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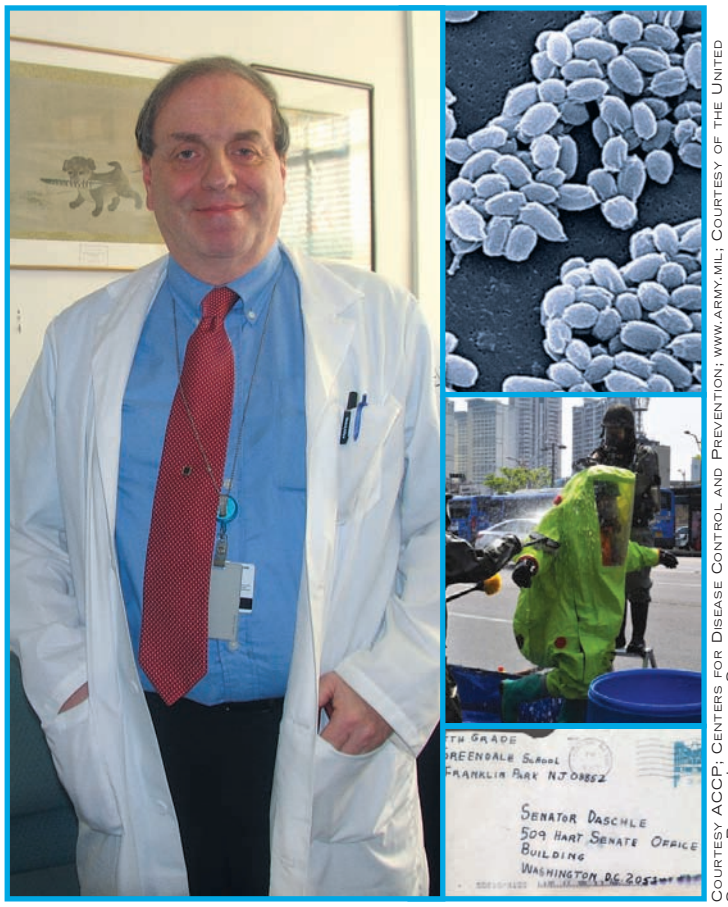

COURTESY ACCP; CENTERS FOR DISEASE CONTROL AND PREVENTION; WWW.ARMY.MIL; COURTESY OF THE UNITED STATES POSTAL INSPECTION SERVICE

Dr. Joseph R. Masci explores current awareness of biologic agents as a terror threat since anthrax-laced letters were found in 2001.

CRITICAL CARE COMMENTARY

Bioterrorism: How prepared are we?

BY DR. JOSEPH R. MASCI

In the weeks after terrorists crashed planes into the World Trade Center and the Pentagon on September 11, 2001, another, more insidious, attack began.

On Sept. 21, 2001, a letter leaking a gray powder was received in the America Media Incorporated building in Boca Raton, Fla. Three days later, the mailroom supervisor developed fever and chills. Three days after that, a photo retoucher who had handled the letter developed fever and cough during a trip

See **Commentary** • *page 12*

Phenotypes may increase targeted pulmonary therapies

Seeking the end of 'one size fits all' era.

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – Accurate phenotyping, in the ascendant over the last decade, equates with more effectively targeted treatments for chronic obstructive pulmonary disease, according to a proponent of personalized pulmonary medicine.

"We know that COPD is not the same, but right now we are treating these patients as though one size fits all," Dr. Nicola A. Hanania, FCCP, of the Baylor College of Medicine, Houston, said in a packed session on COPD at CHEST 2013.

Because phenotypes describe differences in individuals, they should have relevance to clinically meaningful outcomes. "In COPD, that relates to symptoms, exacerbation, disease progression, response to therapy, and survival," he said.

Potential phenotypes that have been identified according to clinical, physiologic, and radiologic criteria include chronic bronchitis, asthma/COPD overlap, frequent exacerbator, radiologic CT, and persistent systemic inflammation.

Chronic bronchitis

Chronic bronchitis tends to occur more in younger peo-

See **Hanania** • *page 22*

INSIDE

Under ACA, tripping over antitrust rules

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – Probably the last thing on the minds of office-based physicians is whether they are running afoul of antitrust regulations.

However, according to Dr. Edward J. Diamond, FCCP, a pulmonary specialist, a faculty member of the American College of Chest Physicians, and president of Suburban Lung Associates – a large network of pulmonary care offices near Chicago, physicians can add that to their list of concerns about the Affordable Care Act.

The danger zone, according to Dr. Diamond, is what's known as "clinical integration": pooling patient and protocol data for the

See **Regulations** • *page 31*

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Post-EBUS electrocautery improved node biopsy yield

BY WHITNEY McKNIGHT
IMNG Medical News

Endobronchial ultrasound–guided biopsies made after an electrocautery incision to the lymph node improved biopsy yields from 39% to 71% in 38 nodes, according to a small study presented at CHEST 2013.

"Because it is not always possible to pass biopsy forceps through defects in the lymph node – the literature indicates a failure rate of between 10% and 29% – we developed a novel technique," said presenter Dr. Kyle Bramley of Yale University, New Haven, Conn.

The technique employs EBUS, and involves passing an electrocautery knife activated at 40 W through the working channel of the scope in order to make an incision in the bronchial wall and enlarge the defect in the lymph node. This facilitates passage of the forceps into the node so that a larger biopsy sample can be obtained.

To test their technique, Dr. Bramley and his colleagues designed a prospective observational cohort study at a single tertiary academic medical center. Twenty patients (mean age, 68 years), including 11 women, who were undergoing EBUS were enrolled. An associated lung mass was present in 14 (70%) of the participants; 6 (30%) had isolated lymphadenopathy. One patient had prior lymphoma, and two others had prior lung cancer.

The researchers evaluated 68 nodes in all; 19 patients had nodes greater than 9 mm. Cautery was only used when initial attempts failed to biopsy nodes 9 mm or larger using EBUS-guided miniforceps of 1.2 mm.

The average node size biopsied using EBUS-transbronchial needle aspiration (EBUS-TBNA) was 5.7 mm.

Yields increased from 39% to 71% in 38 lymph nodes.

The average forceps-biopsied node was 15.8 mm.

In all, 23 nodes were biopsied successfully on the first pass using EBUS-TBNA only. The biopsies yielded diagnostic material such as lymphocytes, malignancy, or granulomas in 15 of these nodes.

Of the 15 nodes that required cautery, 12 yielded diagnostic material, and 3 had no diagnostic material.

The overall yield increased from 39% (15 out of 38) without cautery to 71% (27 out of 38) when cautery was used.

Notably, four patients had clinically relevant discrepancies between their cytologies and histopathologies. "In all four, TBNA provided a definitive diagnosis," said Dr. Bramley. "The forceps provided fibroconnective tissue or necrotic debris."

These results did not negate the efficacy of the cautery technique, according to Dr. Bramley. "We think we had a forceps issue … the 1.2 mm are flexible, but they were unable to push all the way through a tough lymph node capsule."

Dr. Bramley also said that other factors, including the operator learning curve, the smaller size of the nodes the investigators attempted to biopsy, and the "nonideal" population they were studying, contributed to these results.

He and his colleagues have since adjusted the procedure to make cauterization routine and to include a 1.9-mm transbronchial biopsy forceps needle, "which, incidentally, is a lot less expensive than the larger forceps we'd been using," he said.

Although more study is needed, Dr. Bramley said he and his team believed that this technique would be appropriate for future use in isolated mediastinal lymphadenopathy, especially with a low suspicion of non–small cell lung carcinoma; evaluation of lymphoma; and clinical trials requiring core biopsy.

Dr. Bramley reported having no relevant disclosures.

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VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: The authors have again proven that a larger pathology specimen obtained at the time of biopsy significantly improves diagnostic accuracy, especially in the setting of mediastinal nodes that are difficult to access and thus require an electrocautery incision through the airway in concert with EBUS guidance.

IN THIS ISSUE

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Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of *CHEST Physician*.

CHEST PHYSICIAN

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Now approved

Opsumit®

macitentan tablets 10 mg

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

ACTELION

Opsumit®
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

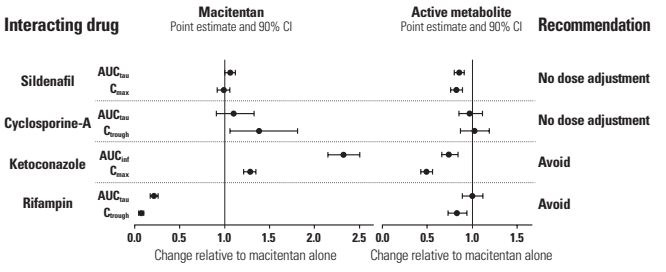
In vitro studies

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

ACTELION

BP therapy didn't boost survival in ischemic stroke

BY MITCHEL L. ZOLER
IMNG Medical News

DALLAS – Immediate blood pressure reduction in hypertensive acute ischemic stroke patients did not reduce death and disability after 14 days, but the strategy was safe and did not worsen patients 14-day outcomes, a randomized controlled study has shown.

The findings suggest that, among patients with relatively mild acute ischemic strokes and a systolic blood pressure of 140-219 mm Hg, "the decision to lower blood pressure with antihypertensive treatment should be based on individual clinical judgment," Dr. Jiang He said at the American Heart Association scientific sessions.

Elevated blood pressure immediately following an ischemic stroke poses a risk of hemorrhagic conversion or cerebral edema, but an elevated blood pressure also might be protective by forcing more blood into the penumbra around the stroke site. Blood pressure reduction measures are not appropriate for patients treated by reperfusion, but they are considered necessary for patients with "markedly elevated" blood pressure, generally defined as a systolic pressure of 220 mm Hg or higher, he said.

U.S. guidelines on stroke management published earlier this year noted that the data to guide recommendations for treating less severe arterial hypertension, in the range studied in this trial, are "inconclusive or conflicting," and that "the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established" (Stroke 2013;44:870-947). Some U.S. clinicians, however, take steps to reduce moderately elevated blood pressure in acute ischemic stroke patients, especially when systolic pressures are at or close to 200 mm Hg.

It was "reassuring" that the patients treated to lower blood pressure in this trial did not do any worse than those who went without blood pressure treatment, commented Dr. Cathy Sila, professor of neurology and director of the stroke and cerebrovascular center at Case Medical Center in Cleveland, who was the designated discussant for the report.

Based on the new findings, Dr. Sila proposed in her formal comments a strategy for managing patients with mild ischemic strokes who do not undergo reperfusion treatment and have a systolic pressure of 140-219 mm Hg more than 15 hours after their stroke onset and no major-vessel stenosis or occlusion. She suggested that a "reasonable" goal was to lower blood pressure by 10%-15% over the first 24 hours of treatment, with a goal blood pressure of less than 140/90 mm Hg within the next 7 days.

The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) randomized 4,071 patients aged 22 years or older with a confirmed ischemic stroke who did not undergo reperfusion treatment at 26 hospitals in China. Their average age was 62 years, they were seen an average of 15 hours after their stroke onset, and they had a median National Institutes of Health Stroke Scale score of 4.

The 2,038 patients randomized to blood pressure reduction received an intravenous angiotensin-converting enzyme inhibitor, enalapril, as their first-line treatment, followed by a calcium channel blocker as second-line treatment and a diuretic as a third-line agent. The objective was to reduce systolic pressure by 10%-25% within the first 24 hours, with a goal blood pressure of less than 140/90 mm Hg after 7 days.

The treatments were effective, resulting in an average 13% reduction in blood pressure in treated patients after 24 hours (an average drop of 22 mm Hg), and an average systolic pressure of 137 mm Hg after 7 days. The control patients had an average 7% reduction in their systolic pressure, an average reduction of 13 mm Hg after 24 hours, and an average systolic pressure of 147 mm Hg after 7 days. All of the differences were significant.

The study's primary endpoint was the rate of death or major disability (a modified Rankin score of 3 or higher) at 14 days or at the time of hospital discharge. This endpoint occurred in 34% of patients in both the intervention and control arms, reported Dr. He, professor of epidemiology at Tulane University in New Orleans. After 14 days or at discharge, the average modified Rankin score was 2 for patients in both treatment arms.

The report by Dr. He and his associates was published online in JAMA (2013;doi:10.1001/jama.2013.282543) concurrently with his presentation.

Dr. He and Dr. Sila said that they had no disclosures.

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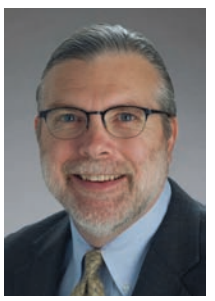
NASEEM S. MILLER/IMNG MEDICAL MEDIA

"Reassuring"': Dr. Cathy Sila says the lack of harm seen in new study findings should lead to a goal of 10%-15% blood pressure reduction over the first 24 hours. Watch a video of her comments online.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments:



I find it interesting that the authors put such a positive spin on these findings. Given that all medications and treatments have unintended side effects, a finding that intervention is no better or worse than nonintervention seems to provide an excellent rationale for avoiding those potential side effects. There is no logical reason to give a medication unless it is clearly going to benefit a patient.

Induced hypothermia after cardiac arrest questioned

BY MICHELE G. SULLIVAN
IMNG Medical News

Two new studies may cast some doubt upon the accepted belief that core cooling improves outcomes in unconscious cardiac arrest patients.

The studies, presented at the American Heart Association scientific sessions, found that neither cooling to hypothermic levels, compared with normothermic, nor cooling pre-hospital, compared with in-hospital, significantly lessened mortality or improved neurologic outcomes in more than 2,000 patients. The results were published simultaneously with the presentations at AHA.

Induced hypothermia is now standard of care for unconscious survivors of out-of-hospital cardiac arrests. Some animal models suggest that the earlier cooling begins, the better outcomes result. Dr. Francis Kim and his colleagues, however, found almost identical outcomes in a group of 1,359 patients, whatever the timing of hypothermia induction (JAMA 2013 Nov. 17 [doi:10.1001/jama.2013.282173]).

Dr. Kim of the University of Washington, Seattle, and his coauthors randomized patients to induction in the field and during transport versus upon hospital arrival. The intervention group received an infusion of up to 2 L of ice-cold normal saline, 7-10 mg pancuronium, and 1-2 mg diazepam, with a target temperature goal of 34° C.

In the control group, hypothermia induction occurred in the hospital, according to each site's protocol, with either surface or intravascular regimens. Patients were divided into two groups: those with ventricular fibrillation and those without. Patients without VF were older (68 vs. 62 years). Other baseline characteristics – includ-

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ing time from the call to the return of spontaneous circulation, heart rate, and blood pressure – were similar.

The in-field intervention decreased mean core temperature by about 1.2° C in patients with VF and 1.3° C in those without VF. These patients achieved the target core temperature of 34° C more than 1 hour sooner

Induced hypothermia did not increase the chances of survival after unconscious cardiac arrest.

DR. NIELSEN

than patients cooled in the hospital.

Survival to discharge was not significantly different between the intervention and control groups (63% vs. 64% of those with VF; 19% vs. 16% of those without VF).

Nor were there significant differences in the neurologic status of full recovery or mild impairment at discharge,regardless of the presence of VF, the investigators said.

The intervention carried some evidence of increased harm, the authors noted. Significantly more of the intervention patients rearrested during transport (26% vs. 21% of the controls). They also had significantly lower oxygenation, increased pulmonary edema on the first chest x-

Timing of hypothermia induction, either in the field or in the hospital, did not affect survival.

DR. KIM

ray, and greater use of diuretics in the first 12 hours of hospitalization.

"Rearrest possibly worsened brain ischemia that did not affect early mortality, but manifested as increased risk of death later during the hospitalization," investigators said.

The second study released at the AHA meeting questioned whether induced hypothermia confers significant benefit over maintaining a near-normothermic temperature. In this study of 939 patients, those cooled to 33° C had no better outcomes than those whose core temperatures were held at 36° C, Dr. Niklas Nielsen of Helsingborg Hospital, Sweden, and his associates reported Nov. 18 (N. Engl. J. Med. 2013 Nov. 17 [doi:10.1056/NEJMoa1 310519]).

The patients were a mean of 64 years old; most of them (about 75%) had VF as the first shocked rhythm. Spontaneous circulation returned a median of 25 minutes after the arrest. All were unconscious when they arrived at the hospital. The mean follow-up was 256 days.

During the first week of hospitalization, 247 patients (132 in the 33° group and 115 in the 36° group) had life support withdrawn. Reasons for withdrawal included brain death, multiorgan failure, and ethical concerns.

At final follow-up, 50% of patients in the 33° group and 48% in the 36° group had died – a nonsignificant difference. There were no significant differences in the composite outcome of death or poor neurologic outcome whether measured by the Cerebral Performance Category or the modified Rankin scales.

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Edoxaban comparable with warfarin in atrial fib

BY PATRICE WENDLING

IMNG Medical News

Two doses of the once-daily, oral factor Xa inhibitor edoxaban were noninferior to warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation in the phase III ENGAGE AF-TIMI 48 trial.

The primary endpoint of stroke or embolic events was seen in 1.50% of patients per year on well-controlled warfarin vs. 1.18% with edoxaban 60 mg (hazard ratio, 0.79; *P* less than .001 for noninferiority) and 1.61% with edoxaban 30 mg (HR, 1.07; *P* = .005 for noninferiority), Dr. Robert P. Giugliano reported at the American Heart Association scientific sessions.

Edoxaban also bested oral warfarin on the study's principal safety endpoint of major bleeding and significantly reduced bleeding and death from cardiovascular causes in the study, published simultaneously with the presentation (N. Engl. J. Med. 2013 [doi:10.1056/NEJMoa1310907]).

Edoxaban is currently approved only in Japan (Lixiana) for venous thromboembolism (VTE) prevention after major orthopedic surgery, although regulatory filings are expected in the United States, Europe, and Japan in 2014 following recent positive phase III results for the treatment and prevention of recurrent symptomatic VTE.

'Being the fourth kid on the block with no unique advantage might challenge its acceptability in clinical practice and marketability.'

Though positive, the results of ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48) do little to distinguish edoxaban from other novel oral anticoagulants entering the market, including the factor Xa inhibitors rivaroxaban (Xarelto) and apixaban (Eliquis), and the twice-daily direct thrombin inhibitor dabigatran (Pradaxa).

Approval of the lower dose of edoxaban is unlikely as it barely meets noninferiority for the primary endpoint in the intention-to-treat analysis (upper 95% confidence interval bound of 1.34; noninferiority margin of 1.38) – and ischemic stroke was significantly worse than warfarin (1.77% per year vs. 1.25% per year; HR, 1.41; *P* less than .001), observed cardiologist Dr.

Continued on following page

VITALS

Major finding: The annualized rate of stroke or embolic events was 1.50% with warfarin vs. 1.18% with edoxaban 60 mg (HR, 0.79) and 1.61% with edoxaban 30 mg (HR, 1.07).

Data source: A prospective, phase III study in 21,105 patients with moderate- to high-risk atrial fibrillation.

Disclosures: Dr. Giugliano and his coauthors reported grant support and other financial relationships with Daiichi Sankyo, the study sponsor. Dr. Kaul reported stock in Johnson & Johnson and consultancy for Boehringer Ingelheim.

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Sanjay Kaul of Cedars-Sinai Medical Center, Los Angeles.

High-dose edoxaban had the same ischemic stroke rate as warfarin, 1.25%.

Annualized rates of hemorrhagic stroke were 0.47% with warfarin, compared with 0.26% with high-dose edoxaban (HR, 0.54) and 0.16% with low-dose edoxaban (HR, 0.33; both *P* less than .001).

High-dose edoxaban also failed to meet superiority over warfarin for the primary endpoint in a prespecified intention-to-treat analysis (1.57% vs. 1.80%; HR, 0.87; $P = .08$), so a superiority claim won't be allowed.

"Marketability might be an issue, as the treatment advantage is not overwhelming," Dr. Kaul said in an interview. "Being the fourth kid on the block with no unique advantage might challenge its acceptability in clinical practice and marketability."

ENGAGE AF-TIMI 48 enrolled 21,105 patients with moderate- to high-risk atrial fibrillation. One-quarter had paroxysmal atrial fibrillation, median follow-up was 2.8 years, and the warfarin group was in the therapeutic range for a median of 68.4% of the treatment period.

Major bleeding occurred in 3.43% of patients per year with warfarin vs. 2.75% with edoxaban 60 mg (HR, 0.80) and in 1.61% with edoxaban 30 mg (HR, 0.47; both *P* less than .001), reported Dr. Giugliano of Brigham and Women's Hospital and Harvard Medical School, in Boston. The corresponding annualized rates of death from cardiovascular causes were, respectively, 3.17% vs. 2.74% and 2.71%, both nonsignificant differences.

Rates of the key composite secondary endpoint of stroke, systemic embolism, or death from cardiovascular causes were 4.43% with warfarin vs. 3.85% with high-dose edoxaban (HR, 0.87; $P = .005$) and 4.23% for low-dose edoxaban, which failed to reach statistical significance (HR, 0.95; $P = .32$), he noted.

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Edoxaban bested oral warfarin on the study's principal safety endpoint of major bleeding.

DR. GIUGLIANO

VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: The direct factor Xa (FXa) inhibitors have gained popularity for use in several indications, most notably for the prevention of stroke in patients with atrial fibrillation. There are several advantages of using these agents, particularly on the PT/INR monitoring which are challenging, especially to stroke patients with limited activities of daily living.

The Achilles' heel of these novel oral anticoagulants is the lack of an antidote, although research is ongoing currently. Widespread use of these agents will mainly depend on their formulary status in health plans as we are moving toward affordable and value-based care.

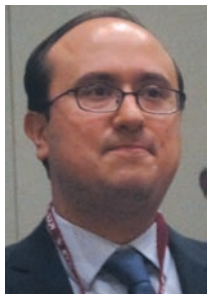
Biologics inch ahead in asthma treatment

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Targeted biological therapies are working in rheumatoid arthritis, cancer, and irritable bowel disease, leading some experts to question whether their time in asthma has finally arrived.

"We're still not there yet, but perhaps we can see the light at the end of the tunnel," Dr. Diego J. Maselli said at CHEST 2013.

Early successes in animal models of asthma have not translated to humans with asthma, in part because of disparities in immunology, biology, and anatomy, but also because of the heterogeneous nature of the disease.



Strong phase II results are being seen with dupilumab, which inhibits both IL-13 and IL-4 signaling.

DR. MASELLI

The benchmark so far for asthma biologics is the anti-immunoglobulin E (anti-IgE) monoclonal antibody omalizumab (Xolair), indicated for moderate to severe persistent asthma that is uncontrolled with inhaled corticosteroids.

Omalizumab gained approval after cutting exacerbations in two trials involving patients with a forced expiratory volume in one second (FEV_1) between 40% and 80% predicted, but the drug had no effect on exacerbations in a third trial that did not restrict screening FEV_1 and allowed use of long-acting $beta_2$-agonists. In all three studies, exacerbations were not reduced in patients requiring oral steroids as maintenance therapy or those with an FEV_1 over 80%.

There is now significant experience with omalizumab, and although there was a concern regarding a slight increase in the incidence of malignancy in the initial studies, large registries have shown no risk for malignant neoplasms or cardiovascular effects, said Dr. Maselli, of the University of Texas Health Science Center, San Antonio.

Promising results with several new agents, however, suggest that phenotypical markers such as IgE, eosinophils, and periostin are necessary to identify patients most likely to benefit from targeted therapy, he noted.

For example, the investigational interleukin-5 (IL-5) antagonist mepolizumab produced mixed initial results, but reduced asthma exacerbations over the course of 50 weeks from a mean of 3.4 to 2 in one study (N. Engl. J. Med. 2009;360:973-84), and by 48% over placebo in a second study when used in highly selected asthma patient populations with confirmed sputum or serum eosinophilia (Lancet 2012;380:651-9).

A recent meta-analysis (PLOS One 2013 March 27 [10.1371/journal.pone.0059872]) of seven mepolizumab studies echoed these findings, but also concluded the drug fails to significantly improve lung function, Dr. Maselli observed.

Provocative results from another

biologic suggest that the presence of nasal polyps in eosinophilic asthma may be useful in further selecting patients for IL-5 antagonist therapy. Intravenous treatment with the anti-IL-5 antibody reslizumab (Cinquil) had a greater effect on sputum eosinophilia and asthma exacerbations in poorly controlled asthmatics with nasal polyps (Am. J. Respir. Crit. Care. Med. 2011;184:1125-32).

Serum levels of the matricellular protein periostin are also being used to better target interleukin-13 (IL-13)-directed therapy, Dr. Maselli said. IL-13 induces bronchial epithelial cells to secrete periostin and is thought to play a central role in asthma by promoting mucus secretion and airway remodeling and hyper-reactivity.

Six monthly injections of the experimental anti-IL-13 monoclonal antibody lebrikizumab significantly improved lung function over placebo in asthmatics who were poorly controlled on inhaled corticosteroids, but produced a more robust increase in FEV_1 and a 60% reduction in exacerbations only in the subgroup with high pretreatment periostin levels (N. Engl. J. Med. 2011;365:1088-98). Interestingly, the investigators had hypothesized that high serum IgE plus high peripheral-blood eosinophil counts would serve as a marker for patients with high IL-13 expression.

To further complicate IL-13 blockade, a more recent lebrikizumab study in asthmatic patients not receiving inhaled steroids reported no meaningful differences in FEV_1 between various lebrikizumab dose groups and placebo in a periostin subgroup (J. Allergy Clin. Immunol. 2013;132:567-574.e12).

The investigational anti-IL-13 monoclonal antibody tralokinumab also recently failed to meet its primary endpoint of improving Asthma Control Questionnaire scores compared with placebo and modestly improved FEV_1 in a phase II study (Eur. Respir. J. 2013;41:330-8).

Finally, strong phase II results are being seen with dupilumab, a monoclonal antibody that inhibits both IL-4 and IL-13 signaling, Dr. Maselli said. Dupilumab cut exacerbations by a dramatic 87%, improved lung function, and decreased biomarkers associated with type 2 helper T-cell-driven inflammation in patients with elevated eosinophil levels and moderate to severe uncontrolled asthma despite use of glucocorticosteroids and long-acting beta-agonists (N. Engl. J. Med. 2013;368:2455-66).

"These agents allow clinicians to target specific asthma phenotypes with the aid of biomarkers such as IgE, eosinophilia, and periostin, and show a glimpse of what the future of 'personalized medicine' may offer," he said in an interview.

Dr. Maselli reported having no financial disclosures.

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VIEW ON THE NEWS

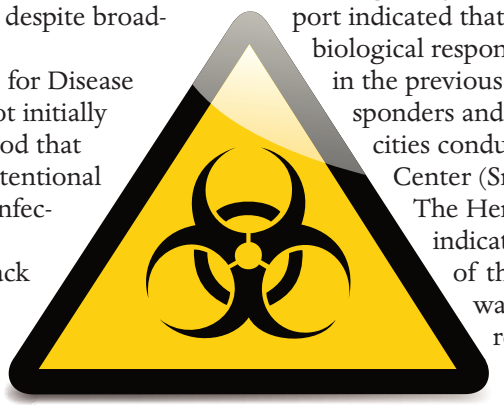
Dr. Vera DePalo, FCCP, comments: Targeted biological therapies offer the promise of broadening the array of treatments for asthma, giving providers more options for better outcomes.

Bioterror threat remains real, readiness slips

Commentary *from page 1*

to North Carolina. The mailroom supervisor was hospitalized on October 1 with fever and confusion. He was found to have mediastinal widening on chest radiograph. He was treated for anthrax and recovered. The photo retoucher was hospitalized on October 2 with fever and confusion, and *Bacillus anthracis* was isolated from his cerebrospinal fluid the next day. He died on October 5 of pneumonia and meningitis despite broad-spectrum antibiotics.

Of concern, the US Centers for Disease Control and Prevention did not initially acknowledge the high likelihood that these events represented an intentional release, through the mail, of infectious anthrax spores.



The subsequent anthrax attack lasted approximately 6 weeks. A total of five letters (four proven and one presumed) were identified as the route of spread of cases in Florida, Washington DC, New York City, and Connecticut. Although it was very limited in scope (12 cases of cutaneous and 11 cases of inhalational anthrax, resulting in five deaths), the attack caused a nationwide wave of fear. Supplies of ciprofloxacin and other antibiotics used to treat anthrax were rapidly depleted, and concern regarding further spread via the postal system led to public alerts regarding suspicious mail.

The source and motive of the attack have not yet been identified with certainty. These events unmasked a disturbing lack of readiness for a more widespread biological attack.

The status of bioterrorism readiness prior to the anthrax attacks

In the years immediately before the 2001 anthrax attacks, a number of studies indicated that preparation for bioterrorism was poor in the United States. A report by the Rand Corporation (Fricker et al. www.rand.org/publications/IP/IP217/index.html.), including data collected between March and September of 2001 from over 600 local and state police, fire, public health, and emergency management agencies, pointed to widespread gaps in preparedness for terrorist attacks by means of weapons of mass destruction.

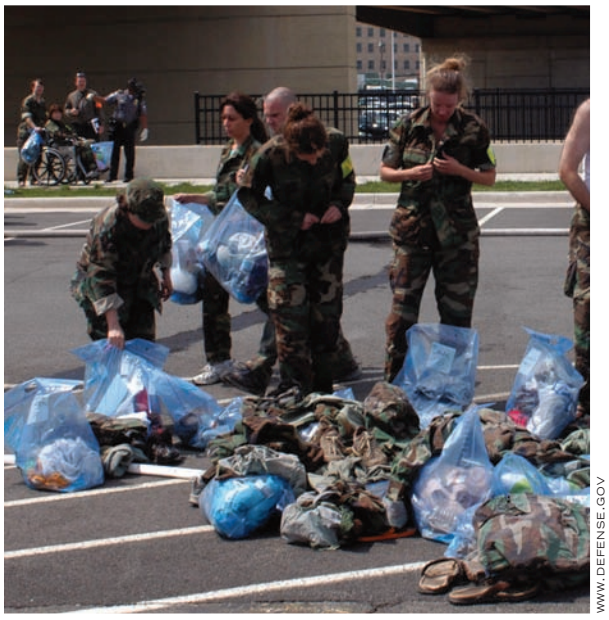
Among many other concerning findings, the report indicated that only 7% of these agencies had biological response plans that had been tested in the previous 2 years. Surveys of first responders and health-care providers in 30 cities conducted by the Henry L. Stimson Center (Smithson et al. Report No. 35. The Henry L. Stimson Center) in 2000 indicated that the level of awareness of the elements of biological attack was rated only 1.7 out of 10 by respondents. Of special concern was difficulty in recognizing clinical features of smallpox or anthrax. Other studies prior to 2001 indicated that few medical providers had received specific training for biological attack, and of those who had received such training, few had confidence in their ability to recognize or respond to infection with agents of bioterrorism.

Strategies to improve readiness since 2001

Largely as a result of the attacks of 2001, emergency preparedness in general and bioterrorism specifically are now identified as key areas of significance by a variety of medical specialties (Lane et al. *Am J Disaster Med*. 2012;7[1]:48). The American College of Chest Physicians, the Society of Critical Care Medicine, the Infectious Disease Society of America, the American College of Physicians, and a variety of other specialty societies have emphasized the importance of education about bioterrorism.

Efforts have been made to improve the capability of the public health infrastructure to respond to biological attack, and the Joint Commission has developed standards for hospital emergency readiness. Other trends may be a cause for concern, however.

Following the anthrax attacks and the rise in concern about terrorism in general, the medical literature reflected a sharp rise in research interest in this field. There were 854 publications with the keyword "bioterrorism" indexed in Medline in 2002 compared with just 62 in 2000. Since 2002, however, there has been a steady decline to 39 such publications in 2013 so far. Publications in recent years have focused on the role of clinicians in emergency preparedness and on parallels between bioterrorism and naturally occurring outbreaks, such as the H1N1 influenza pandemic of 2009. If the medical literature as indicated by these figures is reflective of knowledge among providers, we may be in danger of returning to pre-2001 levels of preparedness.



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At the Pentagon, anthrax-exposure protocols are drilled in a test of agencies' response to an attack.

Clues that a biological attack is underway

The US Centers for Disease Control and Prevention has categorized biological agents by the likelihood that they would be used in a terrorist attack (see box). Since severe respiratory disease and sepsis are common features of infection caused by several of these agents, the critical care practitioner may be the first to become aware of the early stages of biological attack.

Rapidly progressive pneumonia would be the likely presentation of pneumonic plague, tularemia, and pulmonary anthrax. While this syndrome is associated with a variety of other infections, most notably Legionnaire's disease and influenza pneumonia, the most important clue to infection with each of these agents would be the occurrence of multiple cases of severe pneumonia occurring in a short period of time or during a known attack. More challenging would be detection of the first cases of anthrax or pneumonic plague.

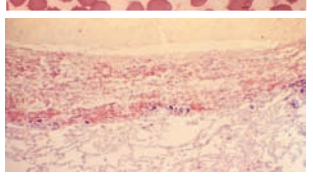
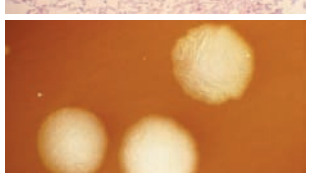
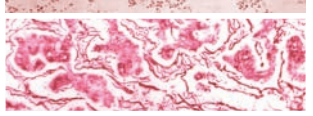
The role of the critical care specialist during a biological attack

In the event of a confirmed biological attack, the critical care provider would be relied upon to take on a variety of tasks. Among these would be:

Triage: In a biological attack, particularly one caused by a respiratory pathogen, large numbers

Continued on following page

Likely agents of biological attack

	Agent	Transmission
	Variola virus (smallpox) Presentation: A painful and progressive nodular-vesicular rash most prominent on the extremities in the setting of progressive systemic disease may suggest smallpox.	Person-to-person, aerosol, fomites
	*Yersinia pestis* (pneumonic and bubonic plague) Presentation: Rapidly progressive pneumonia, severe sepsis; gram-negative rods in sputum and blood.	Person-to-person, aerosol
	*Bacillus anthracis* (anthrax) Presentation: Abrupt onset of severe sepsis accompanying meningitis, mediastinitis, or pneumonia; gram-positive rods in sputum, blood, or cerebrospinal fluid (CSF). A painless, localized area of vesicles progressing over several days to a necrotic eschar coupled with signs of severe sepsis should suggest the possibility of cutaneous anthrax.	Aerosol, food, water
	*Clostridium botulinum* toxin (botulism) Presentation: Unexplained cranial nerve palsies with or without other motor weakness in the absence of explanation should raise suspicion of botulism. It should be recalled that the toxin of *Clostridium botulinum* could cause disease after release as an aerosol as well as a contaminant of food.	Aerosol, food, water
	*Francisella tularensis* (tularemia) Presentation: Progressive pneumonia.	Aerosol
	Viral hemorrhagic fever viruses Presentation: Diffuse petechiae or ecchymoses coupled with other evidence of bleeding diathesis may be indicative of infection with hemorrhagic fever virus.	Person-to-person, aerosol

IMAGES COURESTY CDC

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of patients might present simultaneously. Person-to-person spread, as would be seen in the case of pneumonic plague or smallpox, would be expected to result in a rapidly expanding outbreak over days to weeks. Models of such an attack typically predict a large influx of patients seeking reassurance, the so-called "worried well." A system of rapid screening and triage of patients into various clinical categories for care and, possibly, isolation precautions, would be required to permit the ED and ICU to function adequately.

Establishing rapid means of identification and confirmation of cases: The critical care specialist would occupy a central role in establishing effective communication with the hospital laboratory and with public health authorities for the rapid identification of cases and for the appropriate processing of clinical specimens and to optimize patient flow.

Grouping: If the pathogen can be transmitted from person to person, grouping of infected and of uninfected patients may be necessary when hospital facilities become overcrowded.

Estimating resources and capacity: One of the most important duties of the critical care staff would be to predict the need for needed medications and key equipment, such as ventilators and personal protective equipment. Establishing capacity would also include an evaluation of staffing needs in the critical care areas.

Summary

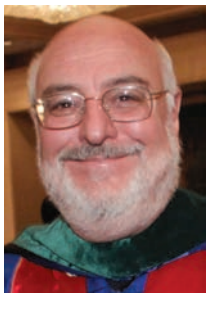
There have been no recognized biological attacks in the United States since 2001. As welcome as this period of calm has been, it is likely that the readiness of our medical workforce to respond to bioterrorism has waned.

A knowledge of the likely agents of attack, including their routes of transmission and spread and means of effective containment and treatment, will be essential if future attacks occur. Critical care specialists will find themselves, perhaps suddenly, on the frontlines of our response.

Dr. Masci is Director of Medicine, Elmhurst Hospital Center, Elmhurst, NY; and Professor of Medicine and Professor of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

VIEW ON THE NEWS

Dr. Peter Spiro, FCCP, comments: In this excellent but sobering commentary, Dr. Masci clearly and correctly points out our relapse into potential unpreparedness. Though his focus has been bioterrorism, we cannot forget the abundance of biologic and chemical agents available and the vital role that critical care practitioners will have to play.



The local providers will be the first to see, triage, and treat the affected. A continued focus on training and updating knowledge bases is paramount to ensure our adequate skill and knowledge. We have been fortunate that no new attacks have occurred in the United States, but it is not so fortunate in the Middle East. All this aside, may we all have a healthy, happy, sane, and safe New Year.

Dr. Spiro is Section Editor, Critical Care Commentary, for CHEST Physician.

Ready or not? Phones, power may fail, but planning shouldn't

BY WHITNEY McKNIGHT
IMNG Medical News

VITALS

Major finding: Although 78% of ICU staff had never performed a vertical ICU evacuation drill, only 23% admitted to feeling "inadequately trained" during Superstorm Sandy evacuations.

Data source: Survey of 68 ICU clinicians in the New York City region, all of whom worked through Superstorm Sandy.

Disclosures: Dr. Evans, Dr. King, and Dr. Grissom reported no relevant financial disclosures.

CHICAGO – When Superstorm Sandy was done barreling across New York City and the surrounding coast 14 months ago, flooding streets and knocking out power to millions, Dr. Laura Evans, director of the medical intensive care unit at Bellevue Hospital along the East River in Manhattan, emerged weary and wiser.

At one point, the ICU faced the real possibility of having just a handful of working power outlets to serve dozens of patients, and the number of crucial decisions to be made rose along with the water level. "Prior to the storm, disaster preparedness was not a core interest of mine, and it's something I hope never to repeat," Dr. Evans told attendees at CHEST 2013.

In a recent survey, ICU practitioners who endured havoc caused by Sandy in the New York City region reported having had little to no training in emergency evacuation care. "When I look at these data, I think there is a mismatch in terms of our self-perception of readiness compared to what patients actually require in an evacuation. It's in stark contrast to the checklist we use every single day to put in a central venous catheter," said Dr. Mary Alice King, who presented her research as a copanelist with Dr. Evans. Dr. King is medical director of the pediatric trauma ICU at Harborview Medical Center in Seattle.

NICK PIEGARI/IMNG MEDICAL MEDIA

Most hospital evacuations occur because of an internal event like a fire or an intruder, Dr. Colin Grissom said at CHEST 2013. See a video online.

Contingency for loss of power

The nation's oldest public hospital, Bellevue, is adjacent to New York's tidal East River. The river's high tide the evening of Oct. 29, 2012, coincided with the arrival of the storm's surge, and within minutes the hospital's basement was inundated with 10 million gallons of seawater. And then the main power went out, taking with it the use of 32 elevators, the entire voice-over-Internet-protocol phone system, and the electronic medical records system, Dr. Evans said. The flood also knocked out the hospital's ability to connect to its Internet servers. "We had very impaired means of communication," Dr. Evans said.

Survey data presented by Dr. King underscored that loss of power affects ICU functions in virtually all ways. The number one tool Dr. King's survey respondents said they'd depended on most during their disaster response was their flashlights (24%); meanwhile, the top two items the respondents said they wished they'd had on hand were reliable phones, since, as at Bellevue, many of their phones were powered by voice-over-Internet protocols which, for most, went down with power outages; and backup electricity sources such as generators.

Leadership plan

Of the 68 survey respondents, 34% of whom were in evacuation leadership roles, Dr. King said only 23% admitted to having felt ill-prepared to manage the pressure and details necessary to safely evacuate their patients. "As nonemergency department hospital providers, we receive little to no training on how to evacuate patients," said Dr. King.

In Bellevue's case, Dr. Evans said that there was a leadership contingency already in place because of the hospital's having been prepared the year before, when Hurricane Irene muscled its way up the Northeast's Atlantic coast, also causing flooding and wind damage, though on a far smaller scale. "We had an ad hoc committee," said Dr. Evans. "Although we

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didn't know exactly who would be on it because we didn't know who would be there during the storm, we knew we would have medical, nursing, and ethical leaders to make resource allocation decisions." Most important about the leadership committee's makeup, she said, was that ultimately, "none of us were directly involved in patient care, so none of us had the responsibility for being advocates. We wanted the attending physicians to be able to advocate for their patients."

The committee calculated that if backup generators failed, the ICU would have only six power outlets to depend on for its almost 60 patients. "The question was, whom would they be allocated for out of the 56 patients?

"Our responsibility was to make the wisest decisions about allocating a scarce resource," Dr. Evans said.

'We knew that if the disaster went very badly, we would be met with much criticism.'

Practice the plan

Dry runs matter. "Forty-seven percent of survey respondents said that patient triage criteria were determined at the time of [the storm]," and a third of those surveyed said they weren't aware of any triage criteria, Dr. King said.

And once plans are made, "it's important to drill them," emphasized Dr. King's copresenter Dr. Colin Grissom, associate medical director of the shock trauma ICU at Intermountain Medical Center, Murray, Utah. Superstorm Sandy, for all its havoc, came with some notice – the weather forecast. However, he pointed out that typically disasters happen without warning: "More than half of all hospital evacuations occur as a result of an internal event such as a fire or an intruder."

Also important to consider, said Dr. King, is that neonatal and pediatric ICUs have different evacuation needs from adult ones. "Regions should consider stockpiling neonatal transport ventilators and circuits," she said. "They should also consider designating pediatric disaster receiving hospitals, similar to burn disaster receiving hospitals."

Ethical considerations

At Bellevue, Dr. Evans said the hospital's leadership planned patient triage according to influenza pandemic guidelines issued by the provincial government of Ontario, Canada, and the New York State Taskforce on Life and the Law guidelines for ventilator allocation during a public health disaster.

"We knew that if the disaster went very badly, we would be met with much criticism," said Dr. Evans, who joked that she was up nights worried about seeing her name skewered in local headlines: "I kept wondering, 'What rhymes with Evans?' "

Using the two sets of guidelines, both heavily oriented toward allocating ventilators, said Dr. Evans, "we did what we thought was ethical and fair. We made the best decisions we could."

The Ontario guidelines, she said, are predicated on Sequential Organ Failure Assessment (SOFA) scores. Just as the ad hoc committee determined that of the 56 patients in the census, there were "far more folks in the red (highest priority) and yellow (immediate priority) group than we had power outlets," the group received word that the protective housing around the generator fuel pumps had failed, and total loss of power was anticipated in 2 hours.

The committee reconfigured and, among other contingencies, began assigning coverage of two providers each to the bedside of every ventilated patient, and preparing nurses to count drops per minute of continuous medication.

The 'bucket brigade'

Although the intensivists who'd participated in Superstorm Sandy evacuations said they felt most frustrated by the lack of communication during the event, 57% said that teamwork had been essential to the success of the evacuations. "We work as teams in our units. That is something I think we bring as a real strength to ICU evacuations," said Dr. King.

And so it was at Bellevue.

"Due to the heroics of a lot of staff and volunteers, we did not have to execute this plan," said Dr. Evans. Instead, the "Bellevue bucket brigade," using 5-gallon jugs, formed a relay team stretching from the ground floor outside where the fuel tanks were, up to the 13th, where the backup generators were located. "The fuel tank up on the 13th floor was only accessible by stepladder, so someone had to climb up there and pour the fuel through a funnel," said Dr. Evans. "But because of this, we never lost backup power, and we successfully evacuated our hospital without complications to our patients."

Individualized plan key to success

While leadership and communication were essential, said Dr. Evans, she concluded that thinking through how existing guidelines can help was also key, but did not go far enough. "Unfortunately, no document can provide for all contingencies. Complete reliance on any [guidelines] is not good. You have to think about how you would individualize things to your own facility."

The survey was sponsored by the ACCP and conducted by Dr. King as part of her role on the ACCP's mass critical care task force evacuation panel, which will issue a consensus on the topic sometime in early 2014.

Dr. Evans, Dr. King, and Dr. Grissom reported no relevant disclosures.

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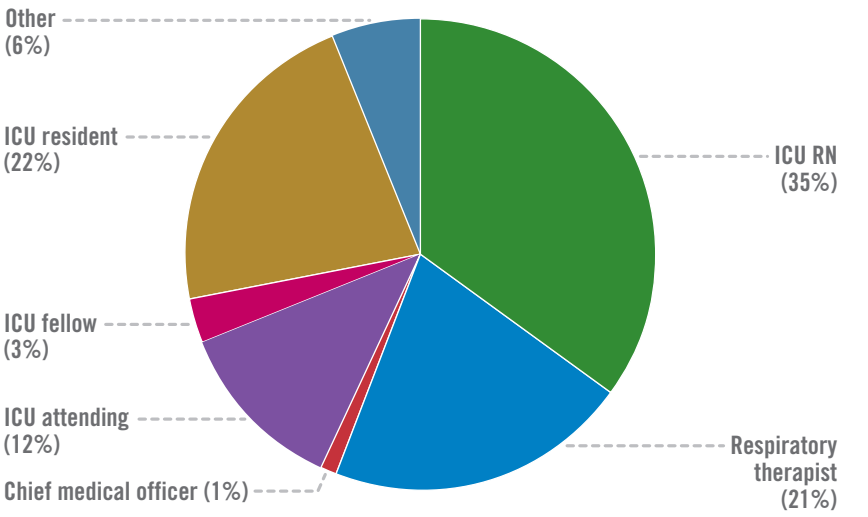
Superstorm Sandy: Survey respondents by ICU provider type



Note: Based on responses from 68 ICU workers in the New York City region.
Source: Dr. King
IMNG Medical Media

VIEW ON THE NEWS

Dr. W. Michael Alberts, FCCP, comments: To paraphrase an old saying about insurance, "disaster preparedness is not needed until it is." Those health care facilities that have a clear documented plan and have drilled on the specifics are very pleased that they devoted time and effort when disaster strikes.

While – knock on wood – the Moffitt Cancer Center here in Tampa has not needed our "Disaster Management Plan" (or as we in Florida say, "Hurricane Management Plan") this year, it is only a matter of time and we'll be ready when the need arises.

We urge you to review your plan before you need it.

Ten keys to ICU evacuation planning

When not under immediate threat

1) Create transport and other agreements with other facilities in region, including triage criteria.
2) Detail ICU evacuation plan, including vertical evacuation plan; simulate so all parties are familiar with their role, including those involved in patient transport.
3) Designate critical care leadership.

During imminent threat

4) Request assistance from regional facilities and appropriate agencies.
5) Ensure power and transportation resources are operable and in place.
6) Prioritize patients for evacuation.

During evacuation

7) Triage patients.
8) Include all patient information with patient.
9) Transport patients.
10) Track patients and all equipment.

Source: Dr. Colin Grissom

Oxycodone-naloxone nips resistant RLS symptoms

BY MICHELE G. SULLIVAN
IMNG Medical News

A combination of extended-release oxycodone-naloxone significantly improved the symptoms of restless legs syndrome among patients who had failed first-line therapy, in a double-blind, randomized placebo-controlled study.

By the end of 12 weeks, 57% of patients randomized to the treatment group were considered responders, compared with 31% of patients in the placebo group; and 42% of patients in the treatment group had remission of symptoms, vs. 19% in the placebo group, Dr. Claudia Trenkwalder of the department of neurosurgery, University of Göttingen (Germany) and colleagues reported (Lancet Neuro 2013;12:1141-50). All of these differences were statistically significant.

"Our findings suggest a new, much-needed, option for management of severe restless legs syndrome for patients who cannot tolerate dopaminergic drugs," for nonresponders, and for those who developed tolerance or augmentation when receiving dopaminergic medications, they wrote.

The industry-funded study randomized 304 patients with severe restless legs syndrome (RLS) to either placebo (154) or to prolonged-release oxycodone-naloxone (150). The starting dose was 5 mg oxycodone with 2.5 mg naloxone twice a day. This could be titrated up to a maximum of 40 mg oxycodone with 20 mg naloxone twice a day. A 40-week open-label extension trial followed.

Patients had a mean disease duration of 10 years. All had failed first-line therapy with a dopaminergic drug. The mean International RLS Study Group symptom severity score was 31.6 on a 40-point scale, with 40 points corresponding to very severe symptoms. Change on this scale was the primary endpoint.

Of the entire 304 patients, 204 completed the 12-week randomized trial. Significantly more dropouts occurred in the treatment group (13% vs. 7%).

The mean daily dose was 22 mg hydrocodone with 11 mg naloxone. Ten patients took the maximum dose at some point during the study.

Symptoms began to decrease after 1 week among those taking the study drug. By 12 weeks, the symptom score had decreased a mean of 16.6 points in the treatment group and 9.5 points in the placebo group. During this part of the study, 13% of the active group and 7% of the placebo group withdrew because of adverse events. The most common side effects were fatigue, constipation, nausea, and headache.

At the end of the extension phase, 43% of the 157 patients still enrolled were classified as being in remission, with 22% having zero symptoms.

The investigators cautioned that the study does not support oxycodone-naloxone as a first-line RLS therapy. The study was sponsored by Mundipharma Research, which developed the treatment. Dr. Trenkwalder and other researchers have ties to the firm and other industry sources.

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Off-label use of opioids relieves refractory dyspnea

BY WHITNEY McKNIGHT
IMNG Medical News

CHICAGO – Low doses of opioids titrated based on patient ratings of breathing difficulty are effective in managing refractory dyspnea, according to Dr. Donald Mahler, FCCP.

Because refractory dyspnea is a neuromechanical dissociation, treating more than the pulmonary system can be beneficial, Dr. Mahler said at CHEST 2013. "We have targets for the lungs to relieve dyspnea, but we may also have potential targets in the central nervous system that may also provide benefit."

Referring to published data from two randomized controlled studies about the effect of naloxone on blocking opioid signals in patients with chronic obstructive pulmonary disease who reported breathlessness and perceived "unpleasantness" of

dyspnea after exercise, Dr. Mahler said that endogenous opioids modulate the perception of dyspnea; exogenous opioids could therefore do the same (Eur. Respir. J. 2009;33:771-7 and COPD 2011;8:160-6).

Opioid receptors in the limbic system have 100 times greater binding density in the bronchioles and alveolar walls. "That may play a role when thinking about a nebulized approach," said Dr. Mahler of Dartmouth-Hitchcock Medical Center, Lebanon, N.H. The number of side effects, including constipation, was lower with this approach, he added.

Because opioids are known to decrease respiratory drive, there is a "presumable" effect on corollary discharge, which can lead to less perception of breathlessness, according to Dr. Mahler. Narcotics' dulling effect on the perception of pain and anxiety might also contribute. "Maybe by relieving symptoms, there's less anxiety as a result," said Dr. Mahler.

He addressed concerns over the "double effect" whereby opioids used to lessen symptoms might actually hasten death in a patient with refractory dyspnea, saying the studies "don't really support that." Dr. Mahler cited data indicating that higher doses of benzodiazepines used in withdrawal of life-sustaining treatment were not associated with a decreased time from withdrawal of life support to death (CHEST 2004;126:286-93).

As for respiratory depression, Dr. Mahler said he had reviewed 11 studies and found only one report of any change in oxygen saturation after opioid administration.

In deciding whether a patient should be given opioid therapy, Dr. Mahler said physicians should be sure that standard therapies are inadequate and that the risk/benefit ratio favors trial treatment. Establishing treatment goals and confirming that the patient and/or the patient's family are on board with a trial of opioid treatment is key, he added.

To determine titration, physicians should ask the patients to rate their breathing difficulty. "This is a critical part of the assessment," said Dr. Mahler, noting that the level of breathlessness determines the dose and duration of action.

If dyspnea is episodic, he said, "it doesn't make sense to administer a long-acting opioid" and so an immediate-release or short-acting form should be considered. If it's constant, sustained release may be effective, he said.

Dr. Mahler, who said his presentation was related to the off-label use of morphine only, said it's important to "titrate the opioid to achieve the lower effective dose based on the patient's rating of the dyspnea." Adding an anxiolytic could also be considered, he said. "It's pretty straightforward that you should discontinue the opioid if there is an unsatisfactory response or if there is an adverse effect."

Dr. Mahler disclosed ties with several drug companies and medical organizations, including GlaxoSmithKline, Novartis, and Sunovion.

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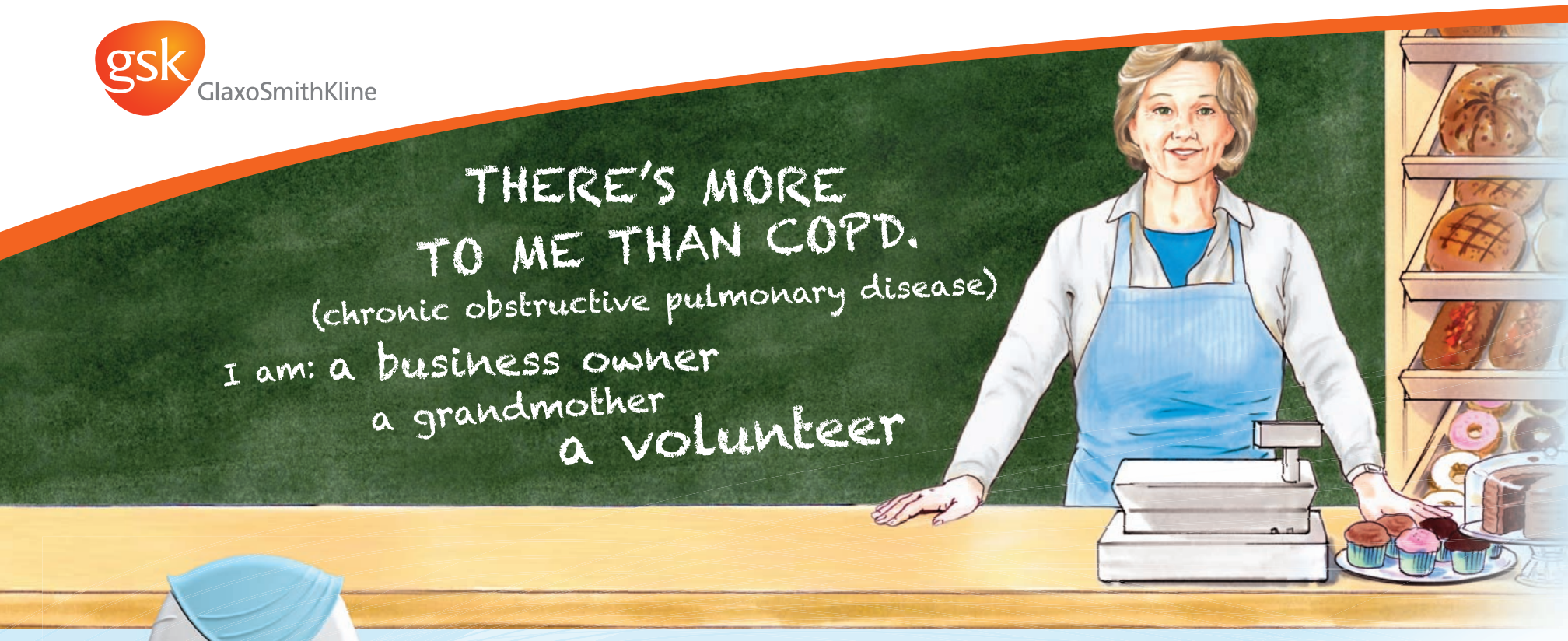
VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: In our chronic disease patients, the attention given to palliation of symptoms often is delayed in favor of other "active" therapies. In the appropriate population, and with responsible implementation, low-dose opiates should be considered for the relief of refractory dyspnea.



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)

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.

GlaxoSmithKline
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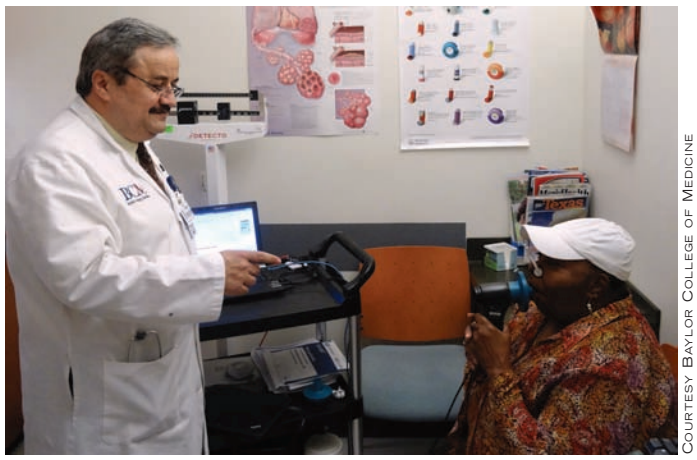
Phenotyping promises more targeted treatments

Hanania *from page 1*

ple who smoke. It also is characterized by more wheezing and thicker airway walls. Data presented by Dr. Hanania also showed that this phenotype has more frequent acute exacerbations (Chest 2011;140:1107-8).

In one study, 290 subjects deemed chronically bronchitic – chronic cough and phlegm lasting 3 months of every year for 2 consecutive years – were compared with 771 subjects who were not chronically bronchitic. Investigators found that patients in the first group had more frequent exacerbations per patient: 1.21-1.62 vs. 0.63-1.12 ($P < .027$). The first group also reported more severe exacerbations: 26.6% vs. 20% ($P < .024$) (Chest 2011;140: 626-33).



Courtesy Baylor College of Medicine

The rate of exacerbations appears to reflect an independent susceptibility phenotype, says Dr. Nicola A. Hanania.

Asthma COPD/overlap

"This is a phenotype that deserves more attention. We all have patients where we scratch our head, 'Is this asthma, or is this COPD?' " said Dr. Hanania. "We don't really know because these patients are notoriously excluded from both asthma and COPD studies." He cited estimates suggesting that 13%-20% of COPD patients overlap with asthma (Arch. Bronconeumol. 2012;48:331-7).

Proposed diagnostic criteria for the overlap syndrome phenotype may include two major criteria: marked response to bronchodilators (>15% and >400 mL in forced expiratory volume in 1 second [FEV_1]), history of asthma if patient is younger than 40 years, and sputum eosinophilia. Overlap also can be diagnosed by one major criterion and two of the following: response to bronchodilation at least two separate times (>12% and >200 mL in FEV_1), history of atopy, and increased total serum IgE. At this time, he said, these criteria are based on expert opinion and on data, "but the clinical implications, once we do the homework, is that these patients deserve to be on antibiotics and corticosteroids early on."

Frequent exacerbator

Defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as two or more exacerbations per year, the frequent exacerbator phenotype was explained in the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), Dr. Hanania said, which showed that, although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype (N. Engl. J. Med. 2010; 363:1128-38).

Frequent exacerbators have higher-stage COPD, more severe obstruction, and more hospitalizations, Dr. Hanania noted.

In addition, the ECLIPSE investigators found that, in 2,138 patients, frequent exacerbator types had an odds ratio of 5.72 of having had an exacerbation in the previous year

Although there are other risk factors implicating this phenotype, "the most important question to ask the patient is whether they have had an exacerbation in the previous year," he said.

Continued on following page

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: Clinicians have long been aware that COPD is a heterogeneous disorder. Evidence that links COPD phenotypes to clinical outcomes provides the clinicians who care for these patients with a powerful tool. Clinicians will be able to optimize treatment plans in accordance with phenotype to provide improved care to patients who suffer from COPD.

WHAT MATTERS: NSAIDs, not antibiotics, for bronchitis

BY JON O. EBBERT, M.D.

'Tis the season to be coughing. A common condition we are seeing and will be seeing in the coming months is bronchitis. Bronchitis is a self-limited inflammation of the bronchi due to upper airway infection (i.e., cough without pneumonia), which is most commonly viral in etiology. Antibiotics are not recommended for treatment.

Reports indicate that more than 60%-90% percent of patients with acute bronchitis who seek care receive antibiotics. Furthermore, 75% of all antibiotic prescriptions are written for upper respiratory infections – yet most patients, if not all, do not need them.

Many of our patients will say that they have tried the usual over-the-counter remedies, which can ruin the best-laid plans for conservative management. But have they tried ibuprofen? (Assuming there is no contraindication, of course.)

DR. EBBERT

Dr. Carl Llor and his colleagues recently published a randomized, blinded clinical trial evaluating the comparative efficacy of an anti-inflammatory, antibiotic, or placebo in the resolution of cough in patients with bronchitis (BMJ 2013 Oct. 4;347:f5762).

Adults aged 18-70 years were eligible to be randomized if they were presenting with a respiratory tract infection less than 1 week in duration and had cough, discolored sputum, and at least one of three symptoms: dyspnea, wheezing, or chest discomfort or chest pain. Subjects were randomized to ibuprofen 600 mg three times a day, amoxicillin-clavulanic acid 500 mg/125 mg three times a day, or placebo three times a day. Treatment was given for 10 days.

The median number of days with frequent cough was numerically lower, but not statistically significantly lower, in the ibuprofen group (9 days; 95% CI: 8-10 days), compared with participants receiving antibiotics (11 days; 95% CI: 10-12 days) or placebo (11 days; 95% CI: 8-14 days). Adverse events were more common in the antibiotic arm (12%), compared with ibuprofen or placebo (5% and 3%, respectively, $P = .008$).

Other nonantibiotic cough remedies have been evaluated in the treatment of patients presenting with cough. Inhaled fluticasone may be effective, but the cost might be prohibitive for many patients.

For ibuprofen, the price is right – and it may buy us some time before we feel compelled to prescribe antibiotics.

Dr. Ebbert is a general internist at the Mayo Clinic in Rochester, Minn.

Continued from previous page

Chronic cough is another factor.

The clinical benefit to identifying the frequent exacerbator, Dr. Hanania said, is that this group has a greater range of comorbidities, including more inflammation, heightened viral susceptibility, and increased cardiovascular risk, among other susceptibilities.

Using CT for phenotyping

Noting that radiologic phenotyping in COPD is more advanced than in asthma at this time, Dr. Hanania said that quantitative and visual assessment of CT radiographs is "promising" and has helped identify COPD subphenotypes such as emphysema because of accurate assessment of lung inflation, wall thickness, and other factors.

Identifying patients with bronchiectasis, pulmonary arterial enlargement, and acute exacerbations in COPD is also possible with CT radiography, making it possible to predict the different outcomes in each situation. "The clinical implication is that these patients tend to have more frequent exacerbation, worse lung function, and infection," he said, noting that nascent research using imaging to determine biomarkers in functional small airways disease also is occurring.

Systemic inflammation

In the ECLIPSE study, 2,164 COPD patients had an odds ratio of 2.23 for being a current smoker and had higher levels of inflammation, as determined using biomarkers such as C-reactive protein, compared with 337 smokers without COPD and 245 nonsmokers. At the 3-year follow-up, this group with persistently higher inflammation also had significantly higher all-cause mortality than the group with less inflammation (13% vs. 2%); exacerbation rates in this group were also persistently higher (1.5 vs. 0.9) (PLOS ONE 2012;7:e37483).

Therapeutic implications

Coupling these phenotypes with molecular descriptions of mechanisms and their underlying pathologies can lead to accurate, personalized treatment of COPD. "Phenotypes without clear implications for prognosis and treatment are of little clinical use," Dr. Hanania said, noting that longitudinal studies to validate these phenotypes are necessary.

"Research can help identify mechanisms and courses in different phenotypes, including gender differences," he concluded. "Examining therapeutic responses to different phenotypes can lead to future interventions."

Dr. Hanania disclosed relationships with a variety of manufacturers, including Genentech, GlaxoSmithKlein and AstraZeneca.

Beyond GOLD: A tale of two COPD guidelines

Both address severity and comorbidity, but only one COPD guideline takes into account the latest research on phenotyping in chronic obstructive pulmonary disease.

"The GOLD guidelines do not include clinical phenotypes," said Dr. Joan Soriano, a presenter at CHEST 2013. "But the Spanish ones do."

In fact, there is really only one area where the two documents overlap, said Dr. Soriano: how they define COPD, and even that is not the same. "They both mention the fundamental aspect, which is airflow limitation, and also that the mechanism involved is inflammation," he said. The GOLD definition, however, recognizes the importance of comorbidities; the Spanish guidelines address the role of tobacco and symptomology.

GOLD (Global Initiative for Chronic Obstructive Lung Disease) is an organization of health care professionals from around the world. "I am not a member of GOLD," Dr. Soriano told the packed session.

The Spanish guidelines are issued by SEPAR, the Spanish Society for Pneumology and Thoracic Surgery. Dr. Soriano is the director of epidemiology and clinical research at the International Center of Advanced Respiratory Medicine (CIMERA) in Palma, Spain.

How the two approach diagnosis also differs. The Spanish guidelines begin with the general COPD diagnosis, then move to the characterization and phenotype, then move to the severity of the disease. They are more specific about age (over 35 years), and have lower limit of normal (LLN) values for persons aged over 70 years and under 50 years. The GOLD guidelines do not address LLN.

To characterize the disease specifically, the Spanish guidelines address the existence of phenotypes, according to Dr. Soriano, beginning with determining the frequency of exacerbation the patient has per year, and then classifying them eventually into four types: mixed, chronic bronchitis, emphysema, and exacerbator. The GOLD guidelines do not mention phenotypes.

When it comes to the multidimensional assessment of COPD, "the GOLD guidelines lump the mild with the severe spirometry. This is very hard for me to understand," he said. Other classification divergence includes that the Spanish guidelines consider the BODE index.

Treatment in the two guidelines begins similarly, but vectors off from there. "Basically, we are looking at the same trials, so the initial treatments should be short-acting bronchodilators," Dr. Soriano said, but because phenotyping allows for more targeted treatment, the Spanish guidelines offer more detailed treatment options.

In a paper coauthored by Dr. Soriano earlier this year, specific treatment per phenotype included phosphodiesterase-4 inhibitors only for those with chronic bronchitis, inhaled corticosteroids for overlap COPD-asthma, and bronchodilators for infrequent exacerbators (Eur. Respir. J. 2013;41:1252-6).

In the end, the guidelines might not follow the same trajectory, but each has value, he said. "Whatever guidelines you choose, don't go back and forth. Pick one and use them."

Dr. Soriano reported relationships with Novartis Spain, AstraZeneca, Pfizer, and several other pharmaceutical and medical manufacturers.

–Whitney McKnight

Stent insertion no better with radiological guidance

In lung cancer patients, technique did not improve outcomes of tracheobronchial procedure.

BY BIANCA NOGRADY
IMNG Medical News

SYDNEY, AUSTRALIA – Use of radiological guidance for tracheobronchial stent insertion in advanced lung cancer makes no difference to outcomes such as complication rates, length of stay, or survival compared with visually guided insertion, according to data from 79 patients.

Researchers from Harefield Hospital, London, examined outcomes from patients with advanced primary lung cancer whose airway obstructions were treated with tracheobronchial stenting; 41 were stented under radiological guidance and 38 with direct vision using bronchoscopy.

No cases of stent migration occurred in either group, and there were no significant differences between length of stay and overall survival, Henrietta Wilson, lead investigator, said at the IASLC world conference on lung cancer.

However, the use of radiological guidance required more staff and equipment and, by its very nature, led to more radiation exposure than did visually guided stent insertion, said Ms. Wilson, a thoracic registrar (medical student) at Harefield Hospital.

"I had noticed that with the use of radiological guidance, it seemed to add an amount of time and organization onto the cases that we were doing, with having to get a larger number of people coming to perform the procedure, with the logistics of getting all of the equipment into theater, and that can sometimes also prolong the time of the general anesthetic while getting all of that set up," she said at the conference, which was sponsored by the International Association for the Study of Lung Cancer.

VITALS

Major finding: The average length of stay following tracheobronchial stent insertion was 2.73 days in the radiologically guided group and 2.26 days in the visually guided group ($P = .93$).

Data source: Retrospective study of 79 patients.

Disclosures: No conflicts of interest declared.

The average length of stay following the procedure was 2.73 days in the radiologically guided group and 2.26 days in the visually guided group ($P = .93$), with 69% of patients discharged on the same day, or the day after. The overall mean survival was 2.6 months, with 20% of patients alive at one year.

"I think probably those who advocate radiological guidance would feel that you get a better position of the stent and so they may have felt that it would get fewer complications from stent migration or malposition of the stent, or people requiring repeat procedures, but that certainly wasn't something that we found," she said.

Ms. Wilson noted that tracheobronchial stenting was used generally in urgent cases of acute airway obstruction, either as a palliative procedure in itself or to provide short-term relief for patients awaiting further radiotherapy or chemotherapy.

"Acute airway obstruction can be very distressing, so if we're able to just improve that then it may only be for weeks or a month at most but we find from a quality of life point of view, that's a real benefit," she said in an interview.

Radiologically guided stenting required an x-ray C-arm to enable real-time imaging of the stent placement, while in visually guided placement, the surgeon would use a bronchoscope to assess the position of the tumor, and then use the guide wire to position the stent, Ms. Wilson noted.

The use of radiological guidance required more staff and equipment and, by its very nature, led to more radiation exposure than did visually guided stent insertion.

Additional research is underway to examine the impact of guidance methods on the duration of the procedure and anesthetic.

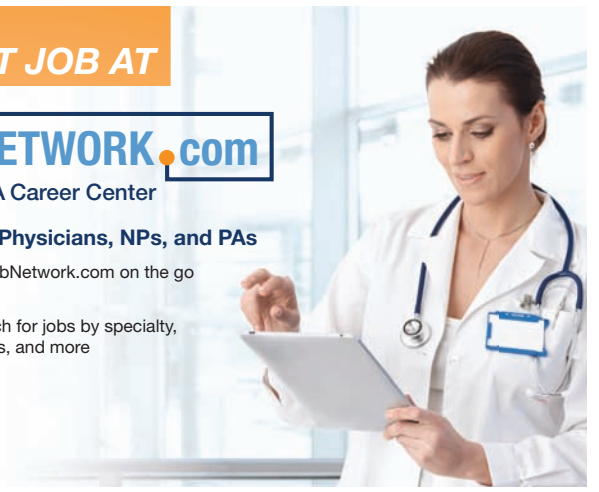
The researchers declared no conflicts of interest.

VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: This small, single-center, retrospective study found no significant differences in rates of stent complications, hospital length of stay, or survival in patients with airway obstruction caused by primary lung cancers stented via direct visualization compared to under radiological guidance.

As the authors note, there are a number of disadvantages to placement under radiologic guidance. These include the need for additional equipment and staffing, as well as more radiation exposure and time under anesthesia.

This study suggests that these measures may not lead to improved outcomes, and will hopefully lead the way to a subsequent multicenter, randomized control trial.



PULMONARY PERSPECTIVES: Achieving mastery in pleural ultrasound

BY DR. PARU PATRAWALLA

Point-of-care (POC) ultrasound is increasingly used in the diagnosis and management of pleural diseases. The diverse applications of POC ultrasound have been cited by the American Medical Association as "within the scope of practice of appropriately trained-physicians." The Accreditation Council for Graduate Medical Education (ACGME) has also added competency requirements for pulmonary and critical care trainees in POC ultrasound, including ultrasound for pleural procedures.

Numerous studies have shown that POC ultrasound improves safety of pleural procedures and increases the accuracy of pleural fluid localization (Gordon et al. *Arch Intern Med*. 2010;170[4]:332). Ultrasound has been shown to improve the accuracy of diagnostic thoracentesis by 26% when compared with clinical examination (and decrease the number of near misses of hitting an organ by 10%) (Diacon et al. *Chest*. 2003;123[2]:436). Ultrasound guidance for thoracentesis is also associated with a reduced rate of pneumothorax and tube thoracostomy (Barnes et al. *J Clin Ultrasound*. 2005;33[9]:442). In patients who had failed clinically guided thoracentesis, 88% had a successful ultrasound-guided thoracentesis (Weingardt et al. *J Clin Ultrasound*. 1994;22[7]:419). Mayo and colleagues reported a low rate of pneumothoraces (1.3%), complicating 232 critical care, physician-performed, ultrasound-guided thoracentesis in patients supported by mechanical ventilation (Mayo et al. *Chest*. 2004;125[3]:1059).


DR. PATRAWALLA

Clearly. use of POC ultrasound for pleural procedures is integral to patient safety. How should physicians be trained in this new procedure? An important first step came when the American College of Chest Physicians outlined the specific technical and cognitive components that define competence in critical care ultrasound, including a defined standard for pleural ultrasound (Mayo et al. *Chest*. 2009;135[4]:1050).


COURTESY ACCP

The ACCP's outlining of specific technical and cognitive components that define competence in critical care ultrasound was an important step in POC training.

Currently, there is no standardized method of assessing competence in ultrasound. How should physicians meet the competency standard defined in this statement? Many physicians who completed fellowship without ultrasound training have attended introductory courses offered by professional societies with variable methods of assessing competency. Although there is no formal method for attaining certification in POC ultrasound, the

Continued on page 27

FROM THE EVP/CEO: Finishing the year poised for the future

BY PAUL A. MARKOWSKI, CAE

Momentum. It's a timely and exciting concept for the American College of Chest Physicians (CHEST). In a word, it's what we've built over the past year, and it's what is propelling us into 2014 and beyond.

We're ending 2013 in an inspiring place. We've focused on our strategic plan throughout the year and have made many notable accomplishments, including:

► The launch of a new chestnet.org website, based on usability research and your feedback.

► A collaborative agreement with the Chinese Thoracic Society to help establish fellowship training programs in pulmonary and critical care medicine.

► Incorporation of CHEST Enterprises, Inc, a for-profit subsidiary that will allow us to develop programs to benefit the worldwide chest medicine community.

► Accreditation from the Society for Simulation in Healthcare (SSH) as the first-ever medical association to earn SSH accreditation, positioning us as a leader in the field.

In our new Global Headquarters, we will be a center for cutting-edge global education, a catalyst for new ideas, and an active partner in promoting better care for patients everywhere.

You can see the full listing of our accomplishments online in our Advancement and Impact Report. It's impressive! I invite you to take a look at chestnet.org/momentum.


PAUL A. MARKOWSKI

As remarkable as 2013 has been, I'm even more excited for 2014. We are poised for the future and poised to achieve our mission to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research. This is due in part to our new building. We're set to move into our new CHEST Global Headquarters in February, where we will become a center for cutting-edge global education, a catalyst for new ideas, and an active partner in promoting better care for patients everywhere.

In addition to our new building, we have a new brand to represent us as we move forward. Our new logo represents a chest and illustrates the connectivity and gathering of experts we foster. More than a new symbol, our brand includes the promise that we will be an essential connection at a critical time. This promise will guide us and keep us focused as we work to advance lung health around the world.

I can't mention advancing lung health around the world without bringing up the CHEST World Congress 2014. The American College of Chest Physicians and SEPAR, the Spanish Society of Pneumology and Thoracic Surgery, are hosting this inaugural congress March 21-24, in Madrid, Spain. This will be the first global gathering of leading respirologists, critical care physicians, sleep specialists, cardiothoracic surgeons, and allied health-care professionals from all parts of the world to share best practices in patient care. I'm anxious to see the outreach and impact this meeting will have.

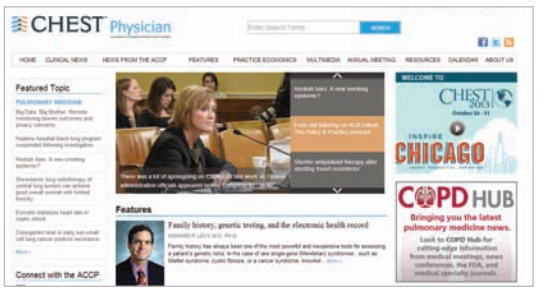
Our collaboration with SEPAR is one of many as we move into 2014. As I mentioned earlier, we're collaborating with the Chinese Thoracic Society to establish training programs in pulmonary and critical care medicine.

This is an extraordinary opportunity to improve clinical chest medicine in the country with the world's largest population. That's a powerful impact! Our work with the Forum of International Respiratory Societies, led by Immediate Past President Darcy Marciniuk, MD, FCCP, has resulted in the recent release of "Respiratory Diseases in the World," a document that outlines practical approaches for combating threats to respiratory health and proven strategies to significantly improve worldwide care. This report will be presented at the World Health Assembly to Address Non-Communicable Diseases in 2014, giving us an opportunity to advance our mission on a global agenda.

I'm proud of what we've accomplished in 2013 but anxious to begin 2014. A lot of good works lie just on the horizon. To stay on top of what's happening next year, follow me on Twitter (@PMarkowskiACCP), where I'll make periodic updates. Better yet, plan to attend the CHEST World Congress, March 21-24, in Madrid, and we can discuss in person. I hope to see you in Spain.

ONLINE EXTRAS

Check it out … chestphysician.org



From fresh clinical news and ACCP events to practice management, annual meeting highlights, and the COPD Hub, the new chestphysician.org website brings you to the forefront of clinical chest medicine. Jump in today!

Here's to you, NetWorks volunteers!

The NetWorks would not exist without the help of our member volunteers—those who serve on steering committees, review guideline manuscripts, and moderate and contribute to the e-Community.

We thank the following steering committee members who rotated off at CHEST 2013 in Chicago.

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Allied Health
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Continued from page 25

American College of Chest Physicians offers an assessment-based Certificate of Completion in Critical Care Ultrasound. Competency-based education, an outcomes-based approach to training, has become the standard in fellowship. Validated competency assessment tools and standardized training are necessary components to this approach.

This year in *CHEST,* Salamonsen and colleagues introduced and validated the Ultrasound-Guided Thoracentesis Skills and Tasks Assessment Test (UGSTAT), an assessment tool for physician-performed thoracentesis on a pleural effusion phantom (Salamonsen et al. *Chest*. 2013;144[3]:930). The development of this tool is an important piece to competency assessment for physicians prior to clinical practice.

The use of phantoms or mannequins for safe practice is quickly becoming the standard for procedural training prior to intervention on patients. Deliberate practice, or repetition with tailored feedback, has been shown to be integral in achieving skill mastery for thoracentesis (Wayne et al. *J Hosp Med*. 2008;3[1]:48). Using didactics, deliberate practice on a thoracentesis model, assessment and feedback, the authors were able to show that 93% of residents were able to achieve mastery within the standard 4-hour training period, and the remaining 7% of residents achieved mastery with an additional training period of 20 to 90 min. Notably, the outcome for each resident was equal; however, the time to achieve competency differed.

This year, reseachers introduced and validated the Ultrasound-Guided Thoracentesis Skills and Tasks Assessment Test, an assessment tool for physician-performed thoracentesis on a pleural effusion phantom.

Although ultrasound was not included in the curriculum for this study, this model of mastery learning offers a safe, practical, and flexible method for ensuring procedural competency in learners.

In response to a higher rate of pneumothorax following thoracentesis noted in an outpatient clinic, Duncan and colleagues initiated a quality improvement program to reduce the rate of pneumothoraces after physician-performed thoracentesis using a structured curriculum in ultrasound training and supervision until competency standards were achieved (Duncan et al. *Chest*. 2009;135[5]:1315). Physicians had simulation training with competency assessment prior to clinical use; they then underwent direct supervision of procedures with feedback until competency was achieved in order to attain clinical privileges. Maintenance of privileges was based on ongoing number of procedures performed.

Although no clear certification process exists for pleural ultrasound, the foundation for safe and practical training methods exists. Future research on the relationship between competency-based education, quality improvement, and patient outcomes will better define this approach.

Dr. Patrawalla is Assistant Professor of Medicine/Assistant Fellowship Program Director, Division of Pulmonary, Critical Care, and Sleep Medicine, NYU School of Medicine, New York, NY.

This Month in *CHEST:* Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

Short- vs Long-Duration Antibiotic Regimens for Ventilator-Associated Pneumonia: A Systematic Review and Meta-analysis. *By Dr. G. Dimopoulos et al.*

Quality Gaps and Comparative Effectiveness in Lung Cancer Staging: The Impact of Test Sequencing on Outcomes. *By Dr. F. A. Almeida et al.*

Attitudes and Beliefs Toward Lung Cancer Screening Among US Veterans. *By Dr. N. T. Tanner et al.*

SPECIAL FEATURE

Alpha$_1$-Antitrypsin Deficiency: What Has It Ever Done for Us? A 50-Year Reflection. *By Dr. R. A. Stockley.*

ICD-10-CM – It's all about the guidelines (part 1 of 3)

Complex coding nuances, hierarchies are explained.

BY BRENDA EDWARDS, CPC, CPMA, CPC-I, CEMC

Where is the best place to find information on how to use the ICD-10-CM codes? The answer is in the *ICD-10-CM Official Guidelines for Coding and Reporting*. The guidelines are beneficial for both the provider and coder to ensure the most accurately described diagnosis is reported to represent the documentation of the service performed. The guidelines are used to give additional instruction when used with the conventions and instructions. Following the guidelines is required under the Health Insurance Portability and Accountability Act (HIPAA).

Anemia is sequenced as a second diagnosis when it is associated with a malignancy (which would be sequenced first). This is an example of a difference between ICD-10-CM and ICD-9-CM.

The general guidelines are provided to give overall guidance for the ICD-10-CM code book. There are some similarities between ICD-9-CM and ICD-10-CM (eg, How to Locate a Code, Level of Detail in Coding), and some different guidelines are specific to ICD-10-CM (eg, Laterality, Borderline Diagnosis).

The chapter-specific coding guidelines explain nuances found with some of the more complex diagnoses. These include HIV infections, sepsis, anemia associated with other conditions, diabetes, hypertension with other diseases, pressure ulcers, pregnancy, and injuries.

The guidelines will assist in sequencing rules, stages for some disease processes, and the hierarchy of certain codes. For example, anemia is sequenced as the principal diagnosis when associated with chemotherapy, immunotherapy, and radiation therapy. It is sequenced as a second diagnosis when anemia is associated with a malignancy (which would be sequenced first). This is an example of where the guidelines are different in ICD-10-CM when compared with ICD-9-CM.

Diabetes can be coded to the highest level of specificity when using the guidelines. This includes the types of diabetes, use of insulin, and diabetes with other conditions. Diseases of the circulatory system can be very complex, but by utilizing the guidelines, explanations are given on coding, such as hypertension with coexisting conditions. Information includes sequencing and use of additional codes when needed.

Whether you are just diving into ICD-10-CM or you have already taken the plunge, you cannot become too familiar with the guidelines. Read and reread them.

Information and definitions also explain acute myocardial infarction (AMI). This is important because there are significant changes from ICD-9-CM to ICD-10-CM in the timeframe for current and old AMI.

Injury coding will see a tremendous increase in the number of code possibilities. The additional information given in the guidelines explains the 7th character requirement for both treatment of a condition and healing status of fractures.

Whether you are just diving into ICD-10-CM or you have already taken the plunge, you cannot become too familiar with the guidelines. Read and reread them, and highlight those trickier areas for quick reference. The provider and coder must work together to successfully implement this expansive change. The extra knowledge you can gain from the coding guidelines will be helpful not only to you but can be an educational tool when training others.

Ensure proper code assignment in ICD-10-CM by studying the conventions and guidelines in greater detail. Watch for part 2 in the January 2014 issue of *CHEST Physician*.

Brenda Edwards entered the coding and billing profession 25 years ago and has been involved in many aspects of the field. Her current responsibilities include chart auditing, coding and compliance education, and contributing articles to AAPC and industry publications. Brenda is an AAPC ICD-10-CM trainer and has presented for AAPC workshops, regional conferences, and local chapter meetings. She has also served on the AAPC local chapter board of directors.

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Frank McCormack, MD
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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:

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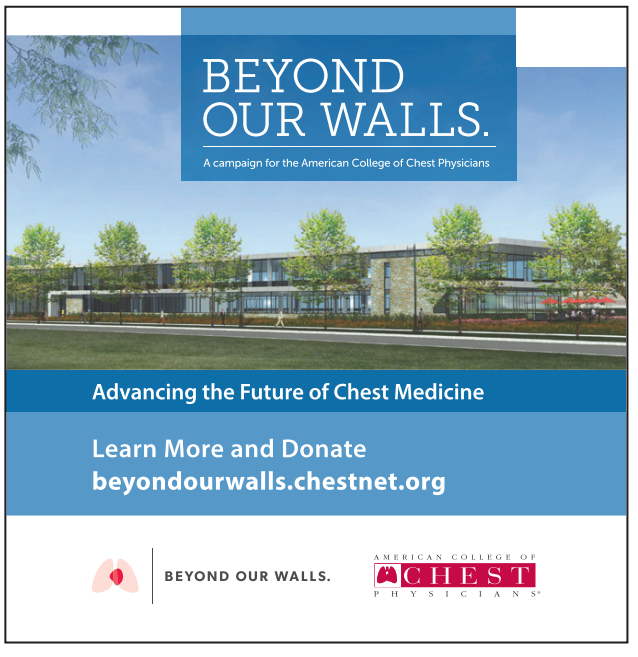

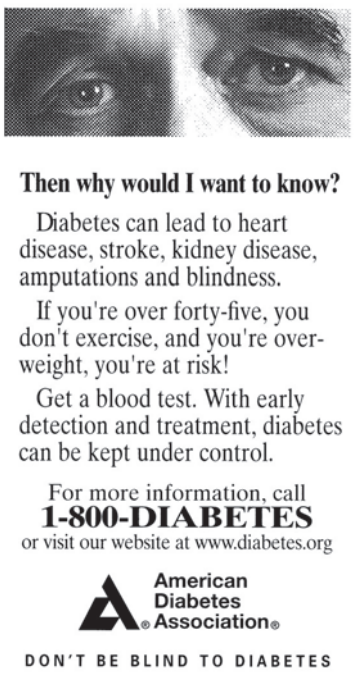

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Antitrust rules can trip up practices

Regulations *from page 1*

purpose of meeting the ACA's data-driven call on providers to improve care and lower costs. This can be achieved for less when physicians in private practice band together, but it's not as simple as a handshake, said Dr. Diamond.

The U.S. Department of Justice specifically defines clinical integration as a "network implementing an active and ongoing program to evaluate and modify practice patterns … and create a high degree of interdependence and cooperation among the physicians to control costs and ensure quality…"

"You have to really adhere to this definition to avoid antitrust issues," said Dr. Diamond, who made his remarks at CHEST 2013.

"The Statements of Antitrust Enforcement Policy in Health Care, issued jointly by the Federal Trade Commission and Department of Justice in 1996, carve out certain safety zones for physician network joint ventures," said Christopher Gordon, a specialist in health care antitrust law at Squire Sanders LLP in Washington.

Mr. Gordon said that the DOJ and the FTC "will typically not challenge an exclusive physician network joint venture where the participants share substantial financial risk and constitute 20% or less of the physicians in each specialty practicing in the relevant geographic market. Where the network is nonexclusive, that number rises to 30% or less."

If they are too large, or if they don't keep to these predetermined percentages of competing physicians by specialty, groups of competing health care providers cooperating to make their ACA mandates could be in danger.

"Networks that fall outside these safety zones – either because they include a higher percentage of physicians or do not involve financial risk sharing – do not necessarily raise antitrust concerns, but instead will have their conduct reviewed under what is known as the 'rule of reason' to determine whether, on balance, the conduct is anticompetitive or not," said Mr. Gordon.

"You have to be very careful you don't end up accused of illegal collective bargaining," said Dr. Diamond. "There is a disconnect between what the Department of Justice and what the ACA are asking."

If not a disconnect, at least a proscribed field of play.

According to Mr. Gordon, providers have latitude in how they cooperate when it comes to developing clinical protocols and best practices, so long as that cooperation does not include pricing agreements among multiple, independent clinics. "Such conduct would arguably constitute a per se violation of the antitrust laws regardless of how small or big the clinics are," he said.

Although the Justice Department and the FTC are primarily focused on conduct that impacts commercial health insurance markets, fee schedules and reimbursements that are part of any Medicare Advantage plan are considered part of the marketplace, because these plans are offered by private insurers contracting with the federal government, Mr. Gordon said. Medicare proper, meanwhile, is unaffected by antitrust concerns because "its pricing is set by the government, so there is little or no risk that provider misconduct could impact those prices," he noted.

Whatever happens, said Dr. Diamond, to survive in the era of the ACA, providers who will thrive with clinical integration are those who can develop areas of expertise such as excellent electronic health record systems, which make them attractive partners to other clinics and health care facilities. "Be a friendly competitor," he said. Above all else, he added: "Embrace change."

Dr. Diamond reported having no disclosures.

wmcknight@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Burt Lesnick, FCCP, comments: Practices can come together via financial integration or clinical integration, each with its own sets of guidelines to avoid antitrust issues. Financial integration requires some degree of risk sharing. Clinical integration does not require risk sharing but has stringent requirements from the Department of Justice. The ACCP's former treasurer, Dr. Diamond, outlines these in this article.

POLICY & PRACTICE

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PQRS reports available

Feedback reports are available from the Centers for Medicare and Medicaid Services for providers who submitted Physician Quality Reporting System data from Medicare Part B Physician Fee Schedule claims in 2012. Individuals can request National Provider Identifier–level reports through the CMS' Communications Support Page. The reports take up to 4 weeks to process, according to the agency. Meanwhile, groups participating in the group practice reporting option can access their feedback through the 2012 Quality and Resource Use Reports (https://portal.cms.gov). Through these feedback reports, physicians and other providers can compare their performance with their peers, and determine how often they are meeting a particular quality metric. To participate, individual providers were required to choose at least three individual measures or one measures group to report to the CMS; groups had to choose three measures and report on at least 80% of their Medicare fee-for-service patients. Those individuals and groups that met the criteria are eligible for a 0.5% incentive payment on all Medicare fee-for-service charges incurred during the reporting period. The PQRS program will penalize providers for not participating beginning with measures collected this year: Providers who do not participate in PQRS will be paid 1.5% less than the Medicare fee-for-service amount for services they provide in 2015. Physicians and other providers can avoid the penalty by applying for the CMS Administrative Claims option, which allows the CMS to calculate the PQRS data for them, or by submitting one valid measure or measures group in 2013.

Plans pursue dual markets

Consumers in 30 states have the option of at least one health plan operating on both health insurance exchanges and as a Medicaid managed care organization, offering current Medicaid beneficiaries a choice of keeping their plan as their income increases, according to an analysis by Avalere Health. The analysis showed that consumers in 22 states will have two or more plans that participate in both markets. Some states, including California and Nevada, are pursuing strategies that urge plans to participate in both Medicaid and exchanges.

Guidance needed on navigators

As multiple states approve legislation limiting the activities of health navigators under the Affordable Care Act, the U.S. Department of Health and Human Services may need to provide clearer guidance on when state laws prohibit those navigators from doing their jobs, according to an analysis in the journal Health Affairs. Navigators, generally funded by state and federal grants, help consumers understand and operate in the ACA's health insurance exchanges. According to the analysis, navigators perform many of the same functions as insurance brokers, who must be licensed and may be required to carry insurance against offering bad advice. Insurance agents and brokers have been pressing states to impose additional requirements on navigators, and so far 17 states have done so. "Looking at some of the state laws, it is clear there are going to be questions as to when state laws prohibit navigators from doing their job," the report stated. "For example, the Maine law says that only licensed producers may make recommendations and enroll people in health plans offered through the marketplace, one of the principal duties of navigators."

AAPS sues on Obamacare

The Association of American Physicians and Surgeons has filed suit in federal court to stop the Obama administration from imposing the Affordable Care Act's individual mandate to purchase insurance while delaying the part of the law that requires employers to provide coverage. The lawsuit from the conservative physicians group, filed in the U.S. District Court for the Eastern District of Wisconsin, notes that both mandates were scheduled to take effect on Jan. 1, but the administration has moved to delay the employer mandate for a year. "This unlawful change will force many Americans, more than Congress intended, to purchase expensive, unwanted health insurance," the group said in a statement.

–Jane Anderson

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