 years and over. Of the 123 subjects who received PERFOROMIST Inhalation Solution in the 12-week safety and efficacy trial, 48 (39%) were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of PERFOROMIST Inhalation Solution has not been studied in elderly subjects.

CLINICAL STUDIES

Adult COPD Trial

PERFOROMIST (formoterol fumarate) Inhalation Solution was evaluated in a 12-week, double-blind, placebo- and active-controlled, randomized, parallel-group, multicenter trial conducted in the United States. Of a total enrollment of 351 adults (age range: 40 to 86 years; mean age: 63 years) with COPD who had a mean pre-bronchodilator FEV_1 of 1.34 liters (44% of predicted), 237 patients were randomized to PERFOROMIST Inhalation Solution 20 mcg or placebo, administered twice daily via a PARI-LC Plus® nebulizer with a PRONEB® Ultra compressor. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (at least 10 pack-years), age (at least 40 years), and spirometry results (pre-bronchodilator baseline FEV_1 at least 30% and less than 70% of the predicted value, and the FEV_1/FVC less than 70%). About 58% of patients had bronchodilator reversibility, defined as a 10% or greater increase in FEV_1 after inhalation of 2 actuations (180 mcg) of albuterol from a metered dose inhaler. About 86% (106) of patients treated with PERFOROMIST Inhalation Solution and 74% (84) of placebo patients completed the trial.

PERFOROMIST Inhalation Solution 20 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated at endpoint (week 12 for completers and last observation for dropouts). Similar results were seen on Day 1 and at subsequent timepoints during the trial.

Patients treated with PERFOROMIST Inhalation Solution used less rescue albuterol during the trial compared to patients treated with placebo.

Examination of age (≥ 65 or younger) and gender subgroups did not identify differences in response to PERFOROMIST Inhalation Solution. There were too few non-Caucasian subjects to assess differences in populations defined by race adequately.

In the 12 week study, 78% of subjects achieved a 15% increase from baseline FEV_1 following the first dose of PERFOROMIST Inhalation Solution 20 mcg. In these subjects, the median time to onset of bronchodilation, defined as 15% increase in FEV_1, was 11.7 minutes. When defined as an increase in FEV_1 of 12% and 200 mL, the time to onset of bronchodilation was 13.1 minutes after dosing. The median time to peak bronchodilator effect was 2 hours after dosing.

Mylan

Mylan Specialty L.P., Napa CA 94558

U.S. Pat. No. 6,667,344

U.S. Pat. No. 6,814,953

PER-2013-0125

CMS investigating doctors' use of incentive programs

BY CHARLES FIEGL
IMNG Medical News

Medicare has hired a contractor to ferret out and recover improper bonuses paid to physicians for quality reporting and electronic prescribing efforts.

Under a $9.9 million contract, Arch Systems of Baltimore will validate the accuracy of data submitted to the Electronic Prescribing Incentive Program (eRx) and Physician Quality Reporting System (PQRS), specifically

Since the inception of the PQRS and eRx incentive programs, reports have uncovered data-integrity issues and suspicious attempts of 'gaming' the system to earn the incentive payments.

targeting quality data submitted through registries and the group practice reporting option. Data submitted via the widely used claims-based reporting option could be included in subsequent reviews.

"Since the inception of the PQRS and eRx incentive programs, there have been reports uncovering data-integrity issues and misunderstandings regarding data submissions, and suspicious attempts of 'gaming' the system to earn the PQRS and/or eRx incentive payment," according to documents from the Centers for Medicare and Medicaid Services. "Despite extensive education and outreach efforts, mandatory support calls, and special training sessions, these data issues persist."

The data have been validated once already, CMS spokesperson Don McLeod said in an interview. During these checks, the agency discovered issues in which information submitted by eligible providers did not match data in the agency's records.

"The intent is to ensure that the data that is used by aligning programs [such as the Physician Value Based Payment Modifier or the Physician Compare website] is accurate and valid," he said.

Most registries are run by third parties, but all are certified by CMS. The agency is seeking to verify that the data sent by registries on behalf of providers are accurate.

Physicians have been encouraged to incorporate registries into their practices because of the potential to improve quality at the point of care, according to Dr. Bruce Bagley, interim president and CEO of TransforMED, a subsidiary of the American Academy of Family Physicians. Some registries can produce a list of patients with a

Physicians have been encouraged to incorporate registries into their practices.

DR. BAGLEY

specific condition, give a snapshot of applicable quality measures, and show gaps in care.

The scope of the review raises a concern of creating another program similar to the CMS recovery audit contractors program, said Dr. Richard Duszak Jr., a Memphis radiologist and chief medical officer of the Harvey L. Neiman Health Policy Institute at the American College of Radiology. The RAC program poses a significant administrative burden for practices as they seek to recoup overpayments to physicians and hospitals. RAC audits have forced providers to return $5.4 billion since October 2009.

Dr. Duszak and Dr. Bagley said they that have not heard of instances of fraudulent quality reporting. If anything, physicians have struggled with capturing clinical encounters that could be reported for quality measures used to earn bonuses, Dr. Duszak said.

"The auditor will find, far and away, the underreporting of metrics for services that were truly performed," Dr. Duszak said.

He also questioned why practices would "game" the system. Reporting PQRS and eRx encounters is difficult and the paperwork is burdensome, he said.

In 2011, 266,521 eligible professionals earned PQRS incentives that averaged $1,059 and totaled $240.4 million, according to data released by the CMS in April. About $270 million in eRx bonuses was paid to 174,189 health care providers that year. For PQRS, nearly 63,000 providers used registries while just 92 practices sent data via the group practice reporting option.

Continued on following page

Continued from previous page

PQRS data will be critical going forward as the CMS uses quality reporting for its value-based modifier program, said Brian Whitman, associate director of regulatory affairs at the American College of Cardiology. The ACC maintains a PQRS registry for its members and has been supportive of using it to submit data and improve quality of patient care.

"This is only going to become more important as they apply 'teeth' to the program through the value-based modifier program," said Mr. Whitman.

The modifier will be used to adjust Medicare pay for physicians practicing in groups of 100 or more eligible health care providers – a total of about 216,000 medical doctors in 1,100 groups – in 2015.

Those physicians who do not participate in PQRS or decline to have the CMS calculate group performance based on quality measures on administrative claims in 2013 could see their payments cut by 1% in 2015.

CMS has proposed expanding the modifier to 491,000 physicians in groups of 10 or more eligible professionals in 2016. That proposal could be finalized in the 2014 Medicare physician fee schedule, expected later this fall.

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: In their inimitable way, the Centers for Medicare and Medicaid Services has announced that once again they are concerned there is doctor fraud occurring in two of their recent incentive programs. They have set up another watchdog group by contracting with a company to validate the accuracy of the data from the complex and burdensome paperwork required by practices to incorporate patient registries in the PQRS and eRx programs, which are hoped to improve the quality of care. The average incentive earned by physicians in 2011 was slightly over $1,000, which likely doesn't even cover the increased administrative costs for their practices. Ultimately the PQRS data will be used to administer their upcoming value-based modifier program. If indeed CMS finds little actual fraud, it is highly unlikely they will publicly announce that doctors are participating in an honest and ethical manner in another of their onerous programs.

Plan to repeal SGR emerges with bipartisan support

BY MARY ELLEN SCHNEIDER
IMNG Medical News

A new bipartisan, bicameral plan to repeal the Medicare Sustainable Growth Rate formula has surfaced on Capitol Hill.

On Oct. 30, the Senate Finance Committee and the House Ways and Means Committee jointly released a legislative framework that would scrap Medicare's Sustainable Growth Rate (SGR) formula and freeze physician payments for the next decade.

'This discussion draft is an important step in a long-term solution to this failed policy.'

REP. CAMP

Starting in 2017, physicians would see their payments tied to cost and quality of care using a single quality incentive program. Under the proposal, Medicare would create the Value-Based Performance Payment Program to adjust physician payments based on quality, resource use, clinical practice improvement activities, and the use of electronic health records.

Since the program is budget neutral, some physicians would see increases while others would see cuts.

At the end of 2016, Medicare would end a group of existing incentive programs including the Physician Quality Reporting System; the Value-Based Modifier Program; and the Electronic Health Record (EHR) Incentive Program, which requires the meaningful use of certified EHR technology.

Physicians who treat few Medicare patients or who receive a significant portion of their payments from advanced alternative payment models, such as accountable care organizations, would be excluded from the new Value-Based Performance Payment Program. Physicians in ACOs and other models that involved taking on financial risk and reporting on quality measures would instead be eligible for bonus payments under the proposal.

After 2023, physicians who participate in these advanced alternative payment models would see an annual 2% payment increase, and other physicians would earn updates of 1% each year, according to the proposal circulated by the two committees.

"This discussion draft is an important step in a long-term solution to this failed policy," Rep. Dave Camp, chairman of the House Ways and Means Committee, said in a statement. "Creating a policy that rewards providers for delivering high-quality, efficient health care is the ultimate goal, and this draft brings us one step closer to that reality." The release of the proposal follows a summer of feverish activity in the House on the issue of the SGR. After months of hearings, the Energy and Commerce Committee unanimously approved a bill on July 31 (H.R. 2810) that would repeal the SGR and provide 0.5% payment increases for physicians through 2018.

Congress understands that 'ending the failed SGR this year is fiscally responsible.'

DR. HOVEN

Momentum slowed after Labor Day with the continuing debate over the Affordable Care Act and the federal government shutdown that began on Oct. 1. This latest plan incorporates ideas from both the Democratic-led Senate and the GOP-controlled House.

While physician groups were still reviewing the proposal at press time, they hailed the renewed focus on the SGR as a move in the right direction.

"Congress is demonstrating that they understand that ending the failed SGR this year is fiscally responsible, and that the current Medicare payment system is a barrier to adoption of health care delivery and payment reforms that will improve health care for America's seniors and rein in overall costs," Dr. Ardis Dee Hoven, president of the American Medical Association, said in a statement.

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What does reform's rocky rollout mean for pulmonary medicine?

TERRY RUDD/IMNG MEDICAL MEDIA

The American College of Chest Physicians' Dr. Scott Manaker and Dr. Akram Khan offer their perspectives on the Affordable Care Act's current woes, and on what health reform will mean for physicians and patients down the road.

Scan the code to watch a video interview at chestphysician.org.

POLICY & PRACTICE

For more health reform news, visit chestphysician.org.

NHLBI launches new centers

The National Heart, Lung, and Blood Institute has created a $31.5 million research initiative that will target technologies to improve the diagnosis, treatment, and prevention of heart, lung, blood, and sleep disorders. The NHLBI's new Centers for Accelerated Innovations includes three separate centers in three regions – Boston, Ohio, and California. The centers are designed to move early-stage biomedical innovations from the research laboratory to commercial development and successful deployment to patients. "These centers essentially will offer a one-stop shop to accelerate the translation of early-stage technologies for further development by the private sector and ultimate commercialization," NHLBI Director Gary Gibbons said in a statement.

ACOs linked to large groups

Accountable care organizations are more likely to form in areas where primary care physicians practice in large groups, a study published in Health Affairs finds. The study, from the RAND Corp., also found that hospital risk-sharing or capitation payment agreements and larger integrated hospital systems were more common in areas where many ACOs have formed. Meanwhile, area income, Medicare per capita spending, Medicare Advantage enrollment rates, and physician density were not associated with ACO formation. "We found that increased provider integration appears to be a key marker of where ACOs are forming," the authors wrote.

Less out-of-pocket spending

Most consumers who get new insurance under the Affordable Care Act should see their out-of-pocket spending for medical care fall, according to a RAND Corp. study. Uninsured people who get new coverage under state Medicaid programs will see the most pronounced drop in annual out-of-pocket spending – from an average $1,463 to $34. However, some people may see their out-of-pocket medical expenses rise, too. Those who will be newly insured and who do not qualify for government subsidies are most likely to pay more overall, since they will be paying premiums for health coverage as well. The authors estimated these individuals would see their out-of-pocket costs rise from $5,368 to $7,202, on average. Low-income people who live in states that don't expand Medicaid also likely will pay more, regardless of whether they remain uninsured or buy insurance on the exchanges, the study found.

Medicaid expansion covers more

Two-thirds of the uninsured population in states planning to expand Medicaid will receive health insurance help from either Medicaid, the Children's Health Insurance Program, or federal exchange subsidies, compared with only 38% of uninsured people in states opting out of the Medicaid expansion, a Robert Wood Johnson Foundation report finds. In total, more than 6 million more uninsured people will be eligible for help in the 25 states, plus the District of Columbia, that elected to expand Medicaid when compared to states that will not expand Medicaid, the report finds. There's huge variation in the percentages of people who will receive help: A total of 81% of the uninsured will receive help in Kentucky, a state that will expand Medicaid, compared with 34% of the uninsured who will be helped in Texas, a state that won't expand Medicaid, the report says.

Med school conflicts remain

U.S. medical schools have made significant progress to strengthen their management of clinical conflicts of interest, but most schools still lag behind national standards, according to a study from the Institute on Medicine as a Profession. The study, published in Academic Medicine, follows a 2008 IMAP study, which showed few medical schools had strong policies to regulate common physician-industry exchanges. The most recent study shows that schools have taken steps to better manage physicians' ties. However, nearly one-third of medical schools still have no policy prohibiting ghostwriting, while a majority have no policies or permissive policies for drug samples or industry-funded continuing medical education, consulting, honoraria, and speakers bureaus, the study shows. "There has been a broad and rapid transformation in how academic medicine manages industry relationships since we looked at this in 2008, but much room for improvement remains," said coauthor and IMAP President David Rothman, Ph.D., in a statement.

–Jane Anderson

Who's at the door? Prepping for new ACA patients

BY MARY ELLEN SCHNEIDER
IMNG Medical News

Millions of Americans can now purchase health insurance through the federal and state exchanges. But while interest is high, no one knows for sure just how many people will end up enrolling in a plan.

And the bigger question for physicians is how many patients will show up in their offices early next year when coverage starts.

The answer may depend on where you live, according to Paul B. Ginsburg, Ph.D., an economist and president of the Center for Studying Health System Change.

HEALTHCARE.GOV

Problems with healthcare.gov website – the health insurance exchange for Americans in most states – added to uncertainty about the new program.

Multiple factors dictate demand

States with the highest number of uninsured residents are likely to have the most people entering the insurance market, Dr. Ginsburg said. But the expansion of Medicaid is also a factor.


DR. GINSBURG

As originally enacted, much of the increased insurance coverage under the Affordable Care Act was to come from the expansion of Medicaid. That changed when the Supreme Court gave states the choice of whether or not to expand eligibility for their programs; so far 25 states are actively moving forward with expansion.

Texas has one of the highest rates of uninsurance in the nation, but is not expanding its Medicaid program. Arkansas, Arizona, and New Mexico – all with high rates as well – are.

The exchanges will allow some patients in the system – who are currently without coverage – to gain insurance, said Dr. Reid B. Blackwelder, president of the American Academy of Family Physicians (AAFP). This should provide some relief for struggling physicians, he said.

In a survey of members, the AAFP found that family physicians provide free or reduced rate visits for uninsured or underinsured patients an average of 10 times a week.

Tough for solo practices

So who will be coming through the front door? Experts say it will be both the sick and the healthy.

The ACA's preventive care benefits make it easier for healthy patients to come in for mammograms and colonoscopies, said Jennifer Caudle, D.O., of Washington Township, N.J. But she predicted that physicians will also see patients who have been out of the health care system for years and have uncontrolled chronic illnesses.

That's what Dr. Richard Dupee saw when Massachusetts enacted its health reform law in 2006.

"Some pretty serious train wrecks came in here," said Dr. Dupee, a solo primary care physician in Wellesley and president of the Massachusetts chapter of the American Geriatrics Society. Overall, he added, Massachusetts is seeing better outcomes for conditions such as diabetes. But the downside is that physicians still don't get paid adequately to provide intensive visits.

"There's no such thing as the 1-hour doctor visit anymore because no one will pay for it," he said.

At his office, which operates as a patient-centered medical home, they work to get complex patients to come in for a series of visits and have them seen initially by either a nurse practitioner or a physician assistant.

Dr. Dupee recommended that physicians who believe they will see an influx of new, potentially sicker patients consider restructuring the way they provide care.

"If you're a single doc, you can't do it," he said.

Redesigning care

Dr. Blackwelder suggested that practices will need to look at different ways to meet patients' needs.

For example, a patient may come to the office with a list of 10 or so questions that he or she would like addressed in a single visit. If the physician has an online patient portal that links to the electronic health record, the patient could winnow that list by viewing lab results and requesting medical refills outside of the office visit structure.

Using existing staff effectively also will be important, according to Dr. Douglas Curran of Athens, Tex.

Dr. Curran, who is part of a 14-physician group, has no plans to make significant investments in staff or technology. "We've got enough flexibility," he said. "We think we can accommodate a lot of these patients."

Instead, he's talking to insurers to figure out which health plans will be available in his area and he's talking to patients to find out who is signing up for insurance.

Dr. Curran said that he is not expecting to see thousands of new patients show up on Jan. 1. Instead, he predicted that there would be a gradual drift in much the same way as when a new employer enters the community and people gain coverage and begin seeking care.

Doubts about the ACA rollout

Not all physicians are positive about the health care law rollout. A new survey conducted by the Medical Group Management Association (MGMA) found that many medical practices have concerns about low payment rates and administrative burdens. And they are still weighing their options when it comes to participation in the new insurance products being sold on the exchanges.

The survey, which included responses from more than 1,000 medical practice executives and administrators, found that about 56% had an unfavorable view of the impact that the ACA's insurance exchanges will have on their practices. About 28% were neutral and 16% had a favorable view.

Less than a third of the practices responding said they planned to participate in the new exchange plans, while 14% said they would not. Most respondents were still evaluating whether to participate.

Conservative groups such as the Heritage Foundation have seized on the results as proof that the ACA rollout is doomed to fail because doctors won't show up.

But Anders M. Gilberg, senior vice president of government affairs for MGMA, said the findings reflect the uncertainty that practices are facing, since many are still awaiting complete information from health plans about the size of their networks and the payment rates.

"You can't make business changes if you don't know what you're dealing with," he said.

The 30% of survey respondents who said they plan to participate have probably received fairly comprehensive information about the fee schedule that made them comfortable enough to sign a contract, Mr. Gilberg said.


MR. GILBERG

He urged physicians who have not yet heard from area insurers to be proactive.

Reach out to any plans with which they already contract. Find out if they will be offering plans on the exchange and if they have an "all product" clause that requires physicians to be part of all their plans. Be vigilant about any addendums that the plans send that may require participation in the new products. This is a critical time to read all the fine print from insurers, he said.

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VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: Be prepared to change and adapt, or follow the dinosaur.

Forewarned is forearmed.

ACCP has evolved and so has our identity

BY SUE REIMBOLD
Senior Vice President, Marketing and Communications

As the American College of Chest Physicians continues to evolve and advance, so does the need to communicate these changes to the clinicians ACCP serves – worldwide. That is why the College's logo and visual identity system have a new appearance, which was launched at CHEST 2013 and reflected in the updated cover of this issue of *CHEST Physician*.

It's not unusual for an organization to update its logo from time to time, to keep it contemporary. Consider how both the NFL shield and AT&T logo have evolved over the years.

The American College of Chest Physicians logo – last updated more than 10 years ago, featured a heart and lungs, plus the color red, typically identified more closely with cardiac issues than with pulmonary, critical care, and sleep medicine. The organization's new logo features bold new colors plus an updated symbol of a chest, while keeping what was most familiar about ACCP's identity – the word CHEST.

"Often referred to as CHEST by clinicians, ACCP is a trusted and essential connection for our members," stated Paul Markowski, Executive Vice President and CEO. "We desired a strong identity that readily distinguishes us as such."

The new symbol represents a chest and illustrates connectivity and the gathering of international experts in a genuine, collaborative exchange of ideas and knowledge. The new color palette is current, fresh, and vibrant, reflecting ACCP members' forward-looking approach to the work they do. Both the symbol and the CHEST signature are clean and bold, strong marks that mirror ACCP's commitment to transparent and relevant communications, building on the trust chest medicine experts have in the CHEST brand.

Beyond the CHEST annual meeting and *CHEST Physician*, over the next several months clinicians can expect to see ACCP's new visual identity applied to the College's educational courses and products, to Web and social media sites, as well as to the journal, *CHEST*. The new logo also is being adopted by The CHEST Foundation and CHEST Enterprises, helping to strengthen the organization through consistent branding.

Help support The CHEST Foundation's important work

Each year, The CHEST Foundation funds vital clinical research and education grants, coordinates youth tobacco prevention outreach events in schools, creates and distributes patient education materials in multiple disease states, and supports ACCP members working on humanitarian projects.

As this season of giving begins, consider adding The CHEST Foundation to the list of organizations you support.

Your donations can help the "Bring the Foundation's Lung Lessons®"– an interactive tobacco prevention program – to a classroom, designed with the goal of keeping children tobacco free. They can also help The Foundation create and distribute lung cancer patient education brochures, or cover the cost of a 1-week supply of asthma medications for a rural community in Nigeria, provided through The CHEST Foundation's Humanitarian Awards.

These are just some examples of how you can help make a difference in the lives of future grant and award recipients and the patients and the public served by our outstanding programs and activities.

In order to take advantage of a tax deduction in 2013, please make your contributions by December 31, 2013.

Donate online by visiting www.onebreath.org. Click the "Donate" tab at the top. If you prefer to send a check by mail, send your check to: The CHEST Foundation, Attn: Annual Fund Manager, 3300 Dundee Rd., Northbrook, IL 60062.

If you have any questions, please contact Patti Steele, CHEST Foundation Annual Fund Manager, at psteele@chestnet.org or by phone: (224) 927-5202.

Make it a new favorite: Chestphysician.org!

Welcome to chestphysician.org! You've read *CHEST Physician* for almost 8 years, and now an exciting complementary website has been launched to extend the capabilities of the publication and to offer you the very latest in breaking news and economic trends.

From clinical news and ACCP events to practice management, annual meeting highlights, and the COPD Hub, the site will bring you to the forefront of clinical chest medicine. The new COPD Hub updates clinicians on the latest pulmonary medicine news based on research and clinical advances presented at medical conferences and meetings, news conferences and regulatory meetings of the FDA, and in medical specialty journals. COPD Hub is powered by IMNG Medical Media, the leader in medical specialty news for nearly 50 years.

Log on today, and explore all that this new website has to offer.

This Month in CHEST: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

COMMENTARY
Developing a New, National Approach to Surveillance for Ventilator-Associated Events: Executive Summary. *Dr. Sherry S. Magill et al.*

GO-WITH EDITORIAL
Quality Measures for Critically Ill Patients: Where Does Ventilator-Associated Condition Fit In? *By Drs. Craig M. Lilly; and Richard T. Ellison III.*

Cumulative Total Effective Whole-Body Radiation Dose in Critically Ill Patients. *By Dr. D. J. Rohner et al.*

Effects of OSA Treatment on BP in Patients With Resistant Hypertension: A Randomized Trial. *By Dr. R. P. Pedrosa et al.*

Left Ventricular Ejection Time in Acute Heart Failure Complicating Precapillary Pulmonary Hypertension. *By Dr. B. Sztrymf et al.*

Factors Affecting Quality of Anticoagulation Control Among Patients With Atrial Fibrillation on Warfarin: The SAMe-TT$_2$ R$_2$ Score. *By Dr. S. Apostolakis et al.*

Use your voice! ACCP survey influences RVU decisions

BY JEANNA STOVALL, MSA, RHIA
CHEST Regulations and Reimbursement Director

Have you ever received a member survey from the ACCP and wondered what to do with it, or pondered why you should take valuable practice time filling it out? This message is for you, so keep reading.

When Medicare transitioned to a physician payment system based on the Resource-Based Relative Value Scale (RBRVS), the American Medical Association (AMA) convened a multispecialty committee known as the **R**elative Value Unit (RVU) **U**pdate **C**ommittee, or RUC. The RUC provides the medical community a voice in describing the necessary resources required to provide physician services to your patients. RUC recommendations are carefully considered by the Centers for Medicare and Medicaid Services (CMS) in assigning values to physician services.

The RUC recommendations to CMS are made from an analysis of data collected via specialty society surveys of members, just like you. A specialty society, like the ACCP, surveys their membership about various procedures in efforts to adequately evaluate the RVUs of physician work, direct practice expenses (clinical staff time, supplies, and equipment), and malpractice expenses. Surveys probe the level of physician physical effort, technical skill needed to perform service, time in providing service, mental effort, medical judgment, and stress. All of these factors have value and are accounted for in assigning an RVU to a procedure.

Give pause and think about the time and effort it takes to provide an excellent service to your patients before completing a survey. You have a voice, and the survey process is your stage to express your concern toward the value of codes.

The ACCP is currently seeking volunteers to participate in a survey on endobronchial ultrasound (EBUS) (Current Procedural Terminology [CPT] code **31620**). The online survey will take approximately 20 minutes to complete. The window for completing the survey will begin on November 6, 2013, and will close on November 22, 2013.

If you have practice experience with EBUS and would like to participate in the survey, please contact JeAnna Stovall at jstovall@chestnet.org. Include "EBUS Survey" in the e-mail subject line; in the e-mail body, include your full name, practice address, telephone number (including area code), and e-mail address.

Unveiling a new ACCP committee

BY JEANNA STOVALL, MSA, RHIA
CHEST Regulations and Reimbursement Director

Many have heard the saying that change is the only thing in life that is constant. In keeping with change, it gives me great pleasure to announce the unveiling of a new ACCP committee, the CHEST Reimbursement and Regulatory (CRR) Committee. The charge of this committee is to serve as subject matter experts in the understanding and development of educational content for members related to regulatory and reimbursement issues of high importance in ACCP's scope of medicine.

Dr. James Parish, FCCP, has been appointed as Chair, and Dr. Kevin Chan, FCCP, has been appointed as Vice-Chair of the CRR Committee. A call for nominations was distributed to ACCP membership via e-mail, newsletter, and website. From these communications, the call for nominations has been well-received, garnering multiple responses for vacant committee member seats through November 4, 2013.

Staff of the CRR Committee have initiated restructuring and constitution of the committee with the creation of committee documents that were reviewed and vetted at our first formal meeting during CHEST 2013.

The CRR Committee looks forward to a successful year and will keep you abreast along the way.

Clinical Trials Registry: A free service from ACCP

Visit chestnet.org to learn about participating in industry trials.

The ACCP Clinical Trials Registry is a free service that helps connect physicians and their patients with ongoing clinical trials in respiratory disease being conducted by participating pharmaceutical companies. Participation in clinical trials provides an opportunity to advance and accelerate medical research and contribute to improved and effective care for patients.

The following is a list of industry clinical trials available on the ACCP website at chestnet.org/About-ACCP/Industry-Support/ACCP-Clinical-Trials-Registry.

PROSPERO

A Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab

Company: Genentech, Inc.
Clinical trial description: The PROSPERO registry is a prospective, observational study designed to examine baseline patient characteristics, including biomarkers, and to evaluate predictors of response to Xolair (omalizumab) treatment in patients with allergic asthma.
Type of patient needed: Patients who are 12 years of age or greater who are initiating treatment with omalizumab for allergic asthma and who have not been treated with omalizumab within the previous year.
Posted: October 11, 2013
ClinicalTrials.gov Identifier: NCT01867125

LAVOLTA I and LAVOLTA II

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients With Uncontrolled Asthma Who Are on Inhaled Corticosteroids and a Second Controller Medication

Company: Genentech, Inc.
Clinical trial description: LAVOLTA I and LAVOLTA II are two parallel phase III studies designed to evaluate the efficacy and safety of lebrikizumab in patients with uncontrolled asthma despite treatment with an inhaled corticosteroid and a second controller medication.
Type of patient needed: Adult patients with asthma who continue to have symptoms after receiving treatment with an inhaled corticosteroid and a second controller medication for at least 6 months may be considered for these clinical trials.
Additional information: Lebrikizumab is a monoclonal antibody that binds to and inhibits IL-13 activity.
Posted: October 10, 2013
ClinicalTrials.gov Identifier: NCT01867125

RIFF

A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients With Idiopathic Pulmonary Fibrosis RIFF

Company: Genentech, Inc.
Clinical trial description: The phase II study (RIFF) is designed to evaluate the safety and efficacy of lebrikizumab in patients with idiopathic pulmonary fibrosis (IPF). The primary outcome measure for the study is progression free survival.
Type of patient needed: Adult patients = 40 years of age with a definite diagnosis of IPF according to the 2011 ATS/ERS/JRS/ALAT consensus statement on IPF within the previous 4 years from the time of screening.
Additional information: Lebrikizumab is a monoclonal antibody that binds to and inhibits IL-13 activity.
Posted: October 10, 2013
ClinicalTrials.gov Identifier: NCT01872689

EXPECT

The Xolair Pregnancy Registry: An Observational Study of the Use and Safety of Xolair® (Omalizumab) During Pregnancy

Company: Genentech, Inc.
Clinical trial description: The Xolair Pregnancy Registry (EXPECT) is an observational study established by Genentech to obtain data on pregnancy outcomes in women who are exposed to Xolair® (omalizumab) during their pregnancy.
Type of patient needed: Women who have been exposed to at least one dose of Xolair within 8 weeks prior to conception or during pregnancy may be included in this registry.
Additional information: Pregnancy Category B. There are no adequate and well-controlled studies of Xolair in pregnant women.
Posted: May 14, 2013
ClinicalTrials.gov Identifier: NCT00373061

ACCP Past President receives Baylor Endowed Professorship

An ACCP Past President is the inaugural recipient of the The Frances K. Friedman and Oscar Friedman, MD, '36 Endowed Professorship for Pulmonary Disorders. Dr. Kalpalatha K. Guntupalli, FCCP, is an internationally recognized master clinician, educator, and scientist who has made numerous contributions to what is now state-of-the-art care of patients with ARDS and other life-threatening acute lung diseases.

Dr. Guntupalli is Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at Baylor College of Medicine.

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GEORGIA, Atlanta

The Atlanta VA Medical Center and Division of Pulmonary, Allergy & Critical Care Medicine at Emory University are seeking a physician-scientist or clinician-investigator to lead the VA Pulmonary Section. Candidates should be Assistant or Associate Professor with demonstrated success in laboratory or clinical research and a strong commitment to mentoring fellows and junior faculty. The VA Pulmonary Section includes 7 physicians with NIH and VA funded research and 3 VA career development awardees. The successful candidate will assume a leadership role integrating clinical and academic functions with the 50 full-time faculty and NIH funded training program of the Pulmonary Division in the Department of Medicine. Atlanta is a thriving metropolitan area. The VA Medical Center is adjacent to the campuses of Emory University and the Centers for Disease Control. Interested applicants should contact:

David M. Guidot, MD, Division Director, at 404-712-2970 or **dguidot@emory.edu** and apply online at **www.usajobs.gov**, announcement JV-13-238CW-874134 for consideration.

U.S. Department of Veterans Affairs

White River Junction Department of Veterans Affairs Medical Center (WRJVA)

The White River Junction Department of Veterans Affairs Medical Center (WRJVA) is seeking one full time BC/BE sleep physician to join our medicine service as a sleep physician, and to start the WRJVA's first sleep program. The physician should also be BE/BC in pulmonary and critical care medicine. WRJVA is a Carey Award-winning 60 acute care hospital providing healthcare to over 23,000 Vermont, New Hampshire, Upstate New York, and Western Massachusetts veterans.

Specialty services include cardiology, pulmonary gastroenterology, nephrology, endocrinology, neurology, advanced radiology, general and vascular surgery, orthopedics, urology, podiatry, psychiatry and hospice care. The ICU is a 7-bed unit. The WRJVA is closely affiliated with Dartmouth Hitchcock Medical Center (DHMC) and is a core teaching hospital of the Geisel School of Medicine at Dartmouth. Candidates will be eligible for a faculty appointment to the Geisel School of Medicine.

The ideal candidate will be a natural leader and possess skills necessary to start a sleep program from the ground level. She or he should possess excellent clinical skills, enjoy teaching, have a strong academic portfolio, and be dedicated to serving our nation's Veterans. The primary responsibility involves the development and ongoing oversight of all aspects of the sleep program including: the evaluation of patients in the clinic setting, supervision and interpretation of sleep studies, and monitoring of ongoing therapy. The physician must possess strong clinical skills to be a consultant on the pulmonary service and attend in the intensive care unit.

Salaries and benefits are commensurate with experience. We have a collegial staff which is committed to providing the highest quality care to our nation's Veterans. Local attractions include beautiful scenery, an academic community, year round sports, excellent schools, and a healthy lifestyle. Come join this exciting academic practice in beautiful New England!

For more information or to apply online, please use the following web address
https://www.usajobs.gov/Getjob/ViewDetails/3512276000
or e-mail **angel.garcialeon@va.gov**

UC Health

Director of Adult Cystic Fibrosis

The University of Cincinnati Division of Pulmonary, Critical Care and Sleep Medicine (PCCSM) has an open faculty position at the Assistant, Associate or Professor level for Director of Adult Cystic Fibrosis. The adult CF team comprises 3 physicians, a social worker, a nurse coordinator and a dietician who care for approximately 120 patients with CF and conduct clinical trials. The successful candidate will be M.D. or M.D., pHD trained, and will bring an established basic or translational research program that is funded or well positioned for funding.

An attractive package that includes laboratory or clinical program support and an endowed chair will be provided. The University of Cincinnati has a long history of exemplary basic and clinical science research within the College of Medicine and Cincinnati Children's Hospital Medical Center (CCMC), including robust clinical and research pediatric CF programs. The PCCSM Division is comprised of 30 full time faculty members and 12 fellows with broad subspecialty interests.

Please contact:

Frank McCormack, MD
Director, UC PCCSM
with a letter of interest and CV via e-mail at
frank.mccormack@uc.edu

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UC Health

University of Cincinnati Sleep Physician

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Candidates who are BC/BE in pulmonary and critical care medicine may also round on pulmonary outpatient and inpatient consult services, MICU services, and provide training for our fully accredited PCCM fellowship.

Please send curriculum vitae to:

Frank McCormack, MD
Division Director
Pulmonary, Critical Care & Sleep Medicine
University of Cincinnati
231 Albert Sabin Way
Cincinnati, OH 45267-0564
Telephone number (513) 558-4858
Email to Frank.mccormack@uc.edu

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New apnea risk study: RSV is not the only culprit

BY JENNIE SMITH
IMNG Medical News

A large prospective study of infants hospitalized for bronchiolitis has revealed a number of previously unknown risk factors associated with apnea, a potentially life-threatening complication.

While high preadmission respiratory rates were found associated with increased apnea risk, so were low respiratory rates, a surprising finding that investigators could not explain. Low room air oxygen saturation was seen as contributing to risk. And one usual-suspect risk factor in apnea – respiratory syncytial virus – turned out not to be more dangerous than other viruses in terms of apnea risk.

Clinicians should not be reassured by either a low respiratory rate or infection with an organism other than RSV in assessing apnea risk, said Dr. Alan R. Schroeder of the Santa Clara Medical Center in San Jose, Calif., and his colleagues.

At 16 study sites nationwide starting in 2007, the researchers collected enrollment and outcome data on 2,156 children under age 2 (median age 4 months, with age corrected for birth at less than 37 weeks). The patients were admitted with bronchiolitis over three consecutive winter seasons. Of these children, 108 (5%) developed apnea while hospitalized, according to the study, which was published online in Pediatrics (2013;132:1-8 [doi: 10.1542/peds.2013-1501]). The study was part of the Multicenter Airway Research Collaboration, a program of the Emergency Medicine Network.

The study confirmed the known risk factors of young corrected age, low birth weight, and previous apnea during the same bronchiolitis episode. Dr. Schroeder and his colleagues found that the statistically significant predictors of apnea included age of less than 2 weeks (odds ratio, 9.67) and 2-8 weeks (OR, 4.72), compared with age 6 months or older; birth weight of less than 2.3 kg (OR, 2.15), compared with birth weight of 3.2 kg or more; and previous apnea during the same bronchiolitis episode (OR, 3.63).

There also was risk associated with preadmission respiratory rates of less than 30 (OR, 4.05) and 30-39 (OR, 2.35), compared with 40-49, as well as a preadmission respiratory rate of 70 or more (OR, 2.26). Risk of apnea was also associated with having a preadmission room air oxygen saturation of less than 90% (OR, 1.60).

Apnea risk was shown to be similar across the major viral infections seen in the cohort. While more infants presented with RSV than with other viruses, there was roughly equal apnea risk seen among children infected with human rhinovirus, adenovirus, human metapneumovirus, coronavirus, enterovirus, and parainfluenza virus.

"These data suggest that using RSV status to drive admission decisions and admission locations (e.g., ward, step-down unit, ICU) due to apnea concerns may be misguided," Dr. Schroeder and his colleagues wrote in their analysis.

The study contained a number of other novel findings. While a recent, smaller study of 42 patients had suggested a possible protective effect associated with acetaminophen administered the week before hospitalization (Resuscitation 2012;83:440-6), the study by Dr. Schroeder and his colleagues found no such effect. It also shed light on the timing of apnea during the course of bronchiolitis.

While previous studies had shown apnea occurring early in the course of RSV infection, "our results challenge this notion," the authors wrote. One-third of the infants with apnea in the study began having difficulty breathing 4 or more days before the preadmission visit. "Furthermore, the time from the beginning of the 'difficulty breathing' to the preadmission visit was not different between children with and without apnea. Therefore, using the duration of symptoms to predict future risk of apnea or need for hospitalization may be problematic."

The investigators acknowledged as limitations of their study the possibility that the reported incidence of apnea may have been biased by oversampling of sicker patients, as the investigators recruited 20% of patients from intensive care. Some infants may have been included based on chart data that did not meet strict criteria for apnea, allowing for overreporting, they said, and apnea may have been harder to detect in intubated patients, leading to underreporting in this population.

The study was funded by the NIH. Dr. Schroeder and his colleagues reported no disclosures.

SLEEP STRATEGIES: The sticky situation of CPAP adherence

BY AMY M. SAWYER, PHD, RN

CPAP is the first-line medical treatment for OSA in adults. It has been shown to reduce or normalize the apnea-hypopnea index (AHI), oxygen desaturations, and arousals from sleep, which are characteristics of OSA. However, the practical benefits of CPAP are limited by patients' use of the treatment. Over the past 20 years, a large body of evidence suggests that average CPAP use is 4.7 h/night and that approximately 50% of adults prescribed CPAP are not adherent to therapy (*Sleep Med Rev.* 2011;15:343). These excessively high rates of nonadherence contribute to discordance between the high efficacy of CPAP and its far more modest effectiveness in clinical practice.


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Health-care providers and researchers historically depended upon self-reported CPAP use as the measure of treatment adherence. Unfortunately, this metric is now recognized as inadequate, as it typically overestimates actual use.

As CPAP manufacturers have continuously improved the devices to be more visually appealing, quieter, and smaller, they have also improved tracking systems to permit objective, real-time (via modem) or historical (via SD card) measurement of patients' use of treatment. This technology, nearly standard on all currently manufactured CPAP devices, includes a microprocessor that records all intervals of CPAP use after more than 20 min at effective pressure.

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This gold standard measure of CPAP adherence has permitted providers to identify patients as adherers or nonadherers based on objective documentation of their treatment use. However, the appropriate definition of CPAP adherence remains a controversial issue that warrants further consideration; unfortunately, there seems to be an absence of thoughtful, evidence-based consideration as to what should constitute CPAP adherence in our current classification strategy. It is imperative that providers, researchers, and third-party payers recognize that classifying individual patients as adherent or nonadherent is a function of the definition of CPAP adherence employed, which may not always correlate with functional or morbidity-related benefits.

Defining adherence as use greater than 4 h per night

The most commonly used definition of CPAP adherence is based on documentation of regular use of therapy at 4 h per night. There is little evidence that supports the utilization of this definition in the clinical setting; it seems that this definition of adherence has been widely employed based only on historic precedence.

Following the first description of CPAP in 1981, (Sullivan et al. *Lancet.* 1981;862), research studies identified the problem of adherence to CPAP as a significant limitation in the treatment of OSA, employing a definition of adherence of greater than 4 h per night of use. This adherence cutpoint has commonly been employed in subsequent studies, sometimes including the criterion "on 70% of nights." Similarly, clinical providers, third-party payers, and a number of CPAP manufacturer usage databases have also endorsed this classification strategy for CPAP adherence, despite the fact that there is mounting evidence since the first description of CPAP that CPAP treatment is best used for the total duration of sleep time (*Sleep Res Sleep Med.* 1995;18:195; *Respir Med.* 1998;92:28; *Chest.* 1991;100:156; *Am J Resp Crit Care Med.* 2011;184:1192).

Few adults sleep only 4 h per night, suggesting that defining CPAP adherence at anything equivalent to at least this amount of time may set too low a bar for most patients to achieve an optimal outcome.

Use as a percentage of sleep time

Recognizing that OSA is persistent during sleep and during periods of CPAP withdrawal, an alternative approach to classifying adherence is to base it on the patient's achievement of use during a certain percentage of total sleep time (TST). Interestingly, the current practice parameters and clinical guidelines do not explicitly state CPAP treatment is indicated for the duration of sleep time (*Sleep.* 2006;29:375; *J Clin Sleep Med.* 2009;15:263), even though providers routinely recommend CPAP use for the entirety of the sleep period on each and every night. Evidence to date clearly indicates re-emergence of OSA during CPAP withdrawal, along with its recurrent symptoms and detrimental physiologic effects (*Am J Respir Crit Care Med.* 2011;184:1192), further detracting from defining CPAP adherence at only 4 h nightly as sufficient.

Though identification of adherers and nonadherers by usage as a percentage of TST is untested to date, this classification strategy is highly consistent with our understanding of OSA and CPAP treatment efficacy evidence, including treatment withdrawal studies. Employing this approach is more complex than other methodologies, as simultaneous assessment of sleep duration would be necessary. This might be addressed by sleep diaries, concurrent actigraphy assessment, or self-reported sleep duration, though that this last option is potentially biased due to recall accuracy (or intentional misreporting). In the future, CPAP manufacturers may develop built-in applications to permit self-reported sleep time assessments in addition to the currently available subjective assessments of sleep quality embedded in some devices.

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Symptom control

The symptoms of sleep-disordered breathing vary between patients, though common complaints include excessive daytime sleepiness, memory impairment, emotional lability, and shortened attention span. Recent studies suggest that control of many of these symptoms is achieved in a dose-dependent fashion, related to the duration of daily treatment with CPAP, not dissimilar to the dose-response profiles of many medications. The necessary dose of CPAP needed to alleviate symptoms seems to vary with outcome of interest, with data existing for both subjective and objective sleepiness and functional impairment outcomes. Significant improvements in subjective sleepiness with CPAP exposure of 4 h per night, objective sleepiness with CPAP exposure of 6 h per night, and functional impairment with CPAP exposure of 7 h per night have been reported (Antic et al. *Sleep.* 2011;34:111; Weaver et al. *Sleep.* 2007;30:711).

Other specific symptoms, such as cognitive impairment, and physiologic outcomes such as blood pressure, have yet to be examined in dose-response studies. It seems appropriate to consider symptomatic control in the labeling of individual CPAP users as adherent or nonadherent, also recognizing that there is likely to be some individual variability in the "dose" of CPAP required for such control. This definition of adherence may be of particular benefit for those patients who are at high risk for injury and accidents, such as occupational drivers, heavy equipment operators, and long-distance commuters and those with comorbidities that are, in part, worsened by untreated OSA.

Moving toward evidence

The practice of classifying our clinic patients as adherent or nonadherent to CPAP therapy serves an important purpose – to define and implement follow-up strategies, including the frequency of visits and use of adherence promotion interventions. Though the most widely used approach of defining adherence (greater than 70% nights of assessment period with 4 h use or more) is easily applied in the clinical setting, it is not evidence-based and not consistent with OSA treatment recommendations. Emerging evidence supports the development of alternate definitions of adherence, which may be better suited as the basis for patient and provider recommendations in an era of quality- and outcome-based provision of care. It is imperative that such new definitions be thoughtfully considered, consistently applied, and therapeutically meaningful.

Only by approaching adherence classification in this way will resource-constrained environments, such as sleep centers and their affiliated outpatient clinics, be able to continue to deliver high-quality, cost-effective, and efficient follow-up care to the adult sleep apnea population.

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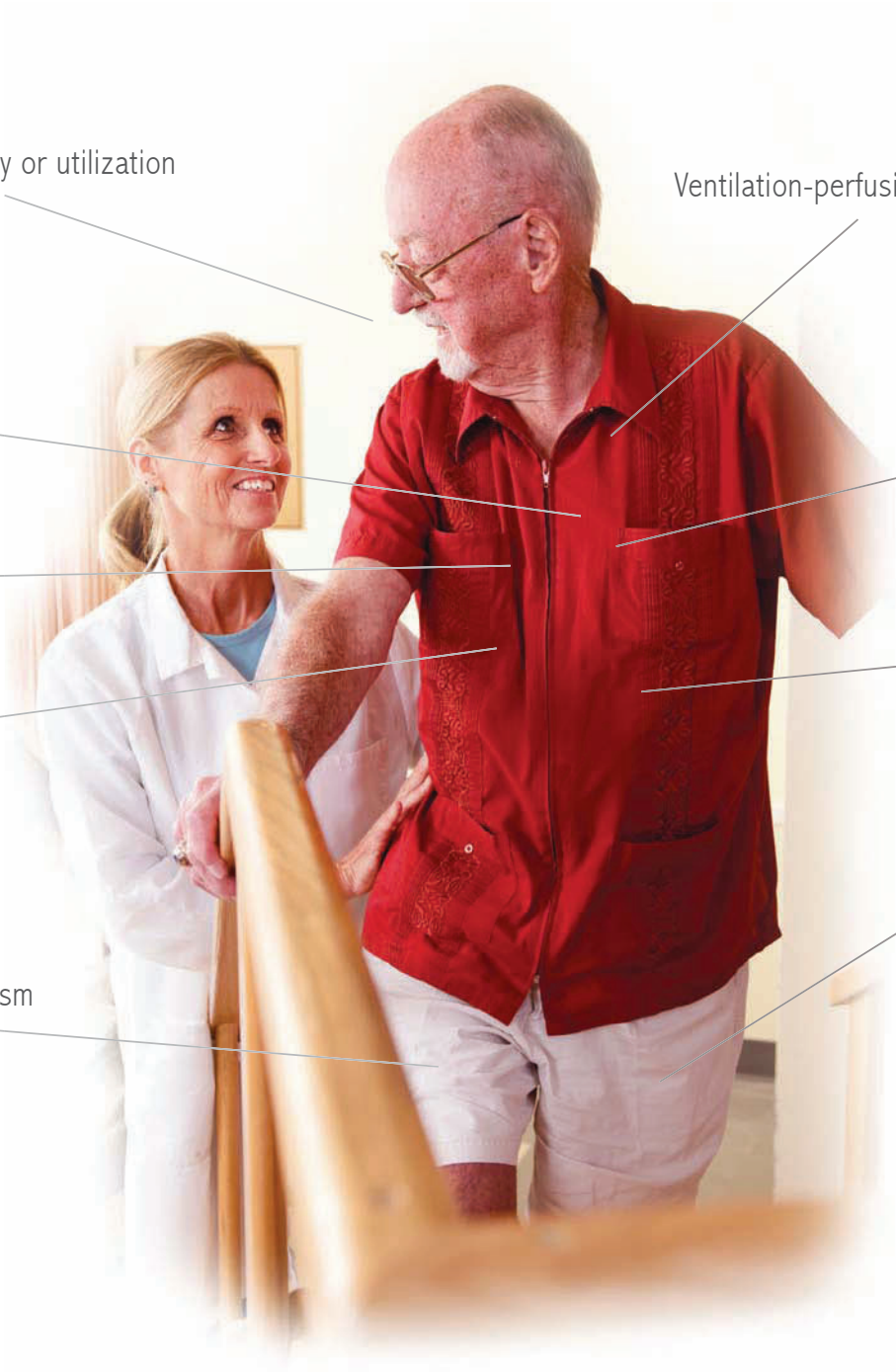

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