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CHEST™ Physician

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COURTESY TEMPLE UNIVERSITY HEALTH SYSTEM

Clinicians may be missing patients who need statins but aren't getting them, says investigator Dr. Gerard J. Criner, FCCP. Watch an interview online.

Statins don't help, may harm in COPD, ARDS

Rigorous trials counter observational data.

BY SHERRY BOSCHERT
Frontline Medical News

SAN DIEGO – Two separate prospective, multicenter trials of statins stopped early when interim results showed they did not help – and potentially harmed – patients with moderate to severe chronic obstructive pulmonary disease or sepsis-associated acute respiratory distress syndrome.

The findings contradict previous observational data suggesting that the potential anti-inflammatory effects of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [HMG-CoA]) might benefit patients with these two diseases.

Statins did not significantly reduce rates of exacerbation of chronic obstructive pulmonary disease (COPD) or the time to first exacerbation in a study of 885 patients with moderate to severe COPD who were at high risk for exacerbations and who did not require statins for other indications. Patients in the STATCOPE study (Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD) received a daily oral dose of either 40 mg simvastatin or placebo for 12-36 months.

The simvastatin group

See **Statins** • *page 22*

PULMONARY PERSPECTIVES

The novel oral anticoagulants: A new frontier

BY MAJ. DAVID HOSTLER, MC, USA

Throughout the modern era of medicine, clinicians have sought to manipulate the balance of clotting and bleeding to their patients' benefit.

DR. HOSTLER

Intravenous unfractionated heparin (UFH) was demonstrated safe in the 1930s and was the standard injectable anticoagulant for the remainder of the 20th century. Warfarin became available for medical use 60 years ago and rapidly became the most popular oral anticoagulant in North America (Holbrook et al. *Arch Intern Med.* 2005;165[10]:1095). Low molecular weight heparins (LMWH) became clinically available at the turn of the current century and are now becoming available as less expensive generic drugs.

These medications have formed the basis of therapy for a broad range of conditions in which the physician wishes

See **NOACs** • *page 28*

Oncogenes in 64% of lung cancers

BY MARY ANN MOON
Frontline Medical News

"Actionable" oncogenic drivers – genetic mutations that are critical to the development and maintenance of a cancer and that are susceptible to targeted therapy – were identified in 64% of tumor samples from 733 patients with lung adenocarcinoma in a proof-of-concept study aimed at determining the frequency of such mutations that was reported in JAMA.

The researchers used multiplexed genetic testing to screen tumor samples for 10 possible oncogenic drivers simultaneously. In some cases, the results allowed clinicians to individually tailor cancer treatment, and patients who received this targeted therapy showed longer survival times than

See **Adenocarcinomas** • *page 26*

INSIDE

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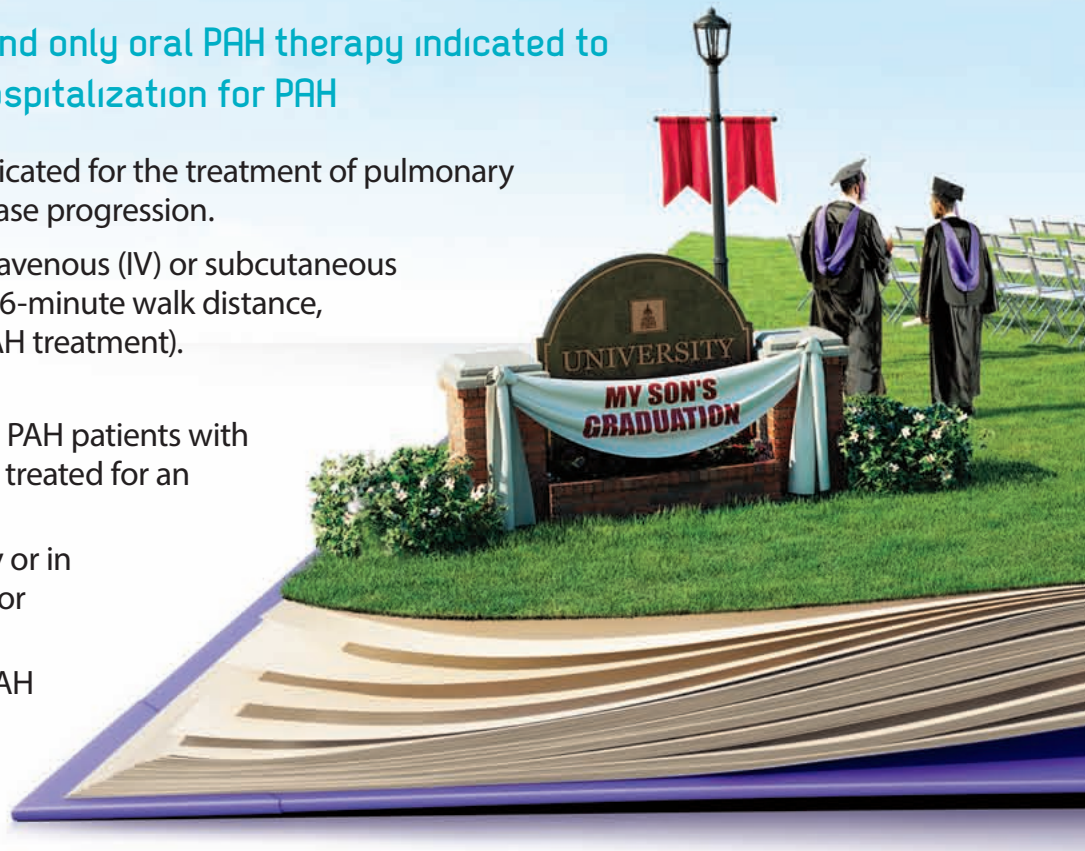
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

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%).



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.**
- **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.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS)**

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- 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.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT 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

Patient dramatization

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 in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. 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.

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.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 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. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

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

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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

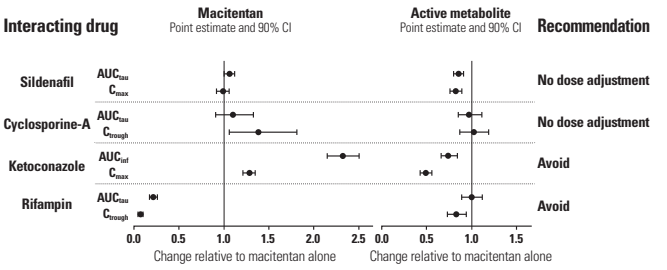
In vitro studies

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.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018

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

Azithromycin benefits older pneumonia inpatients

BY SHARON WORCESTER
Frontline Medical News

Treating pneumonia with azithromycin is linked to lower risk of death but a slightly higher risk of myocardial infarction in older patients, according to a large retrospective cohort study.

Although azithromycin is recommended in combination with macrolides for the first-line treatment of patients hospitalized with pneumonia, recent research suggests that azithromycin is associated with an increased risk of cardiovascular events.

However, the current findings suggest that although the drug is associated with a slight increase in the risk of myocardial infarction (number needed to harm equals 144), it is not associated with "any cardiac event," cardiac arrhythmia, or heart failure, and that the reduction in 90-day mortality risk (number needed to treat of 21) is large enough to provide an overall net benefit.

Dr. Eric M. Mortensen of the Veterans Affairs North Texas Health Care system, Dallas, and his colleagues reported their findings on treating pneumonia with azithromycin in JAMA.

In the current study, 90-day mortality in 31,863 patients aged 65 years and older who were exposed to azithromycin was significantly lower than in an equal number of propensity-matched controls who were not exposed (17.4% vs. 22.3%; odds ratio, 0.73).

The risk of myocardial infarction, however, was significantly increased in the azithromycin group (5.1% vs. 4.4%; OR, 1.17), the investigators reported.

Azithromycin use was defined as patients' receipt of at least one dose of azithromycin during the first 48 hours after admission. Study subjects were a mean age of 77.8 years in the national Department of Veterans Affairs administrative database who were hospitalized with pneumonia between 2002 and 2012 (JAMA 2014 June 4 [doi: 10.1001/jama.2014.4304]).

The myocardial infarction risk was significantly increased in the azithromycin group (5.1% vs. 4.4%).

DR. MORTENSEN

Most patients (98%) were male.

The study had relatively few female subjects and relied "upon ICD-9 diagnosis of cardiovascular events rather than clinical information, which particularly may affect the diagnosis of heart failure." However, researchers said, treating physicians were likely to have believed that the patients in the study indeed had pneumonia and did not show any bias toward azithromycin.

VITALS

Key clinical point: The benefit of azithromycin for elderly pneumonia patients outweighs MI risk.

Major finding: Ninety-day mortality in patients receiving azithromycin was 17.4% vs. 22.3% among controls.

Data source: A retrospective cohort study of 63,726 adults aged 65 years or older and hospitalized for pneumonia.

Disclosures: Support came from a National Institute of Nursing Research grant. Dr. Mortensen had no disclosures. Other researchers received grants from industry sources.

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: Azithromycin is a widely used (perhaps too widely) and effective (it's hard to be too effective) antibiotic commonly used in patients with respiratory illnesses. Recent reports, however, have called the safety of this medication into question. The results of this very large study may ease the practitioner's anxiety, at least when treating patients hospitalized with pneumonia.

For a slight increased risk of heart attack, use of azithromycin provides a significantly lower risk of death. As long as the drug is used for the appropriate indication, I'll take that deal in most situations.

IN THIS ISSUE

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

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Traditional scoring tool limps as VAP screen

BY ELIZABETH MECHCATIE
Frontline Medical News

BALTIMORE – Screening based on a new chest x-ray infiltrate or fever correctly identified more microbiologically confirmed cases of ventilator-associated pneumonia than did a traditional screening tool, in a study of patients in a surgical intensive care unit.

VITALS

Key clinical point: The Clinical Pulmonary Infection Score (CPIS) was less useful than other variables, such as a new chest x-ray infiltrate or fever, in screening surgical ICU patients for VAP and determining the need for empiric antibiotic therapy.

Major finding: The sensitivity of the CPIS tool for VAP in surgical ICU patients was only 21%, compared with 91.1% for a new chest x-ray infiltrate and 89.0% for fever.

Data source: The study evaluated the value of the CPIS and other clinical and gram stain variables in screening for VAP, in 497 adult patients in a surgical ICU.

Disclosures: Dr. Pieracci had no relevant disclosures. The study was funded through institutional monies.

The findings were reported at the annual meeting of the Surgical Infection Society.

In the study, the Clinical Pulmonary Infection Score (CPIS) clinical score (using the threshold of 6) would have missed almost 80% of the cases of microbiologically confirmed VAP.

The finding of a new chest x-ray infiltrate was highly sensitive for diagnosing VAP, identifying most cases of VAP, followed by fever as the next most sensitive variable. Each had a sensitivity of about 90%, according to Dr. Fredric Pieracci of the department of surgery, Denver Health Medical Center, University of Colorado.

Another notable finding of the study was that the presence of organisms on gram stain in the early VAP window (within 5 days of intubation) was highly sensitive for diagnosing VAP, he added.

VAP is the most common nosocomial infection in intubated, critically ill surgical patients and is the most common reason antibiotics are prescribed in the surgical intensive care unit (SICU), he said. Screening criteria for VAP vary widely, but every algorithm includes some variation of the CPIS, with a score that ranges from 0 to 12. Although the CPIS screening tool, which uses variables that include tracheal secretions and chest x-ray results, has come under scrutiny, it is commonly used, with a result over 6 used as the threshold for both obtaining a lower respiratory tract culture and initiating empiric treatment.

The investigators analyzed the results of 1,013 bronchoalveolar lavage cultures from 497 SICU patients aged 18-88 years, over a 3-year period (2009-2012). Most of the patients (81%) were males and 71% were trauma patients; cultures were obtained a median of 8 days after intubation (range, 1-109 days), and

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patients had a median of two cultures.

VAP was defined microbiologically as at least 10^5 CFU/mL if no antibiotics had been given within the previous 72 hours; or at least 10^4 CFU/mL if antibiotics had been given within the previous 72 hours. CPIS scores were calculated retrospectively.

Of the 1,013 cultures, 438 (43%) met the VAP criteria, and 310 of the 497 patients (62%) had at least one episode of VAP.

Most of the CPIS clinical scores were 4, 5, or 6. When the likelihood of VAP was analyzed, CPIS clinical scores from 1 to 9 all correlated with about a 40% chance of VAP, Dr. Pieracci said.

The median CPIS clinical score was 5 for those diagnosed with VAP as well as those not diagnosed with VAP, based on the microbiologic criteria.

The sensitivity of the CPIS clinical score, when the threshold of greater than 6 was used, was only 21%, so by using the CPIS, "we would have missed almost 80% of the VAP cases in this group of patients," he pointed out.

Every case of VAP had at least one of the following: fever, a new chest x-ray infiltrate, or the presence of organisms on gram stain.

Of the individual components of the CPIS, the most sensitive for diagnosing VAP were the new finding on chest x-ray (a sensitivity of 91.1%), and fever (a sensitivity of 89.0%).

We have adopted a screening algorithm 'that is based on either fever or new chest x-ray finding.'

DR. PIERACCI

When the gram stain results were added to the CPIS clinical score, there was a marginal improvement in sensitivity, "but it was still a very poor screening tool," Dr. Pieracci said.

However, the presence of organisms on the gram stain "was highly sensitive for diagnosing VAP, with a reasonably high negative predictive value" in the early VAP window, when cultures were sent within 5 days of intubation, he said.

The results indicate that the CPIS clinical score in the study "had poor discriminative ability for diagnosing VAP in all the clinical scenarios we tested," and it had a sensitivity that was acceptable only at a threshold lower than 6, according to Dr. Pieracci.

"Based on these data, we recommend abandoning the CPIS clinical score as a screening tool for VAP," and instead, adopting the three criteria and withholding antibiotic therapy in patients with no organisms on gram stain in the early VAP window.

"What we've adopted and are now studying is a screening algorithm that differentiates between the early and late period, and is based on either fever or new chest x-ray finding," Dr. Pieracci said. If the gram stain is negative in the early VAP window, then withholding empiric antibiotics is recommended; this is the only scenario identified in which empiric antibiotics could be safely withheld, he added.

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Less severe sepsis goes unrecognized in hospitals

BY M. ALEXANDER OTTO
Frontline Medical News

SAN DIEGO – Although hospitals in recent years have done a good job catching severe sepsis, less severe cases are falling through the cracks and ultimately proving fatal, according to a retrospective database study presented at an international conference of the American Thoracic Society.

That's probably the main reason investigators at Kaiser Permanente Northern California (KPNC) found that up to half of hospital deaths are sepsis related. Of 14,206 adult inpatient deaths at KPNC hospitals between 2010 and 2012, 36.9% had sepsis-related codes. When the team included patients without sepsis codes but with evidence of both infection and acute organ failure – implying sepsis – the number rose to 55.9%.

Most patients had indications of sepsis at admission, and patients with initially less severe sepsis made up the majority of sepsis deaths.

VITALS

Key clinical point: Have a high index of suspicion for less severe sepsis at hospital admission.

Major finding: About 56% of sepsis-related deaths are in people with normal blood pressure and normal or intermediate serum lactate levels (less than 4 mmol/L) on admission.

Data source: A retrospective database study of about 7 million adult hospitalizations.

Disclosures: The work was funded by the Kaiser Foundation, the Department of Veterans Affairs, and others. One author disclosed personal fees from industry sources. Dr. Liu and the other authors said they had no financial disclosures.

FRONTLINE MEDICAL NEWS

Dr. Vincent Liu says that although mortality has fallen for patients with severe sepsis, there's still a long way to go in catching and treating less severe cases in time. Watch a video online.

About 56% of sepsis-related deaths were in people with normal blood pressure and normal or intermediate serum lactate levels (less than 4 mmol/L) on admission. Patients who met the criteria for early goal-directed therapy at admission, but for whatever reason did not get it, accounted for 21% of the deaths (JAMA 18 May 2014 [doi:10.1001/jama.2014.5804]).

The story was similar when the team looked at 143,312 deaths in the 2010 Healthcare Cost and Utilization Project Nationwide Inpatient Sample, which captures about 20% of U.S. community hospitals: 34.7% had sepsis codes, and 52% had codes or evidence of both infection and acute organ failure.

Sepsis could have been the final common pathway in already-ill patients, but the numbers hint that at least in some cases, sepsis that could have been extinguished early got out of hand before it was recognized.

The Surviving Sepsis Campaign and other efforts "have had a huge impact on how we treat the most severely ill sepsis patients. We've seen about a halving of mortality in the past 15 years. Now we need to broaden our perspective to focus intervention on the less severely ill, who tend to be less severe up front and underidentified," said lead investigator Dr. Liu, with the KPNC division of research, Oakland, Calif.

Based on the results, KPNC has started applying its sepsis bundle to patients with intermediate-lactate levels, "but there is very limited data about the benefit of bundle care in less severe sepsis patients, so we are still tracking our outcomes," he said. There's also a culture shift involved, which includes heightening clinician awareness, updating communication protocols, and other measures, Dr. Liu said in presenting the results.

There's a role for more research dollars as well, and education efforts to make the public aware of sepsis and the need for early intervention, similar to what's been done for stroke, he said.

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VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: These national data corroborate data from nearly every individual hospital that has looked at the phenomenon in the Kansas Sepsis Project and other quality improvement efforts with which I work personally.

It is clear that early identification of severe sepsis and aggressive intervention remain suboptimal in U.S. hospitals, in spite of a decade of attempts by numerous organizations, including CHEST, the Surviving Sepsis Campaign, the New York Hospital Association, and others to make providers aware of the need. One hopes that the press engendered by these findings helps to focus more attention in that direction and helps to prevent unnecessary deaths.

Subsyndromal delirium common in critically ill patients

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Subsyndromal delirium was present in 86% of critically ill patients, results from a large observational study demonstrated. In addition, the duration of delirium was associated with increased odds of institutionalization, an association that was modified by the duration of delirium.

"In patients with less delirium, the effect of subsyndromal delirium on institutionalization was actually stronger," lead author Dr. Nathan E. Brummel said in an interview at an international conference of the American Thoracic Society, where the research was presented. "This identifies a cohort of people who previously were considered to have normal brain function, but it appears that this has long-term implications for their lives.

For the study, Dr. Brummel, an instructor in medicine in the division of allergy, pulmonary and critical care medicine at Vanderbilt University Medical Center, Nashville, Tenn., and his associates evaluated 821 medical or surgical ICU patients with respiratory failure and/or shock who were enrolled in the BRAIN-ICU observational cohort study (N. Engl. J. Med. 2013;369:1306-16).

They used the Confusion Assessment Method for the ICU (CAM-ICU) to screen for delirium symptoms twice daily in the ICU and daily thereafter. The researchers considered delirium to be present if the CAM-ICU was positive. If the CAM-ICU was negative, they considered subsyndromal delirium (SSD) to be present if any delirium features were present or if inattention was present with or without other features of delirium.

SSD "is said to be present when a patient exhibits some delirium symptoms but does not meet the full delirium diagnostic criteria," the researchers wrote in their poster. "In patients without critical illness, SSD is associated with institutionalization, mortality, and cognitive decline, but these associations remain unclear in the critically ill."

The researchers tracked discharge location, mortality after hospital discharge and assessed for cognitive impairment at 3 and 12 months follow-up and used multivariate regression to determine the relationship between days of SSD and outcomes.

The mean age of the 821 patients was 61 years and their mean APACHE II score was 25. In all, 702 patients (86%) had SSD that lasted an average of 3 days. The most common SSU pattern based on the CAM-ICU was fluctuation of mental status

Continued on following page

Dabigatran's safety data satisfy FDA's concerns

BY ELIZABETH MECHCATIE
Frontline Medical News

VITALS

Major finding: The risks of ischemic stroke, intracranial hemorrhage, and death associated with dabigatran treatment were lower than with warfarin, but the risks of MI were similar and the risk of major GI bleeding was increased among those on dabigatran.

Data source: An observational cohort study of more than 134,000 Medicare beneficiaries AF compared the rates of different outcomes among patients treated with dabigatran and those treated with warfarin.

Disclosures: The FDA conducted the study.

Current recommendations and labeling regarding the use of dabigatran will not change, based on the results of a large observational cohort study comparing the risks of the direct thrombin inhibitor and warfarin in Medicare recipients, the Food and Drug Administration announced.

The study, which was completed recently and has not been published, found that dabigatran, compared with warfarin, was associated with a lower risk of ischemic stroke, intracranial hemorrhage, and death, according to the FDA's statement on the findings. The risk of major gastrointestinal bleeding, however, was higher with dabigatran, and the risk of myocardial infarction was similar in both groups.

The statement points out that other than the MI finding, the results are consistent with the results of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which found the MI risk was higher among those on dabigatran than with warfarin. Approval of dabigatran in 2010 for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation was based on the results of the RE-LY study. Dabigatran is marketed as Pradaxa by Boehringer Ingelheim.

"As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use," the FDA statement said. "Importantly, the new study is based on a much larger and older patient population than those used in FDA's earlier review of postmarket data, and employed a more sophisticated analytical method to capture and analyze the events of concern."

The study, part of an ongoing review of dabigatran, evaluated the risks of more than 134,000 new users of dabigatran and warfarin, who were over age 65 years and had been diagnosed with atrial fibrillation during the 6 months before the medication was dispensed. The data were for 2010-2012. Patient outcomes were identified in administrative and insurance claims, and the study represented more than 37,500 person-years of follow-up.

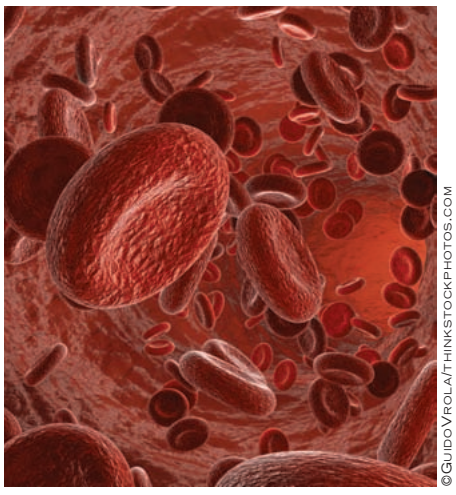
The results were as follows, with warfarin as the reference group, and dabigatran results based on the analysis of both approved doses (75 mg and 150 mg) combined:

- For ischemic stroke, the incidence rates (IR) per 1,000 person-years were 11.3 for dabigatran, vs. 13.9 for warfarin (hazard ratio, 0.80).
- For intracranial hemorrhage, the incidence rates were 3.3 for dabigatran, vs. 9.6 for warfarin (HR, 0.34).
- For major GI bleeding, the incidence rates were 34.2 for dabigatran, vs. 26.5 for warfarin (HR, 1.28).
- For acute MI, the incidence rates were 15.7 for dabigatran, vs. 16.9 for warfarin (HR, 0.92).
- For mortality, the incidence rates were 32.6 for dabigatran vs. 37.8 for warfarin (HR, 0.86).

The FDA statement points out that the results for major GI bleeding in this study are different from a previous FDA analysis of about 10,600 new users of dabigatran and warfarin, reported in 2012, which found that GI and intracranial hemorrhage rates were lower among patients treated with dabigatran, compared with those on warfarin. However, that study included patients under age 65 years (64% were older than age 65 years), and this disparity "may reflect the age differences in the two patient populations," the FDA statement said.

Reassuring results

In an interview, Dr. Sanjay Kaul, professor of medicine at University of California Los Angeles, said the data in the Medicare study were reassuring, "and indicate that the favorable benefit-risk balance observed in the pre-approval randomized controlled trial, RE-LY, are generalizable in real world clinical practice."



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Dabigatran is approved to reduce the risk of recurrent DVT and PE in previously treated patients.

Without a placebo control, he added, "it is unclear what to make of the MI signal observed in RE-LY, but not in this study." And while the exact cause of increased GI bleeding remains unclear, Dr. Kaul pointed out that this risk cannot be mitigated by gastroprotective medications such as H_2 blockers or proton pump inhibitors, and that "it is best to avoid this medication in patients with history of lower-GI bleeding."

Dr. Deepak Bhatt, professor of medicine at Harvard University in Boston, also described the results of the FDA study as reassuring. The study provides real-world data in a large number of patients that complement and largely mirror the results in RE-LY, he said in an interview.

"I think that all those findings regarding death, stroke, and GI bleeding are all true because they were true in the randomized clinical trial dataset, and it is good to see they also appear to be true in real-life clinical practice," he commented.

In addition, the data "further support the idea that the novel oral anticoagulants in patients who don't have contraindications for them, and can afford them, [are] a better option than warfarin," said Dr. Bhatt, the executive director of Interventional Cardiovascular Programs, at Brigham and Women's Hospital Heart and Vascular Center, Boston.

He pointed out that overall, the three novel oral anticoagulants – dabigatran and the factor Xa inhibitors, apixaban and rivaroxaban – approved for the nonvalvular AF indication, appear to reduce the risk of stroke and death, "and across the board, they all show significantly less intracranial hemorrhage."

The FDA plans to publish the Medicare study and will continue to review the risks of bleeding with anticoagulants.

Dabigatran is now also approved for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated.

The FDA has issued two previous safety alerts regarding the bleeding risks associated with dabigatran, in 2011 and 2012.

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Continued from previous page

(which occurred in 50% of assessments) and fluctuation in mental status plus altered level of consciousness (which occurred in 22% of assessments).

Dr. Brummel and his associates also found that the duration of SSD was independently associated with increased odds of institutionalization (odds ratio, 1.90), but SSD did not predict mortality or long-term cognitive impairment at 3 or 12 months. "We don't yet understand the mechanism behind why subsyndromal delirium and institutionalization are associated," Dr. Brummel said. "It probably relates to an association between SSD and factors that drive institutionalization, such as physical disability and cognitive impairment. Once patients survived the hospital stay, subsyndromal delirium wasn't associated with an increased risk of mortality. It may be the fact that this less severe form of brain dysfunction in the ICU does not have the same effect as the full syndrome of delirium."

He acknowledged certain limitations of the study, including the fact that the CAM-ICU measures only four features of delirium and that no assessments of cognitive or physical function were conducted at hospital discharge.

The study was supported by the National Institutes of Health, the Vanderbilt Clinical and Translational Scholars Program, and the Veterans Affairs Tennessee Valley Healthcare System Geriatric Research Education and Clinical Centers. Dr. Brummel said that he had no financial conflicts.

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Study identifies factors in adolescent smoking cessation

BY MIKE BOCK
Frontline Medical News

Investigators have identified 10 significant indicators for smoking cessation by adolescent students and say antismoking efforts should address an array of factors, including dependence, among other factors that affect youth.

"Youth tobacco-control programs that do not consider nicotine dependence symptoms in novice smokers may not be optimally effective," Jennifer O'Loughlin, Ph.D., professor in the department of social and preventive medicine at the University of Montreal, and her colleagues said in a report in Cancer Epidemiology, Biomarkers & Prevention. Their study attempted to gauge smoking habits of youngsters who have smoked for only a year or 2.

Data on teenage smoking habits came from participants enrolled in Nicotine Dependence in Teens, a study that collected self-reported data from 1,293 students every 3 months over the course of 5 years. Students were aged 12-13 years at baseline.

As expected, nicotine dependence had a negative effect on smoking. Although the data were presented with a number of covariables accompanying nicotine dependence – including tolerance – the authors found that "nicotine dependence symptoms, such as cravings, emerge as early as 5 months after initiation in some novice smokers, and that tolerance appears at 14 months," the researchers wrote.

Overall, they said, "Male sex, age, susceptibility to cigarette package warnings, participation in team sports, family stress, worrying about weight, overweight, use of illicit drugs, tolerance, and other nicotine dependence symptoms seem to be associated with smoking discontinua-

Continued on following page

VITALS

Key clinical point: Cessation programs should target young adolescents and focus on specific factors, including dependence symptoms.

Major finding: Out of 620 participants, 40% discontinued smoking during follow-up.

Data source: Longitudinal study of 1,293 Canadian adolescents tracked for 5 years.

Disclosures: The study was funded by the Canadian Cancer Society. The authors reported having no relevant financial disclosures.

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Boys were 80% more likely to discontinue smoking than were girls.

Continued from previous page

tion in novice adolescent smokers" (Cancer Epidemiol Biomarkers Prev. 2014;23[6] June [doi:10.1158/1055-9965.epi-13-0869]).

Conversely, the study found students whose parents smoked, who had stressful family lives, polysubstance abuse, body-weight issues, or adolescents who started smoking earlier in life were less likely to quit than were their peers. The investigators studied 37 potential predictors.

"Tobacco-control programs and policy targeting novice smokers may be more effective if these factors are taken into account in their conceptualization, design, and implementation," Dr. O'Laughlin and her associates wrote.

Data from 620 participants were included in the study. Regular follow-up found that approximately 40% discontinued smoking, defined as not smoking for more than a year. Most who quit were light smokers. Of those who stopped, more than 70% smoked 0-2 cigarettes/per month.

Among the findings:

- ► Boys were 80% more likely to discontinue smoking than were girls.
- ► Older adolescents were 30% more likely to discontinue than were younger adolescents.
- ► Participants who said cigarette package warnings made them afraid to smoke were 44% more likely to quit.
- ► Adolescents who participated in team sports were more likely to quit than were their nonsmoking peers (44% and 40%, respectively).

Students were recruited from 10 secondary schools in Quebec. Data used in the analysis were self-reported; the researchers said that more in-depth research on each predictor would eventually be needed.

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POLICY & PRACTICE

Stop-smoking rule debuts

Comprehensive smoking cessation coverage under the Affordable Care Act should include at least 90 days' worth of any quit-smoking medication approved by the Food and Drug Administration – including both prescription and over-the-counter products, according to guidance released in May 2014 by the Obama administration. The guidance also calls on insurers to pay for at least four tobacco cessation counseling sessions of 10 minutes or more each, regardless of whether they're telephone counseling, group counseling, or individual counseling sessions. Insurers must provide these benefits at no cost to the patient, which means that no copays, coinsurance, or deductibles apply, according to the ACA. The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use and provide interventions for those who use tobacco products.

MDs not Choosing Wisely

A national survey from the ABIM Foundation's Choosing Wisely campaign shows 73% of U.S. physicians say doctors ordering unnecessary medical tests and procedures is a serious problem – but just as many admit they do so at least once every week. Meanwhile, two-thirds of physicians think they have a great deal of responsibility to make sure their patients avoid unnecessary tests and procedures, but more than half say they'll order a test a patient wants even if they know it's unnecessary.

–Jane Anderson

COMMENTARY: In EHRs, copy and paste at your own risk

BY CHRISTINE KANE, J.D., JOHN D. BALAGUER, J.D., AND NEIL SKOLNIK, M.D.

Between "Hangovers," Bradley Cooper starred in a largely forgettable melodrama called "The Words." The main character was an aspiring writer whose career first skyrockets and then implodes when he plagiarizes an entire novel from a dusty manuscript found buried in an old briefcase bought at an antique store.

As art, "The Words" is destined for the on-demand scrap heap, but it may present a cautionary tale for anyone creating electronic health records.

While EHRs have many advantages that can improve health care delivery, including easy access and portability, the same technology that affords these advantages can also promote careless practices that may call into question the accuracy of the entire record and make it difficult, if not impossible, for health care providers to defend themselves in court.

Among the most troublesome EHR misuses we see in litigation is the inappropriate use of copy and paste functions, whereby a health care provider 'plagiarizes' his/her own or a colleague's prior documentation.

Among the most troublesome EHR misuses we see in litigation is the inappropriate use of copy and paste functions, whereby a health care provider "plagiarizes" his/her own or a colleague's prior documentation.


DR. SKOLNIK


MR. BALAGUER


MS. KANE

In medical negligence claims, the accuracy of the patient's medical record and the credibility of the health care providers are often both at issue, and many times the two go hand in hand.

Lawyers representing injured patients love to point out errors in the medical record, whether or not the error caused any patient harm, because – the argument goes – if the medical provider was careless in record keeping, then chances are he/she was also careless in the treatment at issue. So too, if the jury is provided with facts that differ from the medical record, suspicion arises.

Thus, an innocent but preoccupied provider is accused of lying or of trying to cover up a treatment error.

To avoid these insinuations, clinicians must put time and effort, as well as original thought, into medical record documentation.

Our experience in reviewing medical records for litigation suggests that a surprising number of practitioners routinely copy and paste information from a prior entry in the EHR.

The excuses we have heard for this run the gamut from unfamiliarity with the electronic system to lack of time and, ironically, the need to ensure accurate documentation.

Similarly, in "The Words," when Bradley Cooper's character starts copying another author's manuscript – word for word – onto his laptop, he tells himself that he is doing it simply for inspiration.

Excuses aside, this kind of rote replication is seductively easy but fraught with danger, particularly if the EHR later comes under scrutiny.

When data from a prior note in the EHR are copied, little thought or focus is given to context or clarity, and the cobbled-together entry is frequently disorganized and unclear. Worse yet, such copying can result in entering outdated or inaccurate information into the patient's chart.

Even simple errors of this kind can be very damaging.

Imagine trying to convince a jury that you are a careful and caring practitioner when it has been pointed out to them that, in your records, your patient's blood pressure was exactly the same every time she was in your office over the last 5 years.

Or that despite the fact that she was experiencing a precipitous, unexplained weight loss, you continued to describe her as morbidly obese.

Or that even though her husband died 3 years ago, your records show her "accompanied by spouse" at every visit.

Sometimes, EHR plagiarism goes right to the heart of the negligence claim.

Where the claim is inappropriate discharge of a patient who died a few days after leaving the hospital, the defense must show that the patient's condition improved and that troubling symptoms seen on admission responded appropriately to treatment. This effort is hampered by documentation prepared many days or weeks into a hospitalization that copies symptoms and physical findings that are no longer present.

Inaccurate information in the EHR can also confuse other medical providers, and the time necessary to reconcile inconsistent information may delay treatment.

Likewise, if inaccurate information is relied on for treatment decisions, the results can be disastrous.

It is often argued in litigation that if something doesn't appear in the medical record it didn't happen. A corollary to this dubious "rule" is that once bad information is documented in a medical record, it will be redocumented over and over and over again.

Predictably, the more times the erroneous data are repeated in the EHR, the more "reliable" it becomes. This problem has been around a long time, but EHR plagiarism has made it worse.

The medical record is the most important evidence in any medical negligence case. While it is true that only a small fraction of medical records will ever see the inside of a courtroom, you should always document assuming the chart in front of you could end up there.

Imagine trying to convince a jury that you are a careful and caring practitioner if your records show 'accompanied by spouse' even though the patient's husband died 3 years ago.

This requires time, original thought, accuracy, and completeness. Copying and pasting the electronic medical record, while superficially efficient, is the enemy of these goals, and could leave you – like Bradley Cooper in "The Words" – wondering what happened to your promising career.

Ms. Kane and Mr. Balaguer are in private practice in Wilmington, Del. Dr. Skolnik is associate director of the family medicine residency program at Abington (Pa.) Memorial Hospital and professor of family and community medicine at Temple University, Philadelphia. He is also editor-in-chief of Redi-Reference Inc., a software company that creates mobile apps.

This column appears regularly as the EHR Report. Read more online: Scan the QR code or visit internalmedicinenews.com.

COMMENTARY

Dr. James A.L. Mathers Jr., FCCP, comments: In response to financial incentives and impending penalties imposed by the American Recovery and Reinvestment Act of 2009, hospitals and health care providers have been rapidly replacing the traditional, hand written medical chart with computerized health records. As these software driven products from a variety of vendors have been adopted, substantial and often unexpected problems have arisen. As highlighted in this article, auto-populate and recall functions can lead to documentation of items, such as particular physical exam components, that were never performed by the physician entering the note. Another unintended consequence of the electronic medical record has led to what has been described perfectly as documented fraud. Medicare contractors have noted an increased frequency of electronic medical records with identical documentation across services. The Office of Inspector General is in the process of reviewing certain services for high billing providers and beneficiaries with high costs to identify electronic health records documentation practices associated with potentially improper payments. Unless a provider takes the time to audit the electronic record on each visit, inaccurate information can be placed in a record and continued forward leading to serious problems.

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WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO 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 LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO 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 ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO 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, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

ANORO ELLIPTA significantly improved trough (predose) FEV_1 by 167 mL vs placebo (P<0.001) at Day 169[1]

A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of ANORO ELLIPTA (n=413) and placebo (n=280), each administered once daily by the ELLIPTA inhaler. The primary endpoint was trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).[1]

Once-daily ANORO ELLIPTA

The first and only FDA-approved product for patients with COPD combining 2 long-acting bronchodilators in 1 inhaler

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO 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 COPD.
- 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.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Reference: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546.

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

ANORO ELLIPTA was developed in collaboration with Theravance

ANORO™ ELLIPTA™
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

ANORO™ ELLIPTA™
(umeclidinium 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 all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/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.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), 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 ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO 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 ANORO 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 ANORO 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 ANORO 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 ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO 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 ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO 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 use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 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, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO 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.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO 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.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.11 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 medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO 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 ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

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 ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 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 ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with 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 (5.4), 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 ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. 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, such as vilanterol, a component of ANORO ELLIPTA, 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 ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO 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 ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 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 450 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.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments 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).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

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

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were 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

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium 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 case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO 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.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC 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 7,800 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 210 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 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time 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 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death: Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ANORO ELLIPTA was developed in collaboration with Theravance.

GSK
Research Triangle Park, NC 27709

Revised 12/2013 ANR:1BRS

Lower ferritin threshold advised for children with RLS

BY DEBRA L. BECK
Frontline Medical News

MINNEAPOLIS – Using the adult treatment threshold for serum ferritin to guide treatment in children with restless sleep may lead to inappropriate iron supplementation.

In both adults and children, iron deficiency has been linked to the presence and severity of restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS). For adults, a serum ferritin less than 50 mcg/L is the threshold commonly used to guide iron supplementation for patients with RLS or PLMS. A threshold of 40-50 mcg/L also has been used in pediatric studies.

For children, however, a far lower level of 20 mcg/L appears more appropriate, Alyson Connor reported at the annual meeting of the Associated Professional Sleep Societies.

"Our findings raise a question about the best serum ferritin threshold to use when seeing a child with evidence of sleep restlessness, in particular with elevated" periodic limb movement index, Ms. Connor said. "While many children may benefit from iron supplementation for these disorders, this area is worthy of further study as investigation in animals suggests that treatment of iron deficiency with high-dose iron supplementation in early development may differentially affect the development of the brain."

Ms. Connor, a student in the biomedical research program at the University of Michigan, Ann Arbor, and her colleagues conducted a review of 537 children aged 12 months to 18 years who were referred to the University of Michigan pediatric sleep clinic. In this cohort (mean age was 8.9 years; 62% were male), a median serum ferritin level of 23.6 mcg/L was linked with polysomnographic measures of periodic limb movement index (PLMI) per hour of total sleep time of 5 or more, while a median level of 30 mcg/L was linked with PLMI less than 5. About 26% of the subjects had a PLMI of 5 or more.

"There was a significant association between serum ferritin and periodic limb movement index such that, for every 10-mcg/L increase in serum ferritin, it decreased the odds of having an elevated PLMI by 11%," Ms. Connor said. Boys, younger patients, those with lower serum ferritin levels, and those with a shorter time between hematology and polysomnography had significantly increased odds of a PLMI of 5 or more. Only 19% of patients had a serum ferritin above 50 mcg/L, while 50% had below 30 mcg/L.

"The cutoff of 50 is very sensitive, giving few false negatives, but not very specific, whereas a lower cutoff improves specificity," Ms. Connor said.

Studies are needed to assess the link between iron status and sleep measures in a general pediatric population and to determine the best iron dose, timing, and method of delivery, she said.

Apnea-of-prematurity therapy doesn't prevent later OSA

BY DEBRA L. BECK
Frontline Medical News

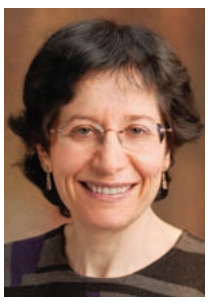
MINNEAPOLIS – Caffeine therapy for apnea of prematurity did not prevent the development of persistent and significant obstructive apnea in children by the time they were 9 years old.

"Apnea of prematurity occurs in more than three-quarters of infants born at under 30 weeks' gestation, and more than half of these apneas are actually obstructive in nature," Dr. Carole Marcus, director of the sleep center at Children's Hospital of Philadelphia, said at the annual meeting of the Associated Professional Sleep Societies. "Caffeine is now the most commonly used drug [to treat apnea of prematurity] in the NICU in infants less than 32 weeks' gestation," she said.

The long-term effects of caffeine on sleep in the developing brain are not well understood. It is not known whether neonatal caffeine administration has permanent adverse effects on sleep architecture and ventilatory control, perhaps increasing the risk of later sleep disorders such as insomnia and obstructive sleep apnea (OSA).

In the earlier CAP (Caffeine for Apnea of Prematurity) trial, 793 premature infants with birth weights of 500-1250 g were randomly assigned to caffeine or placebo until therapy for apnea of prematurity was no longer needed. Caffeine significantly improved the rate of survival without neurodevelopmental disability at 18-21 months in these babies versus placebo (N. Engl. J. Med. 2007;357:1893-902).

The subsequent axillary long-term CAP-S (Sleep) trial of 201 CAP subjects looked at whether neonatal caffeine administration resulted in later sleep abnormalities. The researchers assessed the ex-premature children aged 5-11 years (mean age, 9 years) via sleep questionnaires, actigraphy, and full ambulatory (home-based) polysomnography. The patients assessed in CAP-S were from Canada or Australia, with a high proportion of white patients, high maternal education, and high socioeconomic status, "which is relevant to our obstructive sleep apnea outcomes," noted Dr. Marcus.



No significant differences were noted in terms of subjective measures of sleep quality or quantity.

DR. MARCUS

No significant differences were noted in children who had received caffeine, compared with those who did not, in terms of subjective measures of sleep quality or quantity. Total recording time and total sleep time on polysomnography were somewhat longer in the caffeine arm, but there was no difference seen in sleep efficiency between groups ($P = .91$).

However, OSA (apnea-hypopnea index of more than two episodes per hour) was common in both groups (8.2% of the caffeine group and 11% of the placebo group). In contrast, the prevalence of OSA in the general pediatric population is 1%-4%.

Also, 24% of the caffeine group and 29% of the placebo group had OSA on polysomnography and/or a history of adenoidectomy/tonsillectomy, again with no difference between groups ($P = .35$).

A large proportion of subjects in both arms had elevated periodic limb movements (17.5% in the caffeine group and 11% in the placebo groups; $P = .27$), a proportion that was markedly higher than was the normal prevalence in cases in which the child had more than five episodes of periodic limb movement per hour, which lies between 5% and 8%.

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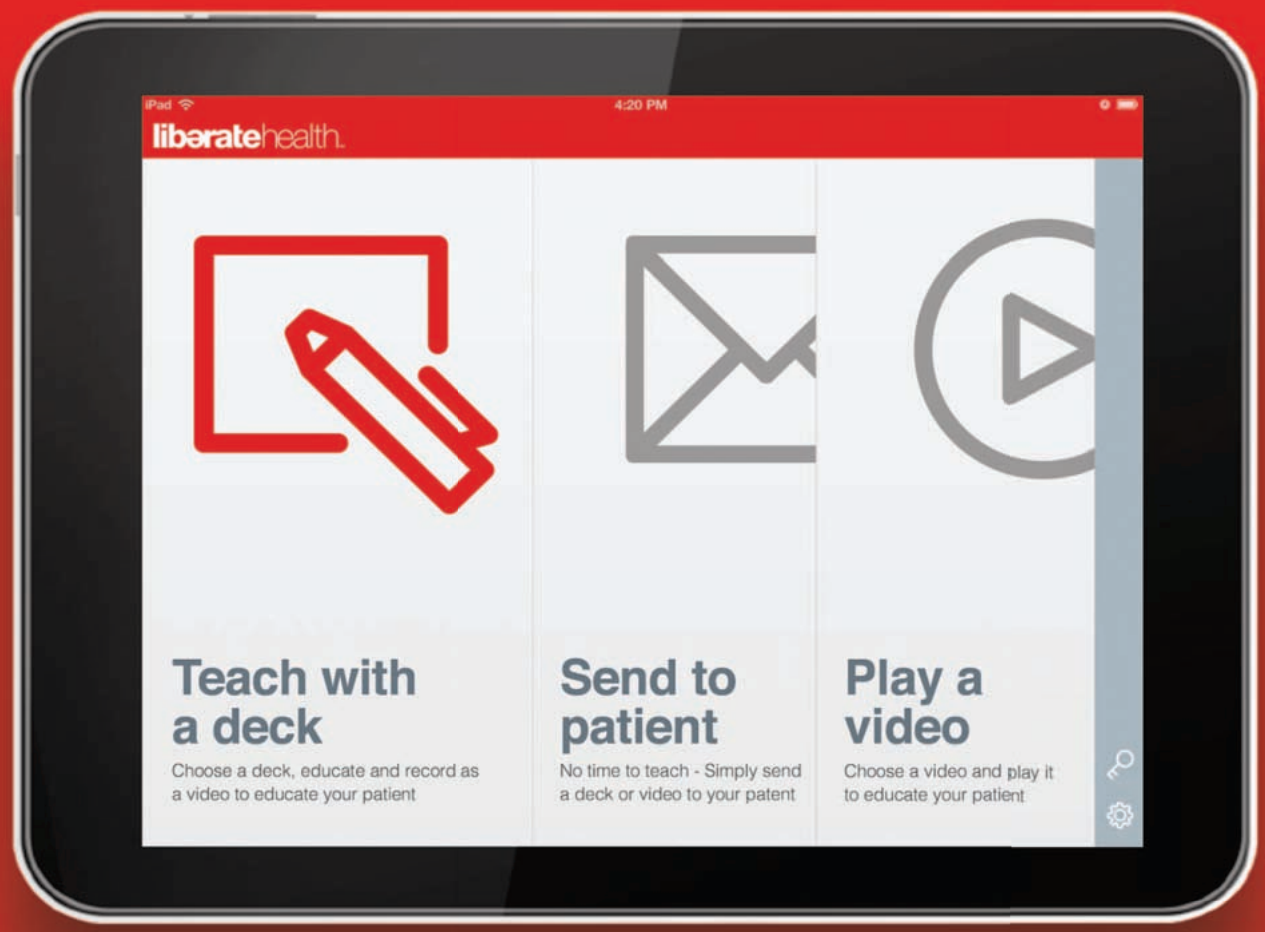

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* Weiss BD. Health literacy and patient safety: Help Patients Understand: *Manual for Clinicians*. 2nd ed. Chicago, IL. American Medical Association Foundation and American Medical Association; 2007.

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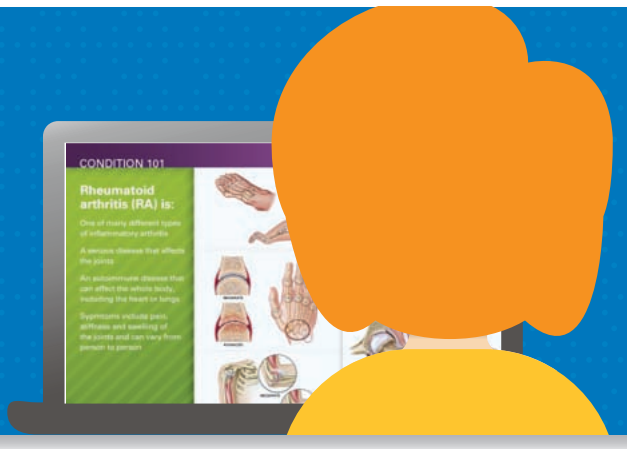

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Statin helped endothelial function in COPD subgroup

BY SHERRY BOSCHERT
Frontline Medical News

SAN DIEGO – Twelve weeks of rosuvastatin therapy was associated with reduced systemic inflammation, but no improvement in pulmonary function in a randomized, placebo-controlled trial in 99 patients with stable chronic obstructive pulmonary disease.

However, a prespecified analysis of patients with elevated results on high-sensitivity C-reactive protein tests (hsCRP) found that those with levels higher than the median of 1.7 mg/dL at baseline showed improved endothelial function with the statin, compared with placebo, Dr. Anke Neukamm reported at an international conference of the American Thoracic Society.

The findings provided a small ray of positivity for the anti-inflammatory effects of statins in chronic obstructive pulmonary disease (COPD) on a day when two larger randomized, controlled studies reported that rosuvastatin did not reduce mortality in patients with sepsis-associated acute respiratory distress syndrome and simvastatin did not reduce exacerbations in patients with moderate to severe COPD.

Dr. Neukamm's RODEO study (Effect of Rosuvastatin Treatment in Patients With Stable Chronic Obstructive Pulmonary Disease) randomized patients with stable chronic COPD to once-daily rosuvastatin 10 mg or placebo for 12 weeks. The groups did not differ significantly in the primary endpoint – peripheral vasodilator function expressed as a reactive hyperemia ratio.

In the subgroup analysis of patients with elevated hsCRP levels, however, the reactive hyperemia index improved from about 2.5 at baseline to 2.8 after 12 weeks of rosuvastatin and worsened from 2.6 to 2.5 in the placebo group, leaving a significant difference between groups at the end of treatment, said Dr. Neukamm of Akershus University Hospital, Lørenskog, Norway.

This suggested "a clear improvement of endothelial function in the statin group," she said.

Some physicians in the audience disputed the results, noting that rosuvastatin's effects would not have reached statistical significance if endothelial function had not worsened in the placebo group.

Dr. Neukamm remained cautiously optimistic. Targeting statin therapy for patients with COPD to those with increased systemic inflammation as indicated by high hsCRP levels might improve vascular function, she said in an interview. Patients in the study were "a very select group with a lower cardiovascular risk" than patients in other COPD studies. Without larger prospective trials, "we don't know if this small improvement in endothelial function would translate" into better clinical outcomes, she said.

Among secondary endpoints, circulating hsCRP levels fell from 1.4 mg/L at baseline to 1.2 mg/L in the rosuvastatin group, versus a change from 1.8 mg/L to 2.2 mg/L in the placebo group. The difference between groups was significant. Levels of the inflammatory marker interleukin-6 were stable at 4.1 pg/mL in the statin group and rose from 3.4 pg/mL to 4.4 pg/mL in the placebo group, also a significant difference between groups.

The trial excluded patients with a history of coronary artery disease, other diagnosed lung disease (except asthma), uncontrolled arterial hypertension, or diabetes, as well as patients who had used statins in the prior 4 weeks or who had a clear indication for statin use.

Thirty-three adverse events included COPD acute exacerbations, constipation, diarrhea, nausea, myalgia, and vertigo. Seven serious adverse events included hospitalizations for COPD exacerbations, as well as atrial flutter in one patient.

Patients had a mean age of 65 years, 48% were female, and 25% had a history of hypertension. They had a smoking history of a mean 37 pack-years. Baseline patient characteristics were similar between groups except for a higher percentage of current smokers in the placebo group (49%), compared with the rosuvastatin group (26%).

Stable COPD and acute exacerbations have been associated with systemic inflammation as reflected in increased levels of CRP and other inflammatory markers. Cardiovascular disease is a major comorbidity in patients with COPD, and inflammation is a hallmark of the atherosclerotic process, Dr. Neukamm said. Endothelial dysfunction, which is an early predictor of atherosclerosis, has been shown to be increased in patients with COPD.

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FRONTLINE MEDICAL NEWS

Dr. Anke Neukamm says targeting statin therapy to patients with increased systemic inflammation may improve vascular function. Watch an interview online.

VITALS

Key clinical point: Focusing statin therapy for COPD patients on those with increased systemic inflammation as indicated by elevated hsCRP might improve vascular function, but larger studies are needed.

Major finding: Rosuvastatin failed to improve pulmonary function overall, but significantly improved peripheral vasodilator function in patients with elevated hsCRP levels at baseline, indicated by a final reactive hyperemia index of 2.8 vs. 2.5 with placebo.

Data source: A randomized, controlled trial of 10 mg of rosuvastatin or placebo for 12 weeks in 99 patients with stable COPD.

Disclosures: The study was funded by the Norwegian Extra Foundation for Health and Rehabilitation and by AstraZeneca, which makes a brand name formulation of rosuvastatin. Dr. Neukamm has been a speaker for AstraZeneca.

Why mixed results from statin studies are reason for hope

SAN DIEGO – Two randomized, controlled trials presented at the American Thoracic Society international conference reported that statins did not improve pulmonary function or reduce exacerbations in patients with chronic obstructive pulmonary disease. But not everyone has given up on statins.

When a drug that showed promise in large observational studies doesn't pan out in randomized, controlled trials, physicians start looking for subgroups of patients that still might benefit, Dr. Nicholas Gross told us. Hear his perspective on the STATCOPE study (in which simvastatin did not prevent exacerbations in moderate to severe COPD) and the RODEO trial (in which rosuvastatin improved endothelial function only in a subset of patients with evidence of systemic inflammation).

Dr. Gross is an emeritus professor of medicine and molecular biochemistry at Stritch-Loyola University, Chicago. He reported having no relevant financial disclosures.

–Sherry Boschert

FRONTLINE MEDICAL NEWS

Dr. Nicholas Gross sees promise in that even when statins flopped for COPD in one trial, researchers didn't give up. Watch an interview on the multimedia page of chestphysician.org

Statins could harm in COPD, ARDS

Statins *from page 1*

had a mean of 1.36 exacerbations/person-year, compared with 1.39/person-year in the placebo group. The median number of days to the first exacerbation was 223 on simvastatin and 231 on placebo, differences that were not significant, Dr. Gerard J. Criner and his associates reported at an international conference of the American Thoracic Society.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The results of these two studies represent two poignant examples of the importance of rigorous trial design and patience prior to changing clinical practice. As has been the case with many interventions in pulmonary and critical care medicine, the conclusions of observational studies were not replicated or contradicted when subjected to more structured study design. The data from these two studies should elicit a thoughtful pause in those who have been overheard stating, "We should just put statins in the water."

The results were published online by the New England Journal of Medicine (2014 May 18 [doi:10.1056/NEJMoa1403086]).

Among the 885 patients for whom follow-up information was available, 1,982 acute COPD exacerbations occurred, 965 in 430 patients on simvastatin and 1,017 exacerbations in 447 patients on placebo, said Dr. Criner, professor of medicine and director of the medical intensive care unit and the ventilator rehabilitation unit at Temple University, Philadelphia.

Overall, 34% of patients had three or more exacerbations of COPD, with similar numbers in each group – 141 in the simvastatin group and 155 in the placebo groups. The proportions of patients who received glucocorticoid therapy or antibiotics for exacerbations did not differ significantly between groups.

The simvastatin group had a significantly higher rate of nonfatal serious adverse events involving the GI tract (mainly nausea and bloating from simvastatin) in 30 patients (0.05 events/person-year), compared with events in 17 patients on placebo (0.02 events/person-year). Rates of other nonfatal adverse events were similar between groups, with pneumonia and other respiratory and cardiovascular events most common. Twenty-eight patients on simvastatin and 30 on placebo died.

Asked why he thinks the STATCOPE study's negative results didn't confirm previous positive findings from observational studies including thousands of patients, Dr. Criner speculated that excluding patients with indications for statins may have removed patients with cardiovascular risks who were included in other studies. "I think a lot of the problems we're seeing for exacerbations in COPD might be related to cardiovascular events in patients who aren't appropriately treated with statins, who should be," he said.

Rosuvastatin sags in SAILS trial

In the separate double-blind SAILS trial (Statins for Acutely Injured Lungs [ARDS] From Sepsis), enteral rosuvastatin did not decrease mortality, compared with placebo, in 745 patients with sepsis-associated acute respiratory distress syndrome (ARDS). Dr. Jonathon D. Truwit, FCCP, and his associates reported their findings, which were discussed at the ATS meeting, in the New England Journal of Medicine (2014 May 18 [doi:10.1056/NEJMoa1401520]).

Researchers found that 28.5% of patients on rosuvastatin and 25% on placebo died before hospital discharge or within 60 days if the patient was still in a health care facility, reported Dr. Truwit, professor of medicine at the Medical College of Wisconsin, Madison.

Patients in the rosuvastatin group received a loading dose of 40 mg followed by daily maintenance doses of 20 mg (or 10 mg for patients with a morning serum creatinine level of 2.8 mg/dL or more who were not receiving renal replacement therapy. Treatment continued until the third day of discharge from the ICU, hospital discharge, or death, whichever came first.

Both the rosuvastatin and placebo groups had a mean of 15 ventilator-free days.

Results also did not differ significantly between groups for the 339 patients who were in shock at the start of the study or for 109 patients who had used statins before the study and who underwent a 48-hour washout period before randomization.

Patients on rosuvastatin had a mean of 10.1 days free of renal failure and 10.8 days free of hepatic failure within the first 14 days, both significantly

Continued on following page

VITALS

Key clinical point: Statins did not help, and possibly harmed, patients with moderate to severe COPD or sepsis-associated ARDS who did not require statins for other indications.

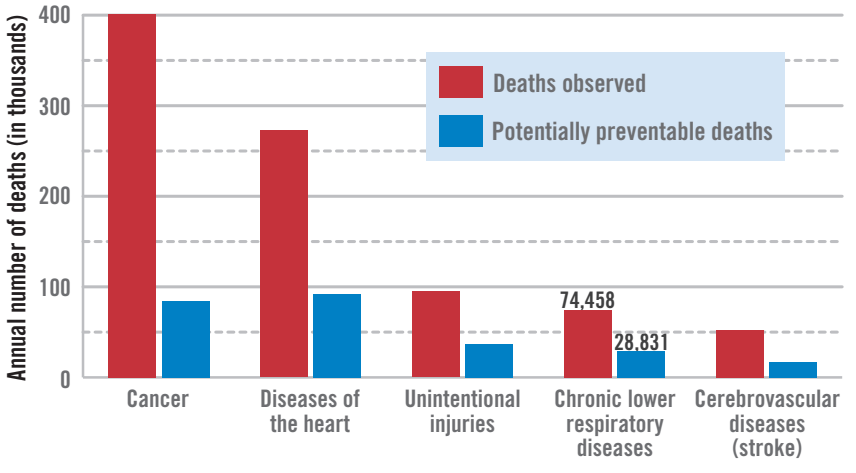
Major finding: The mean rate of COPD exacerbations was 1.36 in the simvastatin group and 1.39 in the placebo group, not significantly different.

Data source: STATCOPE, a multicenter prospective randomized, placebo-controlled trial of daily oral simvastatin 40 mg or placebo in 885 patients with COPD at high risk for exacerbations.

Disclosures: The National Heart, Lung, and Blood Institute and the Canadian Institutes of Health Research funded STATCOPE. Several coinvestigators reported financial associations with dozens of companies, including with Merck, which makes simvastatin.

DATA WATCH

39% of chronic lower respiratory disease deaths are preventable



Note: Based on data for the five leading causes of death for persons under age 80 years according to the National Vital Statistics System, 2008-2010.

Source: MMWR 2014;63:369-74

FRONTLINE MEDICAL NEWS

Corticosteroid doses cut with novel inhalation system

BY SHERRY BOSCHERT
Frontline Medical News

SAN DIEGO – Adults on chronic oral corticosteroids for asthma were able to decrease their doses while maintaining lung function by adding 0.5-1 mg budesonide delivered by an experimental inhaler in a randomized study of 199 patients.

The four-arm phase II/III study compared 18 weeks of twice-daily treatment using the AKITA® inhalation system or a conventional nebulizer while tapering oral corticosteroids. The compressor-driven system is designed to deliver the budesonide suspension to the small airways of the lungs. It is not approved in the United States to treat adults with asthma.

The system delivered budesonide 1 mg, budesonide 0.5 mg, or placebo, compared with an open-label treatment group that used a nebulizer to deliver 1 mg budesonide. Oral corticosteroids were tapered to week 14. Patients were followed to week 20, with lung function parameters measures every 2 weeks.

The mean forced expiratory volume at 1 second (FEV_1) significantly improved in the AKITA 1-mg budesonide group, compared with baseline, Dr. Sebastian Canisius and his associates reported at an international conference of the American Thoracic Society.

Continued on page 24

Continued from previous page

fewer compared with patients on placebo (11 and 11.8 days, respectively). "These differences in organ-failure-free days were small, and their significance may be spurious owing to the number of secondary endpoints analyzed. However, we cannot rule out a detrimental effect of rosuvastatin," the investigators wrote.

The results, combined with previous smaller randomized trials of other statins, suggest no benefits from starting or continuing statin therapy for sepsis-associated ARDS, Dr. Truwit said.

"The finding in observational studies that previous statin use provides a benefit may reflect better access to health care among patients who use statins than among those who do not, with a shorter time to the initiation of antibiotic therapy at the onset of symptoms of infection in statin users," according to the journal article.

The SAILS trial was sponsored by the NHLBI and by AstraZeneca, which makes rosuvastatin. Dr. Truwit reported having no financial disclosures. Several of his coinvestigators reported financial ties to AstraZeneca and other companies.

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Continued from page 22

Mean FEV_1 improved by 239 mL in the 1-mg AKITA group; improvements were lower in the other groups: 126 mL in the AKITA 0.5-mg budesonide group, 93 mL for placebo, and 137 mL in the nebulizer group.

Another surrogate marker of small airway function improved significantly in the AKITA 1-mg group compared with the placebo group – forced expiratory flow 25%-75% of vital capacity, or FEF (25-75), said Dr. Canisius, director of clinical development and drug safety for the Vectura Group, Kassel Area, Germany, which developed the inhalation system.

The FEF (25-75) improved by a mean of 0.2 L/s, compared with baseline in the AKITA 1-mg group, and did not change in the placebo group. Improvements in the other two groups were smaller and not significant compared with placebo.

Patients in the AKITA 1-mg group were significantly less likely to develop an asthma exacerbation, compared with the nebulizer group (8% vs. 22%) and went significantly longer before an exacerbation (96 days vs. 50 days).

Dr. Canisius works for and owns stock in the company that developed the inhalation device.

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who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered *[see Clinical Pharmacology (12.3)]*.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures approximately 3 times the human exposure. In rabbits, riociguat led to abortions at 5 times the human exposure and fetal toxicity at doses with exposures approximately 15 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose is approximately 0.15 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC). Plasma exposure at the highest dose is approximately 3 times that in humans at the MRHD while exposure at the mid-dose is approximately 0.5 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 5 times and 15 times the human dose at MRHD respectively.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. 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 patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas *[see Clinical Pharmacology (12.3)]*.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning and Dosage and Administration (2.2)]*.

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. 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]*.

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis *[see Clinical Pharmacology (12.3).]*

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program *[see Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines *[see Adverse Reactions (6.1)]*. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

Manufactured for:

Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

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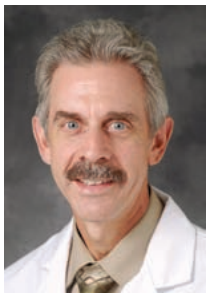
VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: Physicians caring for patients with severe asthma frequently encounter patients who require oral corticosteroid therapy despite being treated with significant complex inhaled regimens. The new AKITA® inhalation system is designed to deliver an aerosol more effectively to the distal airways than traditional nebulizers or handheld inhalant devices. In a recent trial, when compared to budesonide delivered by a traditional nebulizer, use of the system was associated with improvements in spirometric measures, reduction in the number of occurrences of asthma exacerbations, and increased length of time between recurrent exacerbations. The adverse consequences of long-term oral corticosteroid use will make the AKITA system an attractive adjunct to asthma management, if it can be demonstrated that the oral corticosteroid dose can be reduced, or their use eliminated, in severe asthma patients. However, long-term studies will be necessary to determine if there is significant systemic absorption, and thus risk of attendant consequences, of corticosteroids when administered by this device.



No benefit found for acetylcysteine in IPF

BY M. ALEXANDER OTTO
Frontline Medical News

SAN DIEGO – Acetylcysteine does not preserve forced vital capacity in idiopathic pulmonary fibrosis patients with mild to moderate lung function impairment, according to a study presented at an international conference of the American Thoracic Society.

At 60 weeks, there was no significant difference in the change in FVC between 133 patients randomized to acetylcysteine 600 mg three times daily and 131 randomized to placebo (–0.18 L and –0.19 L, respectively; $P = .77$). There were no significant differences between the acetylcysteine group and the placebo group in rates of death (4.9% vs. 2.5%, respectively; $P = .30$) or acute exacerbations (2.3% in each group; P greater than .99) (N. Eng. J. Med. 2014 May 18 [doi: 10.1056/NEJMoa1401739]).

"Our results are applicable only to patients with idiopathic pulmonary fibrosis [IPF] who met the inclusion and exclusion criteria of this trial, and not to patients with more advanced disease or other forms of idiopathic interstitial pneumonia or interstitial lung disease," said the researchers, all members of the Idiopathic Pulmonary Fibrosis Clinical Research Network and led by Dr. Ganesh Raghu, FCCP, director of the interstitial lung disease/sarcoid/pulmonary fibrosis program at the University of Washington, Seattle.

The study originally included a third arm in which patients received prednisone, azathioprine, and acetylcysteine, but it was halted after the data and safety monitoring board saw an increased risk of hospitalization and death, which led to a National Institutes of Health warning against use of the combination for IPF.

Overall, cardiac problems were more common in the acetylcysteine group than in the placebo patients (6.8% vs. 1.5%; $P = .03$), but gastrointestinal disorders were less common (0% vs. 4.6%; $P = .01$). There were trends favoring acetylcysteine in 6-minute walk distance and quality of life measures. Patients in the acetylcysteine group reported having better mental well-being.

Baseline characteristics were well matched in the two groups. Mean age was 67 years; 22% were women; 96% were white. Mean baseline FVC was 73% of the predicted value, and mean carbon monoxide diffusing capacity was 45% of the predicted value. Mean distance on the 6-minute walk test was 373 m.

At 60 weeks, 90.4% of the acetylcysteine group and 94.4% of the placebo group reported taking more than 80% of the recommended doses of the study drug.

"It is reasonable to shift our understanding of the pathogenesis of this disease," Dr. Gary M. Hunninghake, director of the sarcoidosis and granulomatous lung disease service at Brigham and Women's Hospital, Boston, wrote in an editorial (N. Eng. J. Med. 2014 May 18 [doi: 10.1056/NEJMe1403448]). IPF "is a disease perpetuated by aberrant wound healing, rather than primarily by chronic inflammation. With new understanding comes new hope."

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VITALS

Key clinical point: Acetylcysteine treatment of idiopathic pulmonary fibrosis is no better than placebo.

Major finding: At 60 weeks, there was no significant difference in the change in forced vital capacity between 133 patients who had been randomized to acetylcysteine 600 mg three times daily and 131 randomized to placebo (–0.18 L and –0.19 L, respectively; $P = .77$).

Data source: Randomized, placebo-controlled trial.

Disclosures: The work was funded by the National Heart, Lung, and Blood Institute, among others. Dr. Raghu cited grant support and personal fees from Gilead, as well as personal fees from Biogen, Boehringer Ingelheim, and other companies. The other authors disclosed payments for services from those or other companies. Dr. Hunninghake had no disclosures.

Investigational agent preserves vital capacity

BY M. ALEXANDER OTTO
Frontline Medical News

SAN DIEGO – Compared with placebo, the investigative tyrosine kinase inhibitor nintedanib helped preserve forced vital capacity in patients with idiopathic pulmonary fibrosis, according to phase III results presented at an international conference of the American Thoracic Society.

Across two trials, 1,066 patients were randomized 3:2 to 150 mg of nintedanib twice daily or placebo for 52 weeks. In INPULSIS-1, the adjusted annual rate of change in forced vital capacity (FVC) was –114.7 mL with nintedanib versus –239.9 mL with placebo (difference 125.3 mL; 95% confidence interval, 77.7-172.8; P less than .001). In INPULSIS-2, the rate of change was –113.6 mL with nintedanib versus –207.3 mL with placebo (difference 93.7 mL; 95% CI, 44.8 to 142.7; P less than .001).

"The curves for changes from baseline in FVC over time in the nintedanib and placebo groups separated early in the two studies and continued to diverge over time," the researchers wrote (N. Engl. J. Med. 2014 May 18 [doi:10.1056/NEJMoa1402584]). MIs were reported in five (1.6%) nintedanib patients and one (0.5%) placebo patient in the first trial and five (1.5%) nintedanib patients and one (0.5%) placebo patient in the second. Two MIs in the nintedanib groups and one in the placebo groups were fatal.

Idiopathic pulmonary fibrosis (IPF) is a serious disease "for which there are currently no FDA-approved treatments. We are all very excited by these data because they suggest evidence of nintedanib's impact on lung function loss in patients with IPF. Overall, [it's] a positive message that we are making progress," said lead investigator Dr. Luca Richeldi, chair of interstitial lung disease at the University of Southampton (England).

Results were mixed on secondary endpoints. There was no significant between-group difference in death from any cause or respiratory causes; 5.5% of nintedanib patients and 7.8% of placebo patients died. Likewise, the time to first acute exacerbation and progression on the St. George's Respiratory Questionnaire (SGRQ) were significantly delayed only in INPULSIS-2, not INPULSIS-1. On pooled analysis, nintedanib offered no advantage over placebo in time to first exacerbation (hazard ratio, 0.64; 95% CI, 0.39-1.05; $P = .08$) or mean 52-week change from baseline SGRO.

The "difference in the key secondary endpoint between [the trials] was not explained by the differences in baseline characteristics." Exacerbations "are relatively rare events in patients with [IPF] who are in clinical trials and are difficult to assess and categorize, which may explain some of the heterogeneity in our findings," the researchers said.

About 62% of nintedanib patients versus 18% of placebo patients reported diarrhea. Liver enzyme levels three times above normal were found in 5% of nintedanib patients and less than 1% of placebo patients.

Eighty percent of the subjects were men. Average age was 67 years. Baseline FVC was 80% of predicted value in all study arms.

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VITALS

Major finding: In the first trial, the adjusted annual rate of change in FVC was –114.7 mL with nintedanib versus –239.9 mL with placebo. In the second, the rate of change was –113.6 mL with nintedanib versus –207.3 mL with placebo.

Data source: Randomized, controlled trials involving patients with IPF.

Disclosures: Boehringer Ingelheim and the British National Health Service funded the work. Dr. Richeldi disclosed ties with InterMune, MedImmune, Roche, Takeda, Biogen Idec, Sanofi Aventis, ImmuneWorks, and Shionogi. Some coauthors disclosed ties with Boehringer Ingelheim, maker of nintedanib.

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: These two articles address possible treatments in idiopathic pulmonary fibrosis (IPF). IPF can be particularly disabling. Therapies continue to be investigated in an attempt to improve quality of life and functional status. In one of the studies, Dr. Raghu reports no significant difference in the change in forced vital capacity (FVC) between the oral acetylcysteine-treated group and the control group at 60 weeks. However, in an industry-funded trial, the investigational tyrosine kinase inhibitor, nintedanib, helped to preserve FVC compared with placebo. This result lends hope for a trend of improved quality of life in IPF patients.

Oncogenic drivers identified

Adenocarcinomas *from page 1*

VITALS

Key clinical point: Multiplex testing is useful for guiding treatment in the majority of patients with lung adenocarcinoma.

Major finding: Of the 733 specimens tested for all 10 oncogenic drivers, 466 (64%) were found to harbor them; 442 specimens had one oncogenic driver and 24 had two of them.

Data source: A proof-of-concept study to determine the frequency of oncogenic drivers in lung adenocarcinomas by assessing 10 such mutations in tumor samples from 733 patients with stage IV disease over a 3-year period.

Disclosures: This study was supported by the National Cancer Institute. Dr. Kris and his associates reported ties to to numerous industry sources.

those who received conventional therapy.

Thus, this study established that it is feasible to incorporate genomic testing into clinical care for treatment stratification, and that multiplex testing is useful for guiding treatment in the majority of patients with lung adenocarcinoma, said Dr. Mark G. Kris, FCCP, of Memorial Sloan Kettering Cancer Center, New York, and his associates.

Since this study wasn't designed to assess patient survival, further randomized trials are needed to definitively determine whether selecting therapy based on this method of identifying oncogenic drivers improves survival in the real-world setting, the researchers noted.

The study involved patients with stage IV or recurrent lung adenocarcinoma treated at 14 medical centers across the country during a 3-year period. Each site performed multiplex genotyping on tumor samples using one of three available methods, to search for any of 10 oncogenic drivers: mutations in the EGFR gene (which are known to respond to tyrosine kinase inhibitors such as gefitinib and erlotinib), the ALK gene (known to respond to crizotinib), and the KRAS, NRAS, BRAF, ERBB2 (formerly known as HER-2), PIK3CA, MEK1, and AKT1 genes, as well as amplification of the met protooncogene (MET).

These participants' treating physicians decided whether or not to recommend a targeted therapy to patients found to have tumors harboring one of these oncogenic drivers.

A total of 1,007 patients had at least one gene assessed for oncogenic drivers, and 733 patients were fully genotyped. The main reason why full genotyping couldn't be done in all the study subjects was that insufficient tissue had been obtained in some tumor samples. (When this trial began in 2009, tumor sampling was done only to establish a diagnosis. Since then, genotyping has become an essential step in choosing therapy, so larger tissue samples are now obtained routinely.)

Of the 733 specimens tested for all 10 onocogenic drivers, 466 (64%) were found to harbor them; 442 specimens had 1 oncogenic driver and 24 had 2 of them. KRAS mutations were the most frequent, found in 25% of tumors; sensitizing EGFR mutations were found in 17%, other EGFR mutations in 4%, and ALK rearrangements in 8%. Each of the other mutations were found in less than 1%-3% of tumors, Dr. Kris and his associates said (JAMA 2014 May 20 [doi:10.1001/jama.2014.3741]).

It is feasible to incorporate genomic testing into clinical care for treatment stratification, and multiplex testing is useful for guiding treatment in the majority of patients with lung adenocarcinoma.

A total of 260 of these patients received targeted therapy directed at the oncogenic driver(s) found in their tumors, and their median survival was 3.5 years. In contrast, 318 patients who were found to have at least one oncogenic driver did not receive targeted therapy, and their median survival was 2.4 years. And the 360 patients with no oncogenic driver identified in their tumors had a median survival of 2.1 years.

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: Targeted therapy for lung cancer is, no doubt, the most exciting breakthrough in treating metastatic non–small cell lung cancer in the last 2 decades. Most of the significant abnormalities have been identified in adenocarcinomas, where a number of genetic mutations have been found on the cancer cell membrane or in the cytoplasm.

Therapeutic agents have since been developed that target some of these specific mutations that then prevents cell division through a variety of mechanisms. These therapeutic agents aren't cytotoxic, but rather are inhibitory, and generally have mild side effects. In this study, retrospective genetic testing of tumors from 733 stage IV adenocarcinoma patients showed that a large percentage (64%) of the tumors had 1 or more of a panel of 10 genetic abnormalities, so-called oncogenic drivers. Of the patients who had one of these oncogenic drivers and who were treated with targeted therapy, median survivals were far longer compared to patients not treated with targeted therapy. Of the 10 oncogenic drivers, 7 currently have approved or investigational drugs that target the genetic abnormality and likely will have quite positive effects on treatment.

Future randomized trials will document whether targeting specific oncogenic drivers will significantly improve long-term survival in these patients.

Ramucirumab briefly prolonged advanced NSCLC survival

FRONTLINE MEDICAL NEWS

Dr. Maurice Perol parsed data and concerns about the use of a stomach cancer drug to increase advanced lung cancer survival by 1.4 months. Watch the video online.

BY PATRICE WENDLING

Frontline Medical News

CHICAGO – Adding the recently approved stomach cancer drug, ramucirumab (Cyramza) to docetaxel reduced the risk of death in second-line, non–small cell lung cancer by 14% in the phase III REVEL study.

This is the first therapy in roughly a decade to improve the outcome of lung cancer patients in the second-line setting, according to study author Dr. Maurice Perol, head of thoracic oncology at Cancer Research Center of Lyon, France.

In addition, the recombinant human monoclonal antibody showed benefits in nonsquamous carcinoma as well as the squamous subtype, where treatments are limited.

Still, the median survival gain of just 1.4 months did not impress all at the annual meeting of the American Society of Clinical Oncology, where the study was highlighted in a press briefing before its formal presentation.

To hear Dr. Perol wade through the data and controversy, listen to our interview online.

The study was supported by ImClone, a subsidiary of Eli Lilly, which markets ramucirumab. Dr. Perol reported serving as a consultant or adviser with Lilly, Pfizer, Roche, Boehringer Ingelheim, and Genentech.

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Orexin antagonist improved sleep in phase III studies

BY MICHELE G. SULLIVAN
Frontline Medical News

PHILADELPHIA – An orexin receptor antagonist – the first drug to affect a neural system that promotes wakefulness – has proven safe and effective for up to 1 year in a pooled analysis of three phase III studies of patients with insomnia.

The drug (suvorexant) significantly improved both subjective and objective measures of sleep, including sleep onset, total sleep time, and wakefulness after sleep, Dr. W. Joseph Herring said at the annual meeting of the American Academy of Neurology.

Based on these data, the manufacturer, Merck, proceeded last year to preliminary talks with the Food and Drug Administration. The committee considering suvorexant recommended that Merck focus on the smaller of two proposed dose ranges – 20 mg for people up to 64 years of age, and 15 mg for those aged 65 years and older.

The orexin neural system was discovered in the late 1990s. Orexin neurons release two neuropeptides that interact with downstream receptors that promote wakefulness. Secretion follows a circadian rhythm. Suvorexant orexin antagonists block the activity of this wake-signaling system, allowing sleep to occur.

VITALS

Key clinical point: Orexin antagonist suvorexant improved sleep based on both subjective and objective measures, with minimal side effects.

Major finding: In patients with insomnia, suvorexant reduced the time to sleep onset by up to 10 minutes, and wakefulness after sleep by up to 40 minutes.

Data source: Three phase III studies involving almost 3,000 patients.

Disclosures: Dr. Herring is director of neuroscience clinical research at Merck, which sponsored the studies.

So far, studies have investigated the drug in almost 3,000 patients; 160 of these were treated for at least a year. The three phase III trials comprised more than 275,000 exposure nights. Most of the patients were women; 46% of the patients were aged 65 years or older.

Sleep was measured by subjective assessment and objective scales, including polysomnography.

In the two efficacy studies, the higher doses decreased time to sleep onset by 15 minutes on the first night; the lower doses did so by 10 minutes. By 3 months, the high-dose group's decreased time to sleep onset was 5 minutes; the low dose group's time was lowered to 4 minutes.

On the first night, the high-dose drug reduced wakefulness after sleep by 40 minutes; the low-dose drug did so by 35 minutes. After 3 months, the reductions were similar (about 25 minutes).

When the night was divided into thirds, both doses decreased wakefulness significantly and about equally, especially in the second and third fractions of the night.

In the subgroup of 160 patients who were treated for at least 12 months, the drugs showed persistent efficacy overall, although the high doses were somewhat more effective, Dr. Herring, Merck's executive director of neuroscience clinical research.

A multivariate regression analysis found that, compared with placebo, patients who took the high dose were 2.4 times more likely to be considered responders at 1 month and 1.8 times more likely to be responders at 3 months. Those who took the low dose were 1.8 times more likely to respond at 1 and 3 months.

"The drugs really proved about equal in the chances of a good response," said Dr. Herring.

Although there were more adverse events in the active groups than in the placebo groups – and more in the high-dose groups, compared with the low-dose groups – suvorexant was considered safe, he said. The discontinuation rates for drug-related adverse events in the high-dose, low-dose, and placebo groups were 4%, 3%, and 2%, respectively.

The most common issues were next-day somnolence (3% for placebo, 7% with the low dose, and 11% for the high dose, respectively); headache (6%, 7%, and 7%, respectively); and fatigue (2%, 2%, and 4%, respectively).

Neither of the doses was associated with withdrawal symptoms or clinically significant insomnia rebound during the washout periods. "The drug appears to have a low potential for abuse," Dr. Herring noted.

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Home-based OSA testing costs less than lab-based testing

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Home-based testing for obstructive sleep apnea averaged $564 less than laboratory-based testing and did not increase other costs or produce clinically inferior outcomes, based on data from a study of Veterans Affairs patients.

"If you do the home testing approach, that saves you money right off the bat, compared with laboratory testing," Dr. Charles W. Atwood, FCCP, associate professor of medicine at the University of Pittsburgh, said in an interview in advance of an international conference of the American Thoracic Society.

"Everything else for the patients is pretty comparable," he said. "That's a good thing for people in favor of home testing. People don't have deleterious outcomes because they were evaluated in the home setting, or because treatment was initiated in the home setting instead of a laboratory setting. People don't generate more health care bills because they were evaluated in the home instead of in a lab."

In what he characterized as the most comprehensive study of its kind, Dr. Atwood, also director of the sleep disorders program for the VA Pittsburgh Health Care System and his associates enrolled 296 patients from two VA sites who were randomized to standard in-laboratory polysomnography testing (lab group) or unattended home testing (home group). Patients in the home group underwent overnight recording with an Embla type 3 portable monitor followed by at least three nights of using a Philips Respironics auto-titrating positive airway pressure apparatus.

The researchers obtained data from case report forms, staff logs, and VA records, and categorized the costs as sleep-related, pharmaceutical, lab, hospital, or "other."

The majority of participants (95%) were male. Of the 296 patients, 223 (110 in the lab group and 113 in the home group) were initiated on continuous positive airway pressure (CPAP).

After an average follow-up of 2.75 years, the researchers determined that home-based testing costs were $564 lower, compared with lab-based testing (an average per-patient cost of $4,057 vs. $4,621, respectively; $P = .007$). Differences in the other four categories of cost did not reach statistical significance, with P values ranging between .19 and .82. Results of the Functional Outcomes of Sleep Questionnaire revealed no statistical difference in clinical outcomes between the two groups.

VITALS

Key clinical point: Patients did not have poor outcomes because they were evaluated in the home setting, or because treatment was initiated in the home setting instead of a laboratory setting.

Major finding: Home-based testing costs for obstructive sleep apnea were $564 lower, compared with lab-based testing costs, after a follow-up of 2.75 years.

Data source: 296 patients from two VA sites who were randomized to standard in-laboratory polysomnography testing or unattended home testing.

Disclosures: Embla provided the portable monitors used in the study, and Philips Respironics provided the auto-titrating CPAP apparatus. The study was funded by the VA's Health Research and Development Service. Dr. Atwood had no relevant financial conflicts to disclose.

VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: Most doctors who practice sleep medicine would agree with these results, always considering that certain patients would not perform a home study well, such as the frail elderly patients. What is interesting in this study is that patients with comorbidities were not excluded, and yet the outcome was no different.

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Pulmonary Perspectives: NOACs

NOACs *from page 1*

to prevent formation or propagation of maladaptive thrombus. Within pulmonary medicine, special attention has been paid to the prevention of DVT and pulmonary embolism (PE), collectively identified as VTE; treatment of established VTE; secondary prevention of recurrent VTE in patients with increased long-term recurrence risk; and prevention of in situ thrombosis in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

A history of success and frustration

These medications are popular at least in part because of the relative ease of monitoring and, when necessary, reversing their anticoagulant effects. Therapeutic anticoagulation with warfarin is routinely assessed with the international normalized ratio (INR) of prothrombin time, a well-validated mechanism for assessing the relative balance of pro- and anticoagulant forces across a variety of laboratories.

Supratherapeutic anticoagulation with warfarin is readily reversible with fresh frozen plasma, prothrombin complex concentrates (PCC), and vitamin K. UFH may be monitored with activated partial thromboplastin time (aPTT) and reversed with protamine sulfate. LMWH therapy may be monitored with anti-factor-Xa levels and are, to a lesser extent, reversible with protamine sulfate.

The NOACs are far more expensive than warfarin and heparins. However, the paradigm shift away from frequent blood draws and pharmacist or physician visits for therapeutic dose adjustment may result in enough systemic cost savings to balance higher prescription costs.

Despite a long history of broad acceptance, each of these therapies has serious limitations.

Warfarin's numerous drug and dietary interactions require significant modifications to lifestyle and medical care, and numerous investigations have called into question the safety and utility of its use in populations with unpredictable diets and phamacokinetics, such as cancer patients (Lee et al. *N Engl J Med.* 2003;349[2]:146). The persistent need for therapeutic monitoring is associated with a significant cost and infrastructure burden.

Therapy with UFH and LMWH is even more limited by the need to administer weight-based doses to an increasingly obese population. Direct toxicities of the medications, including skin necrosis with warfarin and heparin-induced thrombocytopenia (HIT), are additional concerns.

The era is young

The proliferation of novel oral anticoagulants (NOACs) over the past decade offers the hope for more convenient, less costly therapy. The NOACs include direct thrombin inhibitors such as dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban. These drugs require no therapeutic monitoring, unlike warfarin, and are dosed independent of weight, unlike the heparins. However, the era of NOACs is young, and there remains significant uncertainty about the safety and cost-effectiveness of these medications.

Some clinical applications of NOACs have already been thoroughly examined, with promising results. The studies directly applicable to treatment of established VTE are summarized in the Table.

Dabigatran has received FDA approval for VTE treatment in patients who have had an initial 5- to 10-day course of parenteral anticoagulation and for secondary prevention of VTE. Apixaban is FDA-approved for VTE prophylaxis in certain orthopedic patients and is under consideration for secondary prevention. Edoxaban, while not available in the United States, is under consideration for a VTE indication in Europe.

Rivaroxaban is now approved for the prevention of VTE in certain orthopedic patients and for the short-term treatment of acute VTE. Initial data on extended therapy for secondary prevention are also promising (EINSTEIN Investigators. *N Engl J Med.* 2010;363[26]:2499), although, it is worth noting that the total medication exposure time in this study was only 12 to 24 months. In scenarios calling for lifelong therapy, there may be diminishing returns in VTE prevention, but the risks of bleeding engendered by anticoagulation likely persist or increase over time, so extrapolation of EINSTEIN-EXT to lifelong therapy requires a great deal of caution.

The NOACs are currently orders of magnitude more expensive than warfarin and heparins. However, the paradigm shift away from frequent blood draws and pharmacist or physician visits for therapeutic dose adjustment may result in enough systemic cost savings to balance higher prescription costs. A recent pharmacoeconomic appraisal indicated a 3- to 12-month course of therapy for VTE with rivaroxaban was less expensive than a similar course of warfarin therapy (Seaman et al. *Thromb Res.* 2013;132[6]:647), and a similar analysis indicated apixaban may be more cost-effective than enoxaparin for VTE prophylaxis in surgical patients (Revankar et al. *Postgrad Med.* 2013;125[4]:141).

Some recent publications address the cost of protracted therapy for primary prevention of stroke in atrial fibrillation, with mixed results. Ultimately, the degree of cost-savings realized with long-term and lifelong therapy will depend on the changing costs of these medications as they exit patent protection and on the long-term rates of treatment failure and bleeding complications. The summative effect of differential failure and complication rates and decreasing medication cost may be

Continued on following page

Novel anticoagulants

Anticoagulant	Phase III study	Clinical setting	Comparator	Citation
Rivaroxaban	EINSTEIN PE	Confirmed PE with or without symptomatic DVT	Enoxaparin/VKA	*N Engl J Med.* 2012;366(14):1287-1297
	EINSTEIN DVT	Confirmed DVT without PE	Enoxaparin/VKA	*N Engl J Med.* 2010;363(26):2499-2510
	EINSTEIN EXT	Confirmed symptomatic DVT or PE having undergone 6-12 months of anticoagulation	Placebo	*N Engl J Med.* 2010;363(26):2499-2510
Apixaban	AMPLIFY	Symptomatic DVT or PE	Enoxaparin/VKA	*N Engl J Med.* 2013;369(9):799-808
	AMPLIFY-EXT	Prevention of VTE recurrence or death in patients who have undergone intended treatment for VTE	Placebo	*N Engl J Med.* 2013;368(8):699-708
Dabigatran	RE-COVER	VTE treatment	Warfarin	*N Engl J Med.* 2009;361(24):2342-2352
	RE-COVER II	VTE treatment (identical to RE-COVER)	Warfarin	*Circulation.* 2014 Feb 18;129(7):764-772
	RE-SONATE	Long-term prevention of recurrence after 6-18 months of VKA therapy	Placebo	*N Engl J Med.* 2013;368(8):709-718
	RE-MEDY	Long-term treatment after 3-6 months of anticoagulation	Warfarin	*N Engl J Med.* 2013;368(8):709-718
Edoxaban	HOKUSAI-VTE	Treatment of DVT and/or PE	Warfarin	*N Engl J Med.* 2013;369(15):1406-1415

FRONTLINE MEDICAL NEWS

Continued from previous page

an actual savings several-fold higher than current estimates.

The role of NOACs has also been studied extensively in primary prevention of stroke in patients with atrial fibrillation. Apixaban and rivaroxaban were found to decrease overall costs compared with warfarin therapy, while dabigatran therapy increased costs (Deitelzweig et al. *J Med Econ*. 2013;16[9]:1163). It is unclear whether cost-effectiveness and safety data collected for this indication can be directly extrapolated to secondary prevention of VTE or therapy for CTEPH.

Clinicians whose patients have experienced bleeding events while taking NOACs are understandably hesitant to routinely apply anticoagulants whose effects can neither be monitored nor reliably reversed.

A bridge too far?

Many clinicians instinctively desire to apply the NOACs to all the various anticoagulation roles that have heretofore been filled by warfarin or the heparins. The medications are also seeing broad community use as lifelong therapies indicated for secondary prevention of VTE despite the unavoidable absence of long-term follow-up studies and the corresponding safety and efficacy analyses. Some clinicians have also started to administer NOACs in lieu of warfarin as part of primary presurgical therapy for CTEPH, despite a complete absence of data to support this practice.

Although the NOACs offer an increase in convenience, and possibly a long-term cost savings, there are serious safety concerns, as well. Currently available strategies to reverse the effects of NOACs, including four-factor PCCs (containing factors II, VII, IX and X), are, on the whole, less effective than reversal strategies for traditional anticoagulants. PCCs are also not widely available. While targeted reversal agents are reportedly in varying stages of development, at present, there is no reliable reversal for NOACs. Clinicians whose patients have experienced bleeding events while taking NOACs are understandably hesitant to routinely apply anticoagulants whose effects can neither be monitored nor reliably reversed.

This is an exciting time to practice medicine in large part thanks to the new frontiers being opened daily. The availability of effective therapies with a reduced burden on physicians and patients alike is appealing, and there is a strong temptation to apply NOACs as a panacea for all clotting ailments simply because warfarin and heparin were used likewise. In an era of evidence-based, cost-conscious medicine, however, clinicians must carefully evaluate the available data prior to extrapolating the use of NOACs to populations and indications in which they have not yet been studied.

Dr. Hostler is a Pulmonary and Critical Care Medicine Fellow, Walter Reed National Military Medical Center, Bethesda, Maryland.

Clinical Trials Registry: Powering medical progress

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The CHEST Clinical Trials Registry is a free service that connects physicians to information about clinical trials in respiratory disease conducted by participating pharmaceutical companies.

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FROM THE EVP/CEO: Making essential connections

BY PAUL A. MARKOWSKI, CAE

Last fall, we launched our new brand at CHEST 2013. It included a new logo that represents the chest and illustrates the connectivity of our members. Since then, we've been phasing out the old brand, replacing everything with the updated brand. By now, you've likely noticed our new look on chestnet.org or in course brochures, ads, and e-mails. Incorporating the new brand has been more than simply a facelift, though. When we launched the brand, we also committed to being an essential connection at a critical time. I can say with confidence, we are living up to that promise.

We remain focused on connecting clinicians to relevant chest medicine education opportunities. We opened our Innovation, Simulation, and Training Center for the first live learning event in April. Already, we've had more than 500 health-care professionals attend courses here. That number will continue to grow, as we have courses scheduled in the training center through the end of the year. In March, we hosted CHEST World Congress 2014 in Madrid. The congress drew more than 2,200 clinicians from over 70 countries. It generated 740,600 impressions on Twitter, meaning 740,600 tweets related to our congress were delivered to Twitter accounts around the world—that many potential global connections made in the span of a few days!


MR. MARKOWSKI

Our CHEST annual meeting is always a great event for connecting to relevant clinical education content. Each year, we issue a call for topics, asking members to submit ideas for discussion topics and faculty. This helps ensure the program features content that clinicians want. Topic submissions for CHEST 2014 increased by about 50% over CHEST 2013, indicating this meeting will be especially relevant to attendees. Two years ago, we introduced a new participation opportunity at the annual meeting for medical students and residents by creating the Medical Student/Resident Case Report submission category. Submissions have grown steadily, increasing by 50 cases for CHEST 2014. It's good to see so many medical students and residents taking advantage of this and starting to make important connections early in their careers.

Each month, our premier *CHEST* Journal connects readers to peer-reviewed original research, reviews, and case studies in chest medicine. More than 350,000 readers around the world access *CHEST* monthly, either in print or online. In keeping with our new brand, *CHEST* Journal has been redesigned—inside and out. Starting with the July issue, the cover will better reflect our brand, and layout enhancements inside will make the content easier to scan and read.

In addition, select sections will move to Online Exclusives, where articles can be supplemented and enriched with video and other multimedia content, as well as linked references. This new publishing strategy will enhance the connections readers make to research and keep us at the forefront of content delivery. We're relying more and more on social media to connect health-care professionals. I mentioned the use of Twitter at CHEST World Congress 2014. We've also begun hosting regular Twitter chats. A Twitter chat is a conversation at a scheduled time around a unique topic using a hashtag (#), so anyone can follow the discussion and participate. Twitter chats are commonly used to connect people with similar interests. We've conducted three chats with the hashtag #pulmCC: End of Life in the ICU, Difficult to Manage Asthma, and Current Controversies in Sepsis. Our very first chat, End of Life in the ICU, generated 700 tweets in 1 hour and led to 1.3 million impressions. Clearly, social media is a communication tool with

We're relying more and more on social media to connect health-care professionals. We've conducted three Twitter chats with the hashtag #pulmCC.

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relevant professional value.

Since July 2013, our Twitter followers have increased 40%, and our Facebook followers have increased 80%. We'll continue leveraging social media to connect like-minded people around the world.

While social media has a well-established purpose for us, we still appreciate face-to-face contact. In April, our committees were invited to CHEST Global Headquarters to share their thoughts with leadership and staff on key priority initiatives for the coming year. These sessions were very productive and resulted in excellent feedback our leaders can use to guide our organization into the future. Rest assured, we'll continue making these valuable personal connections to stay on target and relevant to members.

I encourage you to take advantage of the ways we can connect you to education opportunities, the latest research, and your colleagues. Our website, chestnet.org, is always a great place to learn about everything we have going on. If you're interested in education, check out our live learning courses at chestnet.org/live-learning, and watch for developments on CHEST 2014 at chestmeeting.chestnet.org.

Are you familiar with all our social media channels? If not, I encourage you to visit the sites and join the conversations. See the accompanying box for a list of our channels. And, always feel free to connect with me. Follow me on Twitter (@PMarkowskiACCP), or look for me at CHEST events. For certain, I'll be at CHEST 2014, October 25-30, in Austin, Texas, and I hope to see you there.

CHEST social media channels

facebook.com/accpchest
twitter.com/accpchest
instagram.com/accpchest
pinterest.com/accpchest
storify.com/accpchest
youtube.com/accpchest
plus.google.com/+ChestnetOrgACCPCHEST

Something for everyone: Austin cuisine, clinical education at CHEST 2014

From Texas staples like Tex Mex and BBQ, to diverse settings like food trucks and musical brunches, Austin cuisine offers something for everyone. When CHEST 2014 travels to Austin in October, we know you'll satisfy your taste buds and your educational needs.

With so many options to choose from, here are some recommendations to help you plan out your menu:

► Uchi & Uchiko – Both of these restaurants serve Japanese cuisine and sushi. The head chef received the Best Chef Southwest at the 2011 James Beard Foundation awards.

► Franklin Barbecue – Bon Appétit's Andrew Knowlton called this the best barbecue in the USA. The walk-in only restaurant has a constant line of people waiting for their famous brisket and other smoked meats.

► Hula Hut – This local favorite overlooks Lake Austin. The food is a blend of Tex Mex and Caribbean cuisine.

► Qui – Top Chef Texas Winner, Paul Qui, opened this restaurant that fuses influences from his travels in Asia, America, France, Copenhagen, Mexico City, and more.

► Stubb's Bar-B-Q – This BBQ restaurant is known for its Gospel Brunch on Sundays, which includes a soulful performance, Southern-style buffet, and a make-your-own-Bloody-Mary bar.

► Congress – James Beard award nominee and former Iron Chef America competitor, chef David Bull, opened Congress. The restaurant is known for combining traditional American flavors in new ways.

► Parkside – Known for its architecture designed by Michael Hsu and delicious upscale American cuisine.

► Fonda San Miguel – This restaurant stands out in a city known for Tex Mex. It serves only authentic Mexican cuisine.

► Truluck's – This seafood, steak, and crab house is only a 10-minute walk from the Convention Center and was rated Best Food in 2012 by OpenTable.

► Wink – Known for Austin-style hospitality, a commitment to local farms and gardens, sustainable agriculture, and fine dining cuisine.

Austin is also known for its food carts and trailers. You can find a wide variety of cuisine options available on the go at one of Austin's many food truck locations. Learn more at AustinFoodCarts.com.

Austin is sure to satisfy your inner foodie with its wide variety of culinary options. From October 25-30, CHEST 2014 will also offer you a variety of educational options, including hands-on simulation, case- and problem-based presentations, small-group interactive discussions, lectures, self-study opportunities, and more. And, don't miss our keynote speakers—Dan Heath, author of Decisive: How to Make Better Choices in Life and Work and Kevin Pho, founder of KevinMD. CHEST 2014 is dedicated to delivering the latest information in pulmonary, critical care, and sleep medicine to you, ensuring you make the best decisions with your patients.

Register by August 29 to pay the lowest fees. Learn more at chestmeeting.chestnet.org.

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Fired up! Barbecue is on the menu, as is an array of educational opportunities at CHEST 2014, coming October 25-30 to Texas.

CHEST PREP: Disease-state info for clinicians, reps

You know the American College of Chest Physicians (CHEST) provides innovative chest medicine education for clinicians, but did you know CHEST also offers training for pharmaceutical and medical device representatives?

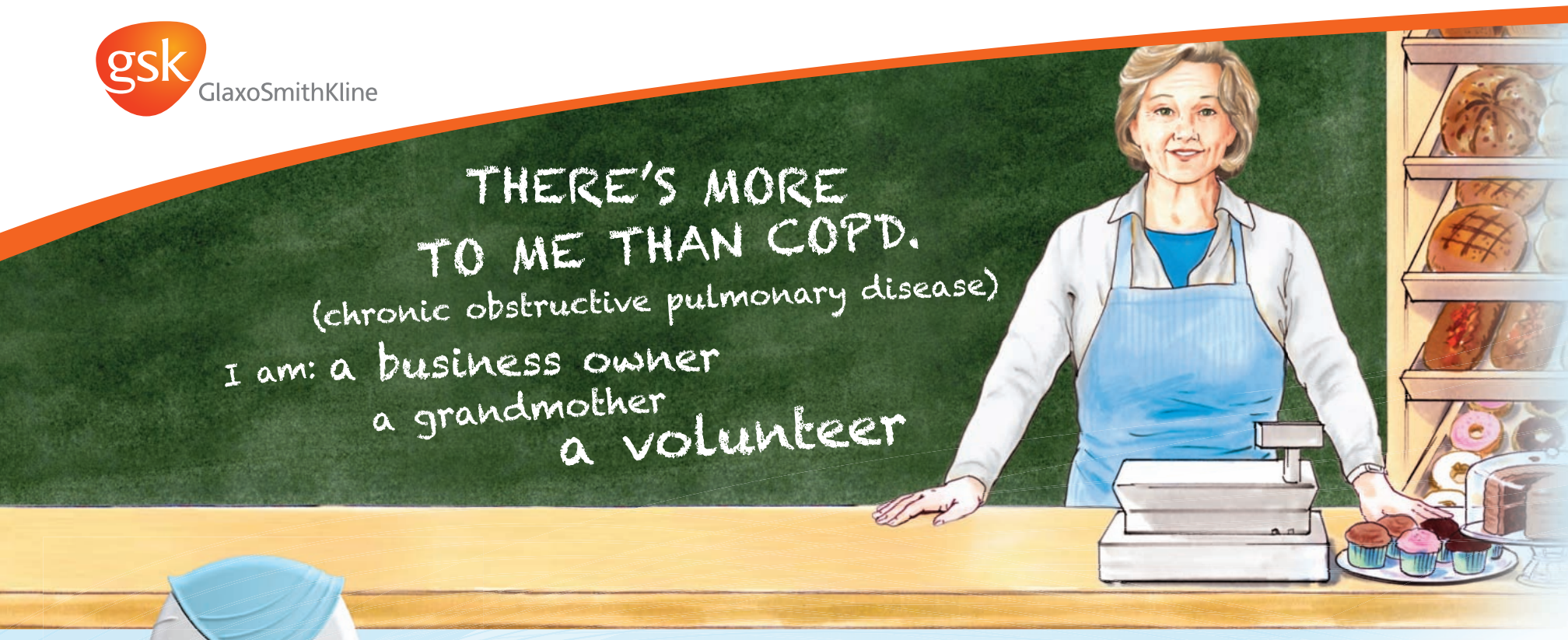
The CHEST Professional Representative Education Program, or CHEST PREP, is unbranded, disease-state training customized to address the learning objectives of our industry partners and the educational needs of their representatives. Each program features didactic presentations, problem-based learning exercises, diagnostic simulations, and collaborative, faculty-led workshops. The PREP curriculum is developed by subject matter experts and delivered by expert faculty, typically drawn from our membership. Our "classrooms" include leading hospitals and academic medical centers.

In April, the CHEST Innovation, Simulation, and Training Center became another PREP site. We've received rave reviews for both the training center and our PREP course contents, with 100% of initial participants rating the course as excellent or good for updating and improving their professional knowledge and skills; and 65% "Extremely Likely" to tell a colleague/coworker about the course.

Upon completion of a 2-day PREP course, participants receive a 3-year certification specific to that disease state. More importantly, they gain the in-depth and current clinical information needed to engage with clinicians—knowledgeably, confidently, and meaningfully.

If you would like to participate as faculty for an upcoming PREP course, or to receive more information about how your hospital can become a course site, please contact Lisa Stanick, PREP Operations Director, at lstanick@chestnet.org or 224/521-9518.

GlaxoSmithKline



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.

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Connect with a new 'brand' of CHEST

'Online Exclusives' are a highlight of the redesigned journal.

BY VICKI TEDESCHI
Managing Editor, CHEST

With the July issue of *CHEST*, a new design synonymous with the new brand of *CHEST* is introduced. The new article pages are designed to present key information, such as abstracts, in a prominent position, making it easier for you to find the information you need. Articles with enhanced content, such as videos, have visual icons both within the table of contents and at the top of the article view.

Along with changes in the design, *CHEST* has made changes to the way content is delivered. The popular case-based sections have been moved to online-only publication and have been curated into a new collection called Online Exclusives. These articles include the following sections: Chest Imaging and Pathology for Clinicians; Selected Reports; and Pulmonary, Critical Care, and Sleep Pearls. Ultrasound Corner, the other case-based series, has been published as online-only since its launch in January 2013.

Publishing these articles online allows *CHEST* to include enhanced content with them, enriching readers' experience. The articles currently are and will continue to be indexed by PubMed, the Web of Science, and all search engines. *CHEST*'s online-only content can be viewed in a smartphone browser or on iOS devices with the *CHEST* app.

Besides moving our case-based series to online-only, we are also moving our Correspondence section into Online Exclusives. Each letter includes a link to the original article it is commenting on, along with the response letter from the original authors. Showcasing these articles as Online Exclusives enables readers to more easily see the referenced and related material, bringing more relevance to these letters.

The Online Exclusives articles will still be included in the print table of contents in each issue with their e-page numbers. Or, if you are not currently receiving our monthly issue alert, you can sign up for it on the *CHEST* website (http://journal.publ3ications.chestnet.org).

This month in *CHEST*: Editor's picks

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

Modified Criteria for the Systemic Inflammatory Response Syndrome Improves Their Utility Following Cardiac Surgery. *By Dr. N. S. MacCallum et al.*

Do Grandmaternal Smoking Patterns Influence the Etiology of Childhood Asthma? *By Dr. L. L. Miller et al.*

The Right Ventricle Explains Sex Differences in Survival in Idiopathic Pulmonary Arterial Hypertension. *By Dr. W. Jacobs et al.*

Surfactant Protein B Gene Polymorphism Is Associated With Severe Influenza. *By Dr. K. K. W. To et al.*

POINT/COUNTERPOINT
Should Storefront Clinics Provide Case Finding and Chronic Care for COPD?
Yes: *Dr. P. Enright and Dr. W. Nevin*
No: *Dr. B. R. Celli*

NETWORKS: Fight for low-dose CT; hypothermia therapy

Allied Health

Advocacy for pulmonary medicine

As a health-care professional in the current environment, take time to ask yourself a few questions—when was the last time you wrote or contacted your state representatives/senator? Do you know the names of local and state representatives? There are ways to receive daily updates on proposals and headline news from Washington, but once read, what do we do with that information?


MS. MISKE

The current decision by the Centers for Medicare and Medicaid Services national coverage determination advisory group has a direct impact on the pulmonary community. Despite the National Lung Screening Trial showing a 20% reduction in mortality when patients at high risk were screened, the advisory group did not endorse low-dose CT screening for lung cancer.

The American College of Chest Physicians (CHEST) includes members who spend much of their day performing, consulting, or writing research-related materials. We all interface with patients at a wide variety of sites and specialties: physician, respiratory therapist, nurse practitioner, nurse, etc. As a direct result of that interaction, the importance of identifying high-risk patients and performing necessary education and referrals for testing relates directly to our practice. If we do not speak up and educate our patients and our government representatives, we can expect more bottom-line decisions to define our practice.

There is time to try to correct this advisory group decision, but the time is now. Otherwise, why would we continue to perform research and refer patients?

Laura J. Miske, MSN
Steering Committee Member

Chest Infections

Is pneumonia an unintended cost of hypothermia therapy for cardiac arrest?

Cardiac arrest is a leading cause of death in North America, resulting in more than 330,000 deaths per year. Anoxic brain injury can occur even after return of spontaneous circulation due to a direct tissue injury or blood-brain barrier disruption.

Therapeutic hypothermia (28°C to 32°C) before cardiac arrest has been used since the 1950s as a neuroprotective strategy during some open-heart surgeries and in various animal models.

In 2002, two prospective randomized trials compared mild hypothermia with normothermia in survivors of out-of-hospital cardiac arrest (Bernard et al. *N Engl J Med.* 2002;346[8]:557) (The Hypothermia after Cardiac Arrest Study Group. *N Engl J Med.* 2002;346[8]:549).

The induced hypothermia cohort experienced better survival and neurological outcomes (number needed to treat 4 and 6, respectively, at discharge).

More recently, pneumonia emerged as a potential complication in survivors of cardiac arrest managed with therapeutic hypothermia (Woo et al. *Am J Emerg Med.* 2014;32[2]:150). It was associated with longer need for ventilatory support, higher tracheotomy rate, longer ICU stay, higher C-reactive protein, higher body temperature, and lower PaO_2/FIO_2 (Pabst et al. Respir Care. 2013;58[9]:1514). Moreover, this risk appears to be different if hypothermia is used in traumatic brain injury or poststroke patients (Lyden et al. *Ther Hypothermia Temp Manag.* 2013;3[1]:3).


DR. BENCHEQROUN

A Chest Infection NetWork highlight session will be presented at CHEST 2014 in Austin, addressing the risk of pneumonia after therapeutic hypothermia. The session will review the current evidence, the risk factors described for developing pneumonia in this cohort, the pros and cons of treatment or prophylaxis, and the impact it may have on future outcomes.

Dr. Hassan K. Bencheqroun, FCCP
Steering Committee Member

Three CHEST boards and IAC meet to talk strategy

A first of its kind meeting for CHEST emerged from a strategic planning session conducted by the Industry Advisory Council (IAC). The strategic planning session was held to discuss how to render the IAC meetings more relevant. The results from that strategy session showed that most important to industry members was to have meaningful dialogue with CHEST leadership on current topics of interest to their businesses. Consequently, on April 30, the CHEST Board of Regents, The CHEST Foundation Board of Trustees, and the CHEST Enterprises Board of Directors connected with IAC members to exchange ideas on healthcare and advance knowledge collaboratively.

The meeting, with breakouts co-chaired and facilitated by CHEST board members, included the following agenda topics:

- ► Innovation on new drug development;
- ► Comparative effectiveness research;
- ► Payment reform;
- ► Sunshine Act;
- ► Patient–reported outcomes (PROs);
- ► Care transitions and new care models;
- ► Personalized medicine / molecular testing; and
- ► Industry-supported education – CME and non-CME.

CHEST

(L-R) Dr. Jay Peters, FCCP (CHEST Foundation Trustee), discusses new drug developments with Dr. Craig S. Conoscenti, FCCP (Director, Idiopathic Pulmonary Fibrosis Program Lead, Clinical Development and Medical Affairs-Respiratory, Boehringer-Ingelheim Pharmaceuticals, Inc); and Mr. Henry McMillan (Director of Respiratory Marketing, Sunovion Pharmaceuticals, Inc).

The Board presidents provided insight into their CHEST entity in a brief introduction and also shared with the IAC ideas on how CHEST and industry might work together toward exchanging ideas and providing the best treatment options for patients with chest diseases.

Following the breakouts, the groups reconvened together to report results of their conversations.

This inaugural event truly exemplified CHEST's mission of championing the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Make a Foundation gift to help people worldwide

The CHEST Foundation offers grants for community service and humanitarian projects making an impact in the United States and around the world.

Dr. Khoulood Fakhoury, FCCP, received the 2013 CHEST Foundation Community Service Grant honoring D. Robert McCaffree, MD, Master FCCP, for the project: Mobile Clinic in Lebanon: Influenza Vaccination and Infection Control Education Among Syrian Refugee Camps.

With funding from The CHEST Foundation, Dr. Fakhoury was able to share her expertise with a mobile clinic supported by Health Outreach to the Middle East. The mobile clinic team used a medically equipped van to travel to villages and rural, underserved areas to provide free medical and dental services for the poor, unreached population in Lebanon.

With an influx of hundreds of thousands of Syrian refugees, this mobile unit has been actively serving through regular trips to the refugee camps since 2012. The mobile clinic was able to travel to several areas in Lebanon, including Beirut, Debayeh, Tripoli, and Zahle. In Zahle alone, more than 500 Syrian refugee families were waiting for help from the mobile clinic.

DR. FAKHOURY

These communities have a high incidence of infection epidemics, and this project provided as many refugees as possible, including many children and older individuals, with influenza vaccine free of charge.

In addition, during those visits, the mobile clinic team conducted medical educational classes on infection control measures concentrating on hygiene, hand washing, and environmental control that included tobacco smoke avoidance. Education material about infection prevention and control, tobacco smoke danger, and basic health care was also distributed during visits.

Countless families expressed, through tears, how thankful they were for the help and medical services provided and for the compassion shown to them.

Contributions to The CHEST Foundation helped support this vital program. This is just one example of the many programs where you can make an impact helping people with the immediate health-care services they need most.

Join us in supporting these life-changing grants and make a donation today at chestnet.org/foundation or contact Patti Steele, Annual Fund Manager, at 224/521-9527.

CRITICAL CARE COMMENTARY: Brain death – patient, law, and family

BY DR. DAVID L. BOWTON, FCCP

Perhaps no other concept in modern medicine is surrounded by as much misunderstanding and controversy as that of death by neurologic criteria, or brain death.

Legal challenges to brain death have spanned the gamut of continuing life support for a legally dead patient to denying a family's request to continue support for their dead child.

DR. BOWTON

Two recent, highly publicized cases highlight the poles of these controversies and concerns. In November 2013, Marlise Muñoz was declared brain dead. She was 33 years old and 14 weeks' pregnant. Concordant with the patient's wishes, the husband requested that the hospital remove the patient from mechanical ventilatory support. Citing Texas law that precludes the withholding of life-sustaining treatment to a pregnant patient, the hospital refused, despite the logical fallacy of withholding life support from a person declared dead.

In December 2013, 13-year-old Jahi McMath was declared brain dead. Her parents obtained a court order to prevent the hospital from discontinuing ventilatory support. A better understanding of the development of the concept of brain death and the incorporation of recent evidence into its determination may reduce the confusion and misunderstandings surrounding the determination of brain death.

Three reports in 1959 describe death of the nervous system and brain death (coma dépassé) building upon clinical and laboratory data from the 1930s relating the cessation of brain blood flow and EEG activity to ensuing apnea and subsequent cardiac arrest (Machado et al. *J Med Ethics*. 2007;33[4]:197). With the increasing sophistication of critical care support, especially mechanical ventilation, the loss of central respiratory drive no longer meant imminent death, and patients could be supported for long periods of time without recovery of brain function.

In 1968, an ad hoc committee at Harvard Medical School proposed a definition of irreversible coma and brain death (Beecher et al. *JAMA*. 1968;205[6]:337). They posited that any organ that no longer functions and has no possibility of functioning again was "for all practical purposes dead." The goals of the committee were (1) to reduce the suffering of patients and families and the care burden of hospitals; and (2) mitigate the controversies that surrounded obtaining organs for transplantation.

The committee then set out their rationale for their proposed characteristics of the permanently nonfunctioning brain. Subsequently, in 1976, The Conference of the Medical Royal Colleges and their Faculties in the United Kingdom required a deeply comatose state, irremediable structural brain damage, and irreversible cessation of brain stem function to ascertain brain death (Spinello. *J Intensive Care Med*. May 2014, in press).

In 1981, the National Conference of Commissioners on Uniform State Laws approved the Uniform Determination of Death Act (UDDA), codifying the legal concept of brain death. Thirty-six states and the District of Columbia have enacted the UDDA, but legal precedent and statutes in the remaining states are consistent with the UDDA. New York and New Jersey require that a family's religious or moral views be considered in the process following the determination of brain death (Gostin. *JAMA*. 2014;311[9]:903); in all other states, clinicians are not required to consult with family prior to withdrawing ventilatory support from the brain dead patient.

'No reports of clinical recovery'

However, the UDDA does not define brain death but rather states that "a determination of death must be made with accepted medical standards" (Wijdicks et al. *Neurology*. 2010;74[23]:1911). The American Academy of Neurology (AAN) published a practice parameter in 1995 to guide clinicians in the determination of brain death; this was updated by their Quality Standards Committee in 2010 (Wijdicks et al. *Neurology*. 2010;74[23]:1911). In the updated guidance document, the committee stated: "There are no reports of clinical recovery in patients after the clinical diagnosis of brain death has been determined using the AAN practice parameter."

It is striking, however, that there appears to be an inconsistent approach and criteria for the determination of brain death across hospitals, and even amongst specialties within a hospital (Powner et al. *Crit Care Med*. 2004;32[6]:1284). Further, in most states, any physician is permitted to ascertain brain death, though some states have now added requirements for specific qualifications and/or confirmation by a second physician (Spinello IM. *J Intensive Care Med*. May 2014, in press).

These inconsistencies in criteria, process, and experience may be responsible for reports in the lay press of recovery following pronouncement of brain death. Every hospital should have a validated, well-defined process for the evaluation of brain death guided by the AAN practice parameter.

A single exam

In most states, a single exam is required to determine brain death. The clinical setting and the results of imaging studies should be used to determine the duration of observation needed to exclude the possibility of recovery. Given that the patient should be normothermic, have a normal systolic blood pressure, have both a history and imaging studies supporting an irreversible cause of coma, and that drugs and toxins must be excluded as a cause of coma, this observation period is uncommonly less than several hours.

Confounded by movement

Movement of the patient with devastating brain injury is often a confounder in the determination of brain death.

This is also a source of confusion and concern for the family. Plantar reflexes have been commonly reported in patients pronounced brain dead. Head turning in response to noxious stimuli, repetitive leg movements, facial myokymia, and other movements have been observed (Wu et al. *Crit Care*. 2013;17[4]:440; Wijdicks et al. *Neurology*. 2010;74[23]:1911). When this is observed, knowledge of the potential reflex arcs is needed, and consultation with a neurologist or other physician skilled in brain death determination is usually appropriate.

Movement can sometimes extend to apparent respiratory activity. This can be caused by ventilator autocycling due to variations in circuit pressure (especially in a noncompliant lung or with large tidal volumes) or triggering due to cardiac-induced alterations in transpulmonary pressure. The latter is most common in a hyperdynamic circulatory state.

Apnea is a critical criterion for the determination of brain death and is most reliably assessed when the patient has been removed from the mechanical ventilator. During testing, apnea should be present despite achieving a $PaCO_2$ of greater than or equal to 60 mm Hg, or 20 mm Hg above the baseline to support the diagnosis of brain death.

Some patients, especially those who are hemodynamically unstable or who require high levels of PEEP to support oxygenation, may not tolerate the apnea test without oxygen desaturation or hypotension.

Most commonly, the apnea test is performed with the patient off the ventilator and 6 L/min of oxygen flowing through an insufflation catheter placed near the carina. We prefer to use a modified Mapleson circuit with enough flow to only partially distend the anesthesia bag in the circuit. With this arrangement, one can look not only at the patient's chest wall and abdomen for signs of respiratory activity but also look for cyclic changes in the level of bag inflation.

In patients with ARDS, trauma involving the chest or other causes of oxygenation failure, CPAP, with or

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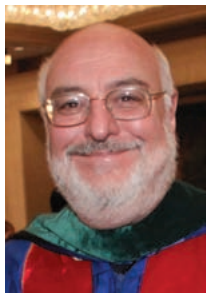
EDITOR'S COMMENT



In this thorough and somber commentary, Dr. Bowton clearly points out how much gray remains in a world that demands black and white certainty.

Brain death, and its implication, is not an exact diagnosis, which impacts the family, society, and the care-giving team, but most of all, the patient.

As there are times that brain death cannot be truly determined, we must be mindful that our primary goal is always the patient, then the families, society, and others. As a practitioner in New York, where family discussion is the law, I have not found this to be a great impediment; with palliative care and pastoral support, most issues can be resolved. As we progress in our knowledge, a more global unified approach would be welcomed.

Dr. Peter Spiro, FCCP
Section Editor

ABIM MOC changed in 2014. Know the facts.

BY PAM BEATON
Manager, CHEST Educational Accreditation and Certification Services

What do Maintenance of Certification changes mean for CHEST members?

► Current certification(s) will be honored through the expiration year on that certificate and diplomates be reported as "certified" on the ABIM website through that year (assuming current and valid license is held).

► If you are currently enrolled in the MOC program and your certification is valid, you will be "Meeting MOC Requirements" in 2014. However, you will need to go to your Physician Login on ABIM.org and indicate which certification(s) you are choosing to maintain. You will need to complete an MOC activity by December 31, 2015, to keep your "Meeting MOC Requirements" status. Note the following:

- 100 points are required every 5 years.
- Some activity is required every 2 years.
- 20 points are required in Part II (Lifelong Learning and Self-Assessment).
- 20 points are required in Part IV (Practice Performance Assessment).
- The other 60 points could be in either Part II or Part IV.

► If you are not currently enrolled in the MOC program and your certification is valid, to be reported as "Meeting MOC Requirements," you'll need to log in to ABIM.org and enroll by indicating which certification(s) you choose to maintain.

What does this mean for 'grandfathers'?

► If you hold certification(s) that are valid indefinitely, you will not lose those certification(s).

► The points earned every 2 years will count toward your 5-year requirement and also count toward the milestones for the certifications you are maintaining. You need to pass the exam every 10 years in each certification area you choose to maintain. ABIM will honor the previous exam program rules for certificates that expire between now and December 31, 2023. Future exams for certificates that are contingent upon "Meeting MOC Requirements" will be due 10 years from when they were last passed. You will also earn 20 MOC points for your first exam attempt in each certification area.

How long will MOC take?

► The changes to the MOC program are designed to spread out the requirements over time so that physicians will not feel pressured to complete multiple activities at one time.

► The ABIM estimates you will be investing anywhere from 5 to 20 hours per year in professional development activities in order to be reported as "Meeting MOC Requirements."

How can CHEST help you meet MOC requirements?

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The above information has been approved by the American Board of Internal Medicine as of May 22, 2014.

For more information about CHEST's MOC products, please e-mail cme@chestnet.org. For questions specific to enrolling in MOC and ABIM requirements, please e-mail MOC2014@abim.org.

Continued from previous page

without an antecedent recruitment maneuver may facilitate successful completion of the apnea test (Hocker et al. *Neurocrit Care.* 2014;20[2]:298).

Controversy over ancillary testing

There are no well-designed prospective studies examining the accuracy of ancillary tests for the determination of brain death using the appropriate control group of patients with coma but who are not brain dead and with blinding of the interpretation of the study results to the clinical setting.

Brain death is not synonymous with complete neuronal death. While cortical areas exhibit moderate to severe histopathologic ischemic changes in the large majority (but not all) of brain dead patients, the basal ganglia and diencephalon inconsistently demonstrate these changes (Wijdicks et al. *Neurology.* 2008;70[15]:1234). Thus, it may not be surprising that both false-positive (test positive for brain death – clinically not brain dead) and false-negative (test negative for brain death – clinically brain dead) results have been reported for virtually all tests proposed for confirmatory testing, including CT angiography, transcranial Doppler, and nuclear brain scan. Confirmatory testing is most commonly used in patients who cannot complete an apnea test.

It has been forcefully argued that, in adults, confirmatory tests should not be done (Wijdicks. *Neurology.* 2010;75[1]:77). There will be some patients in whom brain death cannot be definitively determined. When all criteria of the AAN guidelines cannot be fulfilled, clinicians should err on the side of concluding that the patient is not brain dead and turn their efforts toward counseling the family regarding the likelihood of neurologic recovery and assisting the family in ascertaining the desires of the patient under these circumstances.

It is vital that care providers not lose perspective on the plight of the family in these settings. The symbolic power of a beating heart to a parent, spouse, or loved one cannot be underestimated. Family members who observe resuscitation efforts have been shown to have a lower incidence of posttraumatic stress disorder symptoms (Jabre et al. *N Engl J Med.* 2013;368[11]:1008).

A recent trial demonstrated that family presence during the brain death determination had an increased understanding of brain death without an adverse impact on emotional well being (Tawil et al. *Crit Care Med.* 2013;42[4]:934). A consistent process for determination of brain death, engagement of the family in the brain death evaluation and helping them understand the meaning of patient movements that can be distressingly misinterpreted, and honesty when a definitive determination of brain death cannot be determined will not remove the misunderstanding or controversy surrounding a diagnosis of brain death but will serve to ensure its accurate and humane application.

Dr. Bowton is Professor, Section on Critical Care, Department of Anesthesiology, Wake Forest Baptist Health, Winston-Salem, North Carolina.

Read previous Critical Care Commentaries online.

Nonphysicians coming to ABIM certification boards

BY ALICIA AULT
Frontline Medical News

ORLANDO – The American Board of Internal Medicine is taking a potentially controversial step into the future by adding nonphysicians to both its main board and its subspecialty boards, a move that would give them a say in what defines being a good doctor.

The ABIM began the change in its governance process about 3 years ago, and took the first steps last July when it broke up its 29-member board of directors into two smaller panels: the board of directors and the ABIM council. The board will focus on governance issues, and the council will hone in on the assessment process itself. Recently, the board approved the addition of two new "public" members, including a health care executive and an official with a consumer organization.

Now, the ABIM is reworking its subspecialty boards, which will also soon add public, nonphysician members. There will be fewer subspecialty boards, and they will also add exam committees that are entirely made up of physicians.

Why the new structure?

One of the ABIM's core roles is "to offer a professionally sanctioned definition of what a good doctor is," said Dr. Richard J. Baron, president and chief executive officer of the ABIM, in an interview. Physicians have always defined what that means, he said. But the world has changed, and "the definition doesn't just belong to doctors," said Dr. Baron, who is also a past chair of the ABIM board.

Physicians now have to answer to payers that want to reward performance and measure quality. They also have to answer to patients. "It's hard for us to say whether we are meeting the needs of our patients if we don't find ways to ask them if we are. That's a pretty important evolutionary transformation in assessing how well we do what we do," Dr. Baron said. "Having patients around the table as we think about the standards that we generate will help us have some assurance that we're actually doing that."

By the same token, as physicians start working more with health care teams, having a team member help define what makes a good doctor also makes sense, said Dr. Baron.

The ABIM will soon announce the names of the nonphysicians who were confirmed in April by the ABIM Board. One is a health care executive who has experience heading a Medicaid managed care company and has also been a senior official with the Department of Health & Human Services. The second is the leader of a widely respected consumer organization, said Dr. Baron.

The main board now has 12 directors, with a maximum of 15. Up to 20% of the board's membership can be made up of noninternists.

The council has up to 18 members, and will:

- Determine the requirements for certification and maintenance of certification across all the internal

Continued on following page

ABIM says majority meet new MOC requirements

BY ALICIA AULT
Frontline Medical News

The American Board of Internal Medicine says that "a substantial majority" of the nation's internists have met the new Maintenance of Certification requirements as of May 1, the deadline for doctors to be listed publicly on the ABIM's website as having met those standards.

The ABIM reported that "despite vocal concerns" from physicians, some 150,000 have enrolled in the MOC program, 50,000 since the new requirements were instituted on Jan. 1.

As part of the new MOC, every 2 years, physicians who are certified by the ABIM must earn at least some points by completing some of the educational activities approved for MOC credit. At the 5-year mark, they must earn 100 points, as well as complete patient safety and patient survey activities, to be considered up to date. Previously, physicians were given 10 years to earn 100 points. They must also pass their board exam every 10 years.

"We are listening to the feedback we have received from the community about changes to our program, but at the same time the public is seeking a way to know that their doctor is 'keeping up in their field,' " Dr. Richard Baron, ABIM president and chief executive officer, said in a statement.

A petition to overturn most of the MOC changes begun by Dr. Paul Teirstein, chief of cardiology and director of interventional cardiology for Scripps Clinic in La Jolla, Calif., has collected more than 14,000 signatures since it was posted in late March.

According to the ABIM, since Jan. 1, physicians have claimed more than 245,000 hours of Continuing Medical Education (CME) through their MOC involvement, and nearly 20,000 physicians have already met their MOC requirements through 2015.

"MOC has clearly sparked a national conversation focused on what regular assessments are appropriate for ongoing specialty certification," Dr. Baron said. "We must look at how the MOC process meets the needs of physicians, patients, and others who rely on it as an indicator of a provider's expertise."

The ABIM continues to say that MOC is needed because it is desired by patients and payers. "Those who choose to meet ABIM's MOC requirements are differentiating themselves from some of their colleagues. They are saying, 'I'm a cardiologist or oncologist, or whatever specialty they are certified in, who is meeting a standard set by my peers.' That is a powerful statement to make to their patients, and to themselves," Dr. Clarence H. Braddock III, chairelect of the ABIM Board of Directors, said in the ABIM statement.

The Board also said it is responding to criticism by making changes to the MOC program, including giving "credit" for activities physicians already are doing to maintain their knowledge base and improve their practices. It said it recognizes more than 270 programs created by medical societies, health systems, and others and that 32,000 ABIM diplomates already have fulfilled some requirements of MOC using those pathways. "We recognize that the MOC program is not perfect, and we are committed to constant assessment of it," said Dr. Baron.

That may not be enough for some physicians.

Another group, Change Board Recertification, was started in 2010 with the aim of completely overhauling the MOC process.

VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: The new MOC requirements that became effective on Jan. 1, 2014, have met with significant criticism from practicing physicians. Nevertheless, the majority of physicians with time-limited board certifications have enrolled in the program, as hospital privileges and insurance reimbursements are often linked to active certification.

Whereas it is largely agreed that some measure of ongoing knowledge and competence is vital to setting standards for the profession and protecting the interests of patients, many physicians raise significant concerns regarding the current process. These include overly burdensome costs and time commitments as well as relevance to actual practice.

Finally, there is a paucity of data demonstrating that the MOC recertification process actually translates to improved physician performance in the clinical setting. A number of recommendations have been suggested to improve the recertification process. These include decreasing the costs of recertification by the ABIM; customizing the process to dovetail with an individual physician's actual practice; testing not only rote knowledge, but also physician ability to accesses and utilize information; and further research to demonstrate efficacy in achieving and demonstrating physician competence.

Continued from previous page

medicine disciplines.

► Harmonize ABIM standards with those of other recognized physician education and assessment initiatives.

► Set and integrate operational policies and procedures across the specialty boards.

► Evaluate proposals for new specialties/focused practice areas.

Some subspecialty board members migrated to the council. And the council has some at-large members with expertise in performance improvement, quality measures, or health information technology. The council also will add members who can offer the patient, caregiver, and health care team perspective.

Overhaul of subspecialty boards

The ABIM also decided it was time to reorganize the subspecialty boards, in part so they could more effectively design quality improvement and performance assessment modules for the MOC process.

The role of the subspecialty boards is to define, refine, and set standards in certification and MOC in the discipline; perform oversight/review of performance assessments in the discipline; and build partnerships with societies and other organizational stakeholders in support of ABIM work.

In the past, the subspecialty boards were mainly charged with developing the exam for each specialty. But as the certification and MOC processes have evolved, the subspecialty board members have not been equipped to flesh out the exam, said Dr. Baron.

Each new board will have from six to eight members, with physicians from the particular specialty. But the committees also will have at least one community physician in nonacademic practice and two public, nonphysician members. This will include, for example, a nurse practitioner who's part of a patient-centered medical home. And it also will include someone who can give the patient or caregiver perspective, said Dr. Baron. Each of the boards will also have an committee that develops the exam questions in that discipline.

The ABIM has selected subspecialty board members for pulmonary disease, internal medicine, critical care medicine, endocrinology, diabetes and metabolism, gastroenterology, geriatric medicine, hematology, infectious disease, medical oncology, nephrology, and rheumatology.

Members of the committees will be announced in July.

COMMENTARY

Dr. Daniel Ouellette, FCCP, comments: Thirty years ago, passing a board examination in internal medicine or one of its subspecialties was a rite of passage. The successful examinee had proven that they had mastered the complexities of their chosen medical discipline. One understood that there was more to clinical practice than medical knowledge, but the public demonstration of sufficient medical knowledge was a core requisite of that practice.

As a profession, we grudgingly accepted first recertification, and then the mysterious Maintenance of Certification process, as proof of our continued intellectual competency. We assented without much complaint to the increased costs and the constantly changing specifics of the certification process.

Now we learn that others, such as community physicians, health care executives, and consumer advocates, will have a place on the ABIM to pass judgment on the professional, knowledge-based, assessment of experts in internal medicine and its subspecialties. Instead of just "taking our boards," it may well be time to speak up and take them back!

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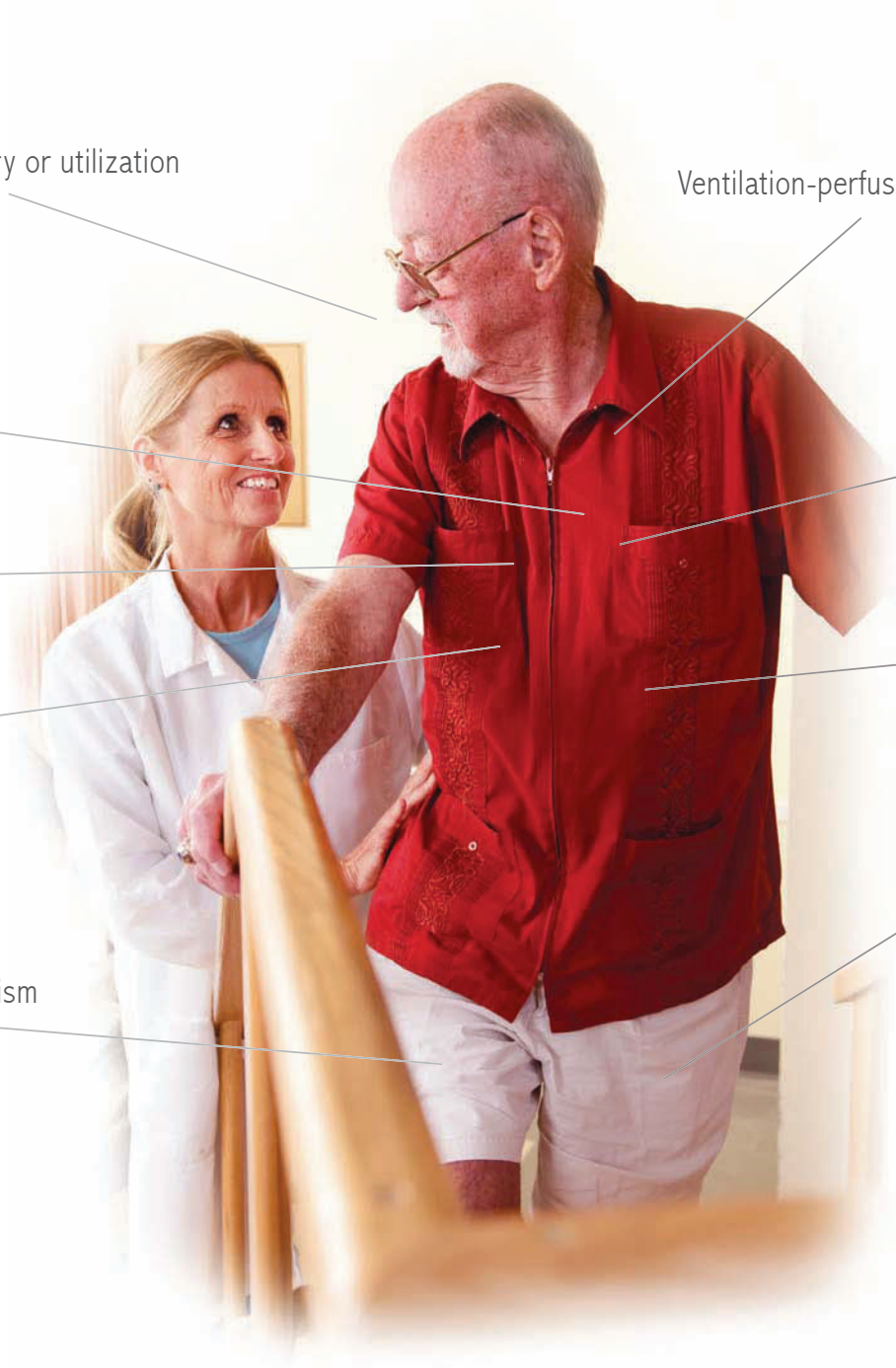

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