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Up-to-date status was protective against severe disease, involving seizures, encephalopathy, or pneumonia.

Pertussis vaccination cuts disease severity

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Pertussis vaccination does not eliminate the risk of disease, but it does appear to reduce disease severity, according to findings from a study of more than 10,000 cases.

In fact, despite high acellular pertussis vaccine coverage in the United States, 48,277 cases were reported in 2012, and many of these were among vaccinated individuals – a result of waning protection over time following childhood pertussis vaccination, Lucy A. McNamara, Ph.D., of the Centers for Disease Control and Prevention in Atlanta reported at the International Conference on Emerging Infectious Diseases.

To assess whether severe symptoms or complications are more common in those who are not fully vaccinated, Dr. McNamara and her colleagues identified a total of 10,092 pertussis case patients from the Enhanced Pertussis Surveillance/Emerging Infections Program network in 2010-2012 and collected case information through vaccine registries and interviews with physicians and patients at six network sites. Of those aged 3 months to 19 years, 81% were up to date for pertussis vaccinations for their age, and of adults, 45% had received Tdap.

See **Pertussis** • *page 16*

Quality of care not tied to pneumonia readmissions

Readmission causes are multifaceted.

BY SHANNON AYMES
Frontline Medical News

Lower quality of care was not associated with pneumonia readmissions, according to a study using a commercially available software program to examine possibly preventable readmissions.

Rates of hospital readmission are now being used to demonstrate hospital performance and the Centers for Medicare & Medicaid Services may even penalize hospitals with high rates of readmissions. As a result, it has become increasingly important to recognize clinical situations that may lead to a potentially preventable readmission.

The Potentially Preventable Readmission (PPRs) software was developed by 3M Health Information Systems to identify such cases and is being adopted by some state Medicaid programs. Dr. Ann M. Borzecki of the Center for Healthcare Organization and Implementation Research in Bedford, Mass., and her colleagues sought to understand if patients with pneumonia flagged by the PPR software as preventable readmissions were associated with failures in the process of care.

See **Readmissions** • *page 9*

INSIDE

Bevacizumab prolongs survival in unresectable mesothelioma

BY SUSAN LONDON
Frontline Medical News

DENVER – Adding the antiangiogenic antibody bevacizumab to chemotherapy improves outcomes in patients who have unresectable mesothelioma, with little downside, according to results of MAPS (the Mesothelioma Avastin Plus Pemetrexed-Cisplatin Study).

Median overall survival in the multicenter randomized phase III trial was 2.75 months longer for patients given bevacizumab in addition to the doublet of pemetrexed plus cisplatin, first author Dr. Arnaud Scherpereel reported at a world conference on lung cancer. This benefit was achieved with only a small increase in the rate of grade 3 or 4 toxicity and no detriment to quality of life.

"We feel that the treatment

See **Mesothelioma** • *page 11*

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

HELP HER WRITE FUTURE CHAPTERS

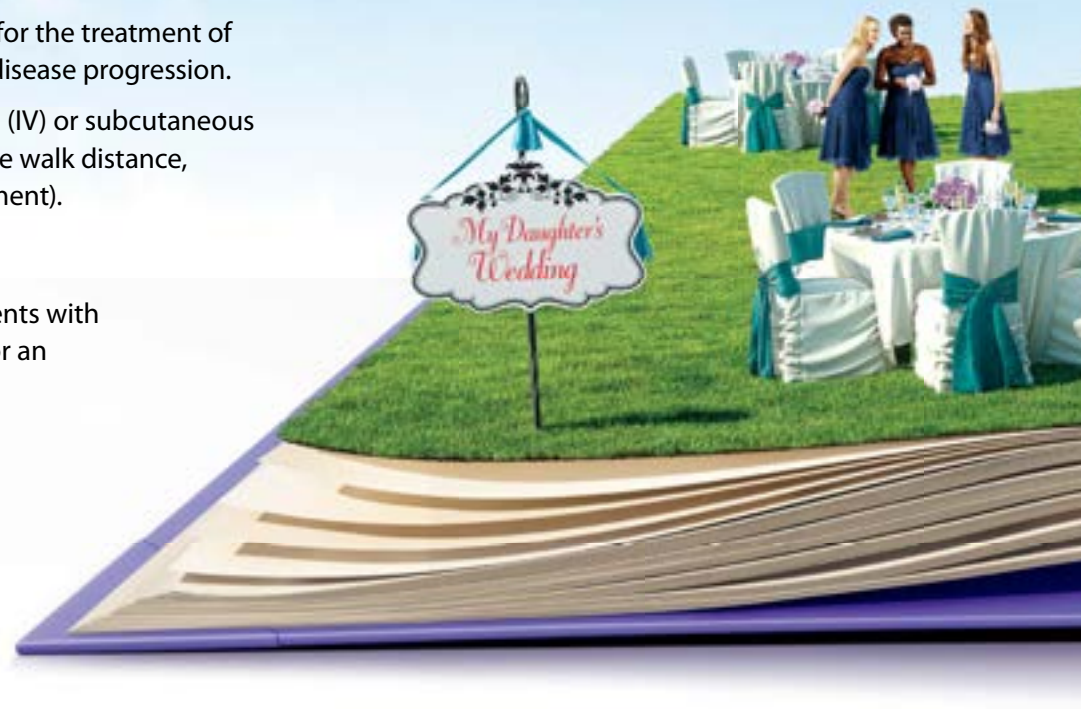
OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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.

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase type 5; SC: subcutaneous; SERAPHIN: **S**tudy with an **E**ndothelin **R**eceptor **A**ntagonist in **P**ulmonary Arterial **H**ypertension to **I**mprove Cli**N**ical Outcome; ULN: upper limit of normal; WHO: World Health Organization.

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

Patient dramatization

SERAPHIN: The first long-term outcome trial in PAH (average treatment 2 years) to demonstrate the use of both monotherapy and combination therapy to delay disease progression[1,2]

Patients were treated with OPSUMIT monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients[3]
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years[3]
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study[3]

SERAPHIN was a randomized, double-blind, placebo-controlled, event-driven outcome study to assess the effect of OPSUMIT on disease progression (time to first significant morbidity or mortality event), as defined by death, atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1,2]

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN was 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 when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

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

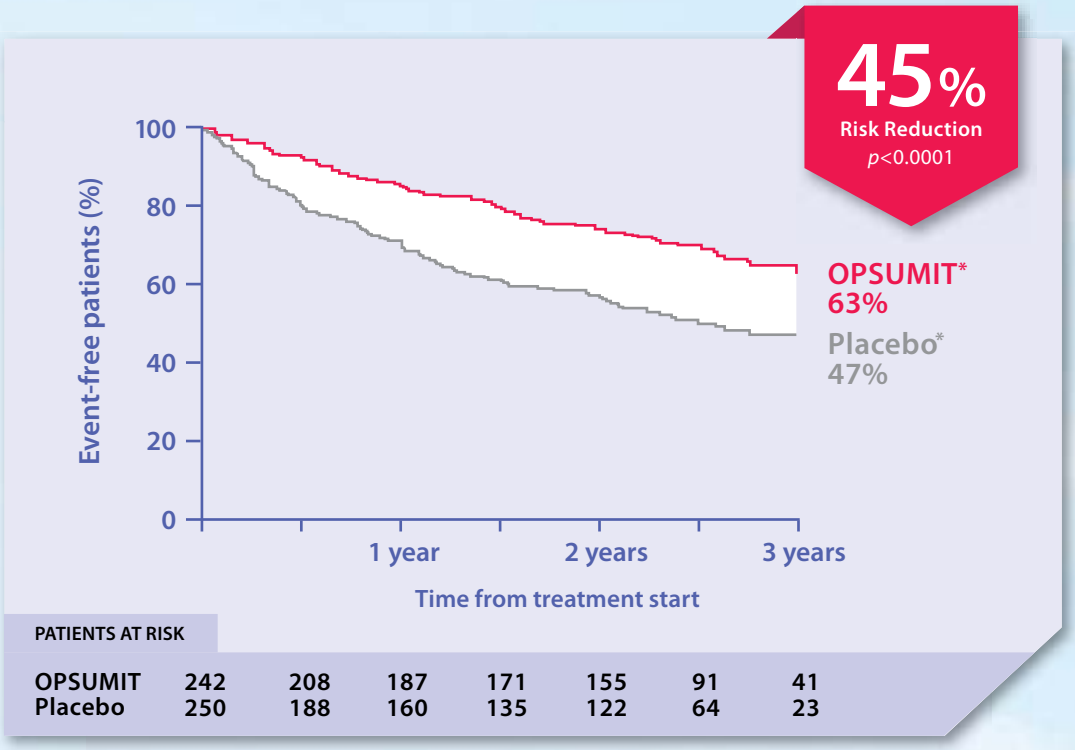
FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

INDICATION

OPSUMIT® (macitentan) 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.

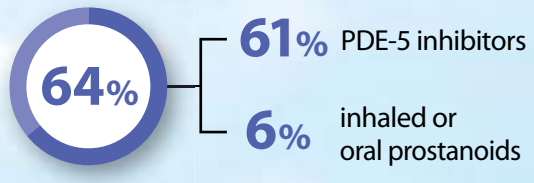
Keep disease progression in mind from the start of therapy: OPSUMIT is the only ERA approved to delay disease progression in FC II and III patients[1]

Kaplan-Meier estimates of risk of first primary endpoint event in SERAPHIN



Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms and need for additional PAH treatment).[1]

***Patients on PAH-specific background therapy at baseline**



Summary of primary endpoint events

	OPSUMIT 10 mg (n=242) n (%)	Placebo (n=250) n (%)
Patients with a primary endpoint event†	76 (31.4)	116 (46.4)
Component as first event		
Worsening PAH	59 (24.4)	93 (37.2)
Death	16 (6.6)	17 (6.8)
IV/SC prostanoid	1 (0.4)	6 (2.4)

The beneficial effect of OPSUMIT was primarily attributable to a reduction in clinical worsening events (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1]

†No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT 10 mg treatment groups.

WARNINGS AND PRECAUTIONS (continued)

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.

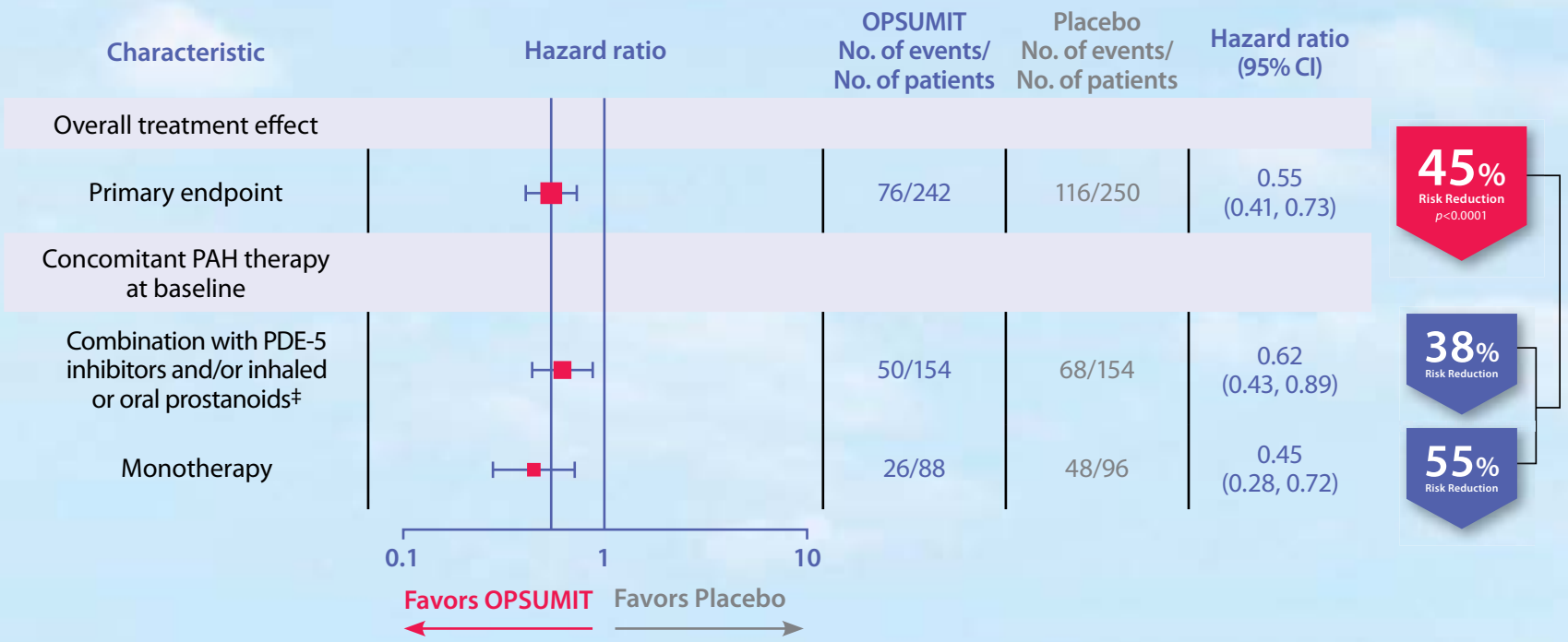
Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

INDICATION (continued)

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%).

OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

Subgroup analysis of the primary endpoint in the SERAPHIN study



‡The OPSUMIT indication includes combination with phosphodiesterase-5 inhibitors or inhaled prostanoids, but not oral prostanoids.

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

Don't delay, treat today—keep disease progression in mind from the start of therapy in FC II and III patients.

OPSUMIT is approved for use as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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.

References: 1. OPSUMIT full prescribing information. Actelion Pharmaceuticals US, Inc. February 2015. **2.** Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-818. **3.** Center for Drug Evaluation and Research, Food and Drug Administration. Opsumit (macitentan) NDA 204410. Medical Review(s). 19 October 2013. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf. Accessed April 15, 2015.

CI: confidence interval; CYP: cytochrome P450; FC: functional class; HIV: human immunodeficiency virus.

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

ACTELION

FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

Opsumit®
macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

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

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

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

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

Hepatotoxicity

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

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

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

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

Table 2: Adverse Reactions

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

Postmarketing Experience

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

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)
Respiratory, thoracic and mediastinal disorders: nasal congestion

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.

OPSUMIT® (macitentan)

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.

Drug Interactions

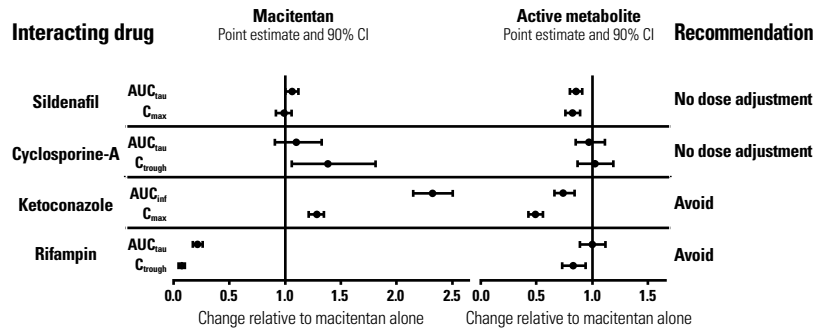
In vitro studies

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

ACT20150219

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. February 2015.

2016 Medicare fee schedule: What you should know

BY ALICIA GALLEGOS
Frontline Medical News

The comments are in and shaping of the final Medicare Physician Fee Schedule for 2016 rests now in the hands of officials at the Centers for Medicare & Medicaid Services. What are the key provisions you need to know about to practice successfully in 2016? Experts gave their opinions in a webinar sponsored by the American Health Lawyers Association (AHLA).

VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: This article provides one with a good summary of a few of the potential changes that may be coming in the next Medicare Physician Fee Schedule. These changes may impact not only your reimbursement but also your reputation. Medical societies, including the ACCP, often comment on the fee schedule to minimize the potential impact on physician practice and maximize the potential for reimbursement. While individual practitioners would have a difficult time keeping up with all of the changes on yearly basis, a knowledge of the changes that impact one's reimbursement is imperative. This will allow one to implement adjustments rather than paying penalties.

Physician Quality Reporting System (PQRS)

CMS proposes to audit not only physician participants, but also vendors who submit quality measure data on behalf of doctors, under the 2016 proposed fee schedule. The agency recommends that vendors make available contact information for each eligible practitioner on behalf of whom it submits data and retain data submitted to CMS for PQRS for 7 years.

Doctors who fail to report on nine quality measures for PQRS will not automatically face trouble, according to Daniel F. Shay, a health law attorney in Philadelphia. In general, individual physicians in PQRS must report on at least nine measures covering three National Quality Strategy (NQS) domains for at least 50% of their Medicare patient base. But if fewer than nine measures are reported, physicians have the chance to explain themselves.

"In some cases, a practice may not have at least nine measures that apply to it, Mr. Shay said. "The [eligible practitioner] would then be able to report on fewer than nine measures, but would be subject to the measure application validity process, which basically means CMS audits the provider to prove they couldn't have reported on all of the required measures."

Also, CMS proposes extending participation in PQRS to doctors who practice in critical access hospitals, according to the 2016 proposed fee schedule. PQRS is a voluntary quality reporting program that applies adjustments to payments based on benchmarks. CMS is suggesting that physicians who practice in certain critical access hospitals now have the option to participate in the program – such doctors were previously excluded.

Incident to service

When overseeing care that is "incident to" service, CMS proposes that billing physicians also act as supervising physicians. The proposal could impact group practices who do not typically use that structure, said Washington health law attorney Julie E. Kass during the AHLA webinar.

Incident to is defined as services furnished incident to a physician's professional services over the course of a patient's diagnosis or treatment. Medicare pays for services rendered by employees of a physician only when all incident to criteria are met. Those criteria include that services rendered by nonphysicians are under the direct supervision of a physician physically in the same office suite. In the proposed 2016 rule, CMS seeks to clarify that the billing physician must be the same physician who supervises the ancillary personnel. Previously, group practices may have billed under the provider who ordered the treatment, according to Ms. Kass.

"It sounds simple, but then you put it into the context of what happens in a real life practice," she said. "I think a lot of practices, in operationalizing this rule, have generally used the ordering physician as the physician who billed for the service without paying a lot of attention to who was the actual supervising physician."

Group practices may want to rethink how they bill for incident to services, and ensure the billing physician is the one who supervises the treatment, she advised.

The Stark Law

Proposed changes to regulations implementing the Stark Law could make it easier for physicians to hire new nonphysician providers (NPP) to provide primary care. Under the fee schedule proposal, hospitals would be allowed to assist in the recruitment of health professionals for physician practices. Currently, hospitals may not because remuneration could be considered a compensation relationship between the hospital and physician practice. The proposed change aims to promote care team collaboration and help curb primary care shortages.

The exception would permit recruitment assistance and retention payment from a hospital, rural health clinic, or federally qualified health center to a physician practice to employ an NPP. However, the NPP would have to be a bona fide employee of the physician practice and provide primary care services. CMS defines an NPP as a physician assistant, nurse practitioner, clinical nurse specialist, or certified nurse-midwife. CMS is also recommending a cap on the total remuneration and duration of assistance provided.

You will want to ensure the billing physician also supervises treatment for 'incident to' services.

MS. KASS

The limits aim to "make sure the physicians have skin in the game in bringing in the NPP," Ms. Kass said. "It's not all going to be the burden of hospital to provide recruiting assistance, but rather the physician has to need and want the NPP enough to be willing to bring them in as well without total support and assistance."

Value-Based Payment Modifier Program

CMS proposes a new way to determine the extent of payment cuts and bonuses in the Value-Based Payment Modifier program. The program evaluates the performance of solo practitioners and groups on the quality and cost of care they provide to fee-for-service Medicare patients.

In 2016, the agency proposes to adjust payments based on the size of the participating group and to determine that size by reviewing claims data and its Provider Enrollment, Chain, and Ownership System (PECOS)–generated list. CMS would apply whichever number is lower in PECOS or claims data.

Now is a good time for doctors to check their PECOS data to ensure the information is accurate and up to date, Mr. Shay recommended.

As many expected, the Value-Based Payment Modifier is slowly expanding to encompass more physicians. Beginning Jan. 1, 2015, the value modifier was applied to physician payments under the fee schedule for groups of 100 or more. In January, it will be applied to physician payments for doctors in groups of 10 or more. In 2017, the modifier will apply to solo practitioners and physicians in groups of two or more. (All modifiers are based on performance periods 2 years prior.)

PQRS will continue to play a central role in the Value-Based Payment Modifier system, Mr. Shay added. CMS is proposing to use the PQRS reporting period for 2016 as the basis for the 2018 value modifier. The agency will draw from the group reporting option and individual eligible professional (EP) reporting mechanisms proposed for 2016.

Physician Compare

Physicians should expect to have more information about their performance reported to the Physician Compare website under the proposed 2016 fee schedule. The site already contain information on physician education, location, group affiliations, and status in quality programs. CMS now wants to include performance rates on 2015 PQRS cardiovascular disease prevention measures for doctors who report them, in support of the Million Hearts program. Additionally, CMS proposes that groups receiving a pay increase under the Value-Based Payment Modifier Program report the data to the website. Doctors also would continue reporting information about patient experiences under the Consumer Assessment of Healthcare Providers & Systems (CAHPS) survey program. The surveys are designed to capture a patient's experience receiving care from their physician.

Mr. Shay noted that one concern with the Physician Compare website is that doctors have little recourse to challenge information on the site. Physicians have only a 30-day window to review information about themselves and correct errors.

"There is no formal appeals mechanism for the website," Mr. Shay.

CMS is currently reviewing feedback and comments submitted about the proposed physician fee schedule before issuing the final schedule, usually in November.

No link to inferior quality of care

Readmissions *from page 1*

The researchers conducted a cross-sectional retrospective observational study with Veterans Affairs electronic medical record (EMR) data from October 2005 to September 2010.

Patients with diagnoses of pneumonia and a 30-day readmission were identified and then flagged as PPR-yes (for example, readmissions associated with quality of care problems) vs. PPR-no, using the 3M PPR software. A tool to measure quality of care was applied to 100 random readmissions abstracted for full review. The study was published online in BMJ Quality and Safety.

GEO MARTINEZ/THINKSTOCK

Of all the pneumonia readmission cases, 72% were PPR-yes vs. 77% of the 100 abstracted cases.

There were no significant differences between the groups other than a trend toward more comorbidity in the PPR-yes group.

After researchers adjusted for comorbidities and demographics, they noted no significant difference in quality of care between the PPR-yes and PPR-no groups. Interestingly, the PPR-yes group had slightly higher quality scores than did the PPR-no group (total scores, 71.2 vs. 65.8 respectively, $P = .14$).

The authors write, "Among veterans readmitted after a pneumonia discharge, we found no significant difference in quality of care, as measured by processes of care received during the index admission and after discharge, between cases flagged as PPRs and nonflagged cases.

"Indeed, contrary to our hypothesis, quality scores were slightly higher among PPR-flagged cases."

The authors emphasized that causes of readmissions are multifaceted and many aspects may be out of the control of the hospital. However, they noted a concern for a lack of postdischarge documentation and emphasized the need for thorough documentation at all levels of care.

The authors report no competing interest. The study was funded by the U.S. Department of Veterans Affairs Health Service Research and Development Service.

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: Physicians and health care systems face increasing scrutiny for readmission of patients for the same admission diagnosis. In some cases, payment is being denied for such readmissions on the basis that the prevention of readmissions is a quality indicator. Researchers at the U.S. Veterans Health Administration have demonstrated in a cross-sectional study that pneumonia readmissions were not linked to inferior quality. If this important finding is extended to other diagnoses, it raises the possibility that the real driver for payment denial for readmissions is cost, not quality.

VIEW ON THE NEWS

Even with potentially preventable readmissions having a slightly higher, although not significant, quality score, the question remains: Do the flagged cases actually represent avoidable readmissions? The results bring up further questions on including preventable readmissions in quality measures.

Rates of readmission may reflect several aspects of care including the patient's financial, environmental, and psychosocial factors. Furthermore, failure to address patient factors that contribute to readmission rates may abate hospital interventions to prevent those readmissions.

Dr. Christine Soong is affiliated with Mount Sinai Hospital in Toronto. These comments are taken from an editorial accompanying Dr. Borzecki's study (BMJ Qual Saf. 2015. doi: 10.1136/bmjqs-2015-004484). No competing interests were declared.

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EDITORIAL OFFICES 5635 Fishers Lane, Suite 6100, Rockville, MD 20852, 240-221-2400, fax 240-221-2548

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HIT risk strongly correlated with body mass index

BY SHARON WORCESTER
Frontline Medical News

AT THE AAST ANNUAL MEETING

LAS VEGAS – High body mass index is strongly associated with increased rates of heparin-induced thrombocytopenia, based on findings from a review of prospectively collected data from surgical and cardiac intensive care unit patients presumed to have the condition.

Of 304 patients included in the review, 36 (12%) were positive for heparin-induced thrombocytopenia (HIT). The rates increased in tandem with BMI. For example, the rate was 0% among 9 underweight individuals (BMI less than 18.5 kg/m^2), 8% among 119 normal-weight individuals (BMI of 18.5-24.9 kg/m^2), 11% among 98 overweight individuals (BMI of 25-29.9 kg/m^2), 18% among 67 obese individuals (BMI of 30-39.9 kg/m^2), and 36% among 11 morbidly obese individuals (BMI of 40 kg/m^2 or greater), Dr. Matthew B. Bloom reported at the annual meeting of the American Association for the Surgery of Trauma.

The odds of HIT were 170% greater among obese patients, compared with normal-weight patients (odds ratio, 2.67), and 600% greater among morbidly obese patients, compared with normal-weight patients (odds ratio, 6.98), said Dr. Bloom of Cedars-Sinai Medical Center, Los Angeles.

Logistic regression showed that each 1-unit increase in BMI was associated with a 7.7% increase in the odds of developing HIT, he noted.

Additionally, an anti-heparin/PF4 (platelet factor 4) antibody OD (optical density) value of 2.0 or greater, but not of 0.4 or greater or 0.8 or greater, was also significantly increased with BMI, and in-hospital mortality increased significantly with BMI above normal, he said.

Warkentin 4T scores used to differentiate HIT from other types of thrombocytopenia were not found to correlate with changes in BMI in this study, nor were deep vein thrombosis, pulmonary embolism, or stroke.

The increase in PF4 with increasing BMI may be a marker for overall increasing levels of circulating antibodies in the obese ICU population, but more biochemical studies are needed to tease this out, he said.

Patients included in the review were all those admitted to the surgical and cardiac ICUs at Cedars-Sinai over a more than 7-year period. They had a mean age of 62.1 years, 59% were men, and their mean BMI was 27 kg/m^2.

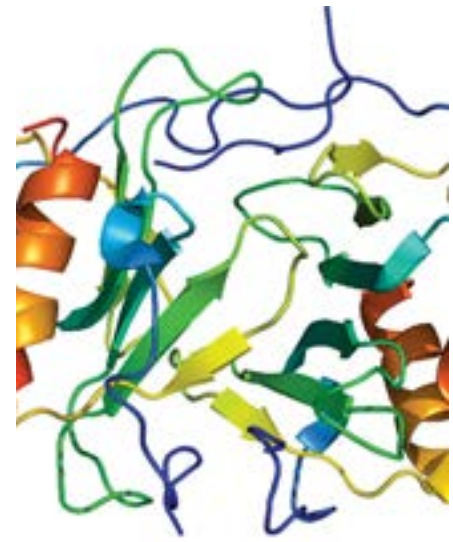
The findings are among the first to show a strong association between BMI and HIT in ICU patients, Dr. Bloom said, noting that several other studies have shown that obesity is linked with increased incidence and increased severity of immune-mediated diseases, including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.

"And HIT is an immune-mediated disease," he added.

"BMI may be an important new clinical variable for estimating the pre-test probability of HIT, and perhaps, in the future, patient 'thickness' could be considered a new 'T' in the 4T score, he concluded.

Dr. Bloom reported having no disclosures.

sworcester@frontlinemedcom.com



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PF4 antibody OD value of 2.0 or more increased significantly with BMI.

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Thrombocytopenia is a common disorder in the ICU and the work-up can be complex. Although the overall incidence of HIT is low, it has potentially devastating complications. As the obesity epidemic in our society continues to climb, there has also been an increase in the incidence of autoimmune diseases. Adipose tissues secrete "adipokines," which participate in the chronic low-grade inflammatory state that is associated with obesity. These mediators are involved in both immunity and inflammation. HIT, which is also an antibody-mediated disease, appeared to have a strong correlation with rising BMI in this review of 304 patients in an ICU setting. The overall incidence of HIT in this review was 12%, but the odds were far greater in the obese and morbidly obese, 170% and 600%, respectively. Since the focus in this review was on surgical and cardiac patients, generalizability to other ICU populations may not have the same results. However, when determining pre-test possibility for HIT, obesity may become a significant variable in the assessment of the patient who requires further work-up for HIT.

Clothing may transmit respiratory syncytial virus in NICU

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Clothing worn by caregivers and visitors may be an important vehicle for the transmission of respiratory syncytial virus in the neonatal intensive care unit setting, according to findings from a prospective study conducted in an Australian hospital. In an effort to identify potential sources of RSV transmission and to facilitate development of infection control strategies, the investigators swabbed all health personnel, every third neonate and their visitors, and any child clinically suspected of having an RSV infection. They detected RSV in 1 of 81 nasal specimens collected from 55 neonates and in 4% of 80 visitors' clothing swabs, Nusrat Homaira, Ph.D., of the University of New South Wales, Sydney, and her colleagues reported in a poster at the International Conference on Emerging Infectious Diseases.

RSV also was detected in 1% of nose swabs from the visitors and in 1% of nose swabs from 84 health care workers.

No RSV was detected on the clothing of health care workers or on the hands of visitors or health care workers, which may be explained by the presence of alcohol-based hand rub at the point of care and by prevalent hand hygiene practices within the neonatal intensive care unit (NICU), the investigators noted.

The investigators also collected environmental swabs and detected RSV on 9% of high-touch areas, including bed rails; chairs; bed surfaces; countertops; and nurse's and doctor's station tables, computers, and chairs.

Samples were collected once each week for 8 weeks during May and June of 2014.

RSV is a major cause of morbidity in very young children, and premature infants have a 10-fold increase in the risk of acquiring RSV infection. Hospital-acquired cases are an important cause of prolonged hospitalization, Dr. Homaira and her associates noted.

The findings suggest that personal clothing may be one of the modes of virus transmission, they said.

"Though the detection rate is low, personal clothing of caregivers/visitors do get contaminated with RSV," Dr. Homaira said in a written statement, noting that caregivers and visitors are not required to change clothing when they walk into the NICU.

"There is a need for further research to evaluate how long the virus remains infectious on personal clothing, which will have policy implications in terms of need for use of separate gowns by the visitors while they are in the NICU," Dr. Homaira added, concluding that frequent cleaning of high-touch areas and periodic screening of visitors for RSV as they enter the NICU during seasonal epidemics also may help limit disease transmission.

The investigators reported having no disclosures.

sworcester@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Fomites are porous or nonporous surfaces or objects that can become contaminated with viruses and serve as transmission vehicles. RSV is known to live on these fomites for many hours, making our littlest patients very susceptible. Clothing is a new concern!

A new treatment paradigm

Mesothelioma *from page 1*

of pemetrexed-cisplatin with bevacizumab is a new treatment paradigm for mesothelioma patients eligible for bevacizumab and not candidates for curative surgery. And I think that most of them may be eligible for this drug because these patients are not so often smokers and [have] lung conservation, they have less comorbidities," he said. "Perhaps this treatment may be accepted as a new standard of care for these patients."

The control arm had much better survival than had been seen historically with this chemotherapy, noted Dr. Scherpereel, who is head of the pulmonary and thoracic oncology department and a professor at the University Hospital (CHRU) of Lille, France. This may have been because of the trial's eligibility criteria, chosen to ensure that patients could receive bevacizumab, or to the facts that patients had to be fit enough to undergo thoracoscopy and that some received pleurodesis before enrollment.

Bevacizumab benefit may therefore differ in other patients, he acknowledged. "We will see in the real life. I hope first to have the drug [available] for this indication," he said an the conference sponsored by the International Association for the Study of Lung Cancer.

Press conference moderator Dr. James R. Jett, conference cochair and a professor of medicine at National Jewish Health in Denver, noted that pemetrexed-cisplatin remains the standard of care in the United States. "We don't have bevacizumab as the standard, but this [trial] may very well change that," he said.

He wondered if the unusually good outcomes in the control arm were related to earlier diagnosis, but said that regardless, bevacizumab still showed a benefit. "I think the main message here is that it's important to do concurrent controls because if we were comparing to a historic control, it would be very difficult," he said.

MAPS was sponsored by the French Cooperative Thoracic Intergroup and was open to patients with mesothelioma who were not candidates for surgery and had not received chemotherapy. Those who had pleural effusion were allowed to undergo a talc

Continued on following page

'Perhaps this treatment may be accepted as a new standard of care for these patients.'

DR. SCHERPEREEL

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: This is welcome news in the treatment of malignant mesothelioma – a devastating diagnosis to receive. In this study, it is encouraging that the hard endpoint of overall survival was examined, and the results represent the hope that we may be beginning to make recognizable progress in treating this disease. With the addition of more directed therapies such as bevacizumab to treatment regimens, we hold great anticipation that the future offers additional and increasingly beneficial discoveries for these patients.

Continued from previous page

pleurodesis at the time of diagnostic thoracoscopy.

A total of 448 patients were randomized to open-label cisplatin and pemetrexed, with versus without bevacizumab (Avastin). The bevacizumab group additionally received the drug alone as maintenance therapy after completing chemotherapy. Cross-over was not allowed.

'We don't have bevacizumab as the standard, but this [trial] may very well change that.'

DR. JETT

With a median follow-up of 39.4 months, the bevacizumab arm had better median overall survival (18.82 vs. 16.07 months; hazard ratio, 0.76; $P = .015$) – the trial's primary endpoint – and progression-free survival (9.59 vs. 7.48 months; hazard ratio, 0.61; P less than .0001).

"Usually the progression-free survival in the trials with best medical treatment was between 6 and 7 months," Dr. Scherpereel pointed out. Similarly, "the best [overall survival] results with the standard treatment is close to 13 months."

"There was no significant difference between the two arms in the percentage of drug delivery or the percentage of patients having second-line treatment which could explain the increase of survival in the bevacizumab arm," he reported.

The proportion of patients experiencing grade 3 or 4 toxicity was higher with bevacizumab (71.2% vs. 62.1%; $P = .04$), largely because of more nonhematologic toxicity such as hypertension and venous thromboembolism. However, this additional toxicity was manageable, according to Dr. Scherpereel.

Furthermore, in terms of quality of life measures, patients in the bevacizumab arm had a greater improvement in fatigue from baseline ($P = .046$) and scores for other measures did not differ between arms.

"We did not find some predictive clinical or biological marker [of bevacizumab benefit] for this study," he said. In particular, patients' pretreatment levels of vascular endothelial growth factor (VEGF) did not identify a group more likely to benefit. But an ongoing companion study is still evaluating other biomarkers, such as mesothelin and endocan, he added.

Dr. Scherpereel disclosed that he and coinvestigators had affiliations with Roche and other companies. Roche supplied bevacizumab and a research grant for the biomarker studies.

Prolonged sepsis increased inpatient mortality risk

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The longer patients have sepsis, the more likely they are to die while in the hospital, a retrospective, single-center study showed.

However, lower respiratory tract infection, methicillin-resistant *Staphylococcus aureus* infection, Charlson score, and time to first antibiotic dose were not significantly associated with increased odds for mortality.

"Sepsis is a life-threatening acute condition that is commonly associated with inpatient mortality," lead study author Joseph J. Carreno, Pharm.D., said in an interview in advance of the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. "To date, numerous interventions have evaluated the impact of interventions on sepsis-related mortality. However, few have

VITALS

Key clinical point: Prolonged duration of sepsis is an early predictor of inpatient mortality.

Major finding: Significant risk factors for inpatient mortality were time (in days) to sepsis resolution (OR, 1.13) and being initially admitted to the ICU (OR, 5.21).

Data source: A retrospective case-control study of 248 patients at Albany (N.Y.) Medical Center Hospital with documented sepsis who received antimicrobial therapy.

Disclosures: Dr. Carreno reported having no financial disclosures.

examined duration of sepsis as a predictor of mortality."

An earlier analysis conducted by Dr. Carreno and his associates at the Albany (N.Y.) College of Pharmacy and Health Sciences found that the duration of sepsis may be reduced through the use of multimodal interventions implemented by interdisciplinary teams.

For the current study, the researchers set out to evaluate the relationship between time to sepsis resolution and inpatient mortality by reviewing the records of 248 patients with documented sepsis who received antimicrobial therapy at Albany Medical Center Hospital. They defined time to sepsis resolution as time in days from blood culture to first date with fewer than two signs of systemic inflammatory response syndrome.

The mean age of the patients was 63 years, 67% were male, and 31% initially were admitted to the intensive care unit. The most prevalent sources of infection were genitourinary (24%), lower respiratory tract (17%), and endovascular (17%), while the most prevalent organisms isolated were coagulase-negative *Staphylococcus* (20%), *Escherichia coli* (18%), *Streptococcus* (15%), and methicillin-sensitive *S. aureus* (8%).

What was surprising to me was the increase in mortality that was seen with each day of unresolved sepsis.

DR. CARRENO

In all, 21 patients (9%) died. On multivariable analysis, the only significant risk factors for inpatient mortality were time (in days) to sepsis resolution (odds ratio, 1.13) and being initially admitted to the ICU (OR, 5.21).

"What was most surprising to me was the steady increase in mortality that was seen with each day of unresolved sepsis," Dr. Carreno commented. "We hypothesized that there would be an association between time to sepsis resolution and mortality, but we thought that there would be a natural cut point rather than a steady increase in risk."

Others factors such as lower respiratory tract infection, Charlson score, methicillin-resistant *S. aureus* infection, and time to first antibiotic dose didn't have a significant association with increased odds for mortality.

"In our study, prolonged duration of sepsis was an early predictor of inpatient mortality," he concluded. "Hence, patients' response to therapy should be evaluated early in therapy. Our study supports recommendations from the Food and Drug Administration's new guidance for clinical trials and the Centers for Disease Control and Prevention's antibiotic 'time out' concept."

dbrunk@frontlinemedcom.com

TCAD regimen shows promise against H3N2 flu

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Triple-combination antiviral drug therapy offers a broad-spectrum treatment option for H3N2 variant influenza virus, according to findings from an in vitro study.

The findings suggest that the combination could play an important role in the event of an influenza pandemic, Carrie Sitz reported in a poster at the International Conference on Emerging Infectious Diseases.

After a human infection with the novel A/H3N2 variant was reported in 2011, and trivalent inactivated influenza vaccine was found to be of limited use, as it provided protection against H3N2 but not the H3N2 variant (H3N2v) in ferrets and elicited cross-protection against H3N2 in young adults but not older adults or children, a triple-combination antiviral therapy (TCAD) regimen was considered.

Amantadine, oseltamivir carboxylate, and ribavirin each were tested alone and in double and triple combinations against the novel H3N2 variant virus carrying genes from avian, swine, and human origins. Triple therapy achieved a therapeutic effect with lower doses of component drugs, compared with monotherapies of antivirals as single agents, said Ms. Sitz, a microbiology research assistant at the Naval Health Research Center, San Diego.

The agents, which each have different mechanisms of action and which function at distinct points in the virus life cycle, were tested using the various combinations in 96-well plates seeded with Madin-Darby Canine Kidney (MDCK) epithelial cells. They were found to produce synergistic antiviral activity, she noted.

A control experiment in the absence of the drugs also was performed.

Of note, amantadine had no activity as a single agent against H3N2v, even at 100 mcg/mL, the highest dose tested. However, amantadine did contribute to the synergy of the TCAD regimen. This effect was concentration dependent; the potential synergy volume increased steadily and significantly from about 300 to about 450, to about 575, and to about 600 as the amantadine concentration increased from +0.32, to +1.0, to +3.2, to +10, Ms. Sitz noted, adding that this may indicate that amantadine, which is known to have widespread resistance, can still play a therapeutic role in the setting of the TCAD regimen.

Vaccines are usually an effective safeguard against seasonal influenza but may be inadequate in seasons when a novel influenza emerges, resulting in compromised standard of care for treating the emergent viruses, she said, noting that this is especially true in immunocompromised patients.

"These issues point to the likelihood that we may be unprepared for a novel influenza virus displaying both virulence and transmissibility," she added.

The current findings suggest that TCAD, which has previously been shown to be effective against seasonal and H5 influenza strains, is a broad-spectrum treatment option that could potentially play a role in pandemic preparedness. The mechanism by which oseltamivir carboxylate and ribavirin potentiate amantadine in combination therapy is unknown, and further testing is needed for evaluation, she concluded.

This study was sponsored by the Armed Forces Health Surveillance Center. The authors had no disclosures.

sworcester@frontlinemedcom.com

60% risk reduction

Pertussis *from page 1*

Up-to-date status was protective against severe disease, defined as disease involving seizures, encephalopathy, pneumonia, or hospitalization, in children aged 7 months to 6 years, who had about a 60% reduction in risk, compared with those who were not up to date. Up-to-date status also reduced the risk of posttussive vomiting, which sometimes accompanies severe coughing fits, by about 25% in those aged 19 months to 64 years, she said, adding that the risk of vomiting after coughing was about 38% lower in this age group when patients received antibiotic treatment within 1 week of the start of the illness.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The conclusions from this study have significant implications in clinical medicine and may run contrary to the generally held belief that up-to-date vaccination status confers near-complete protection against the disease for which we are vaccinating. As such, it is apparent clinicians need to consider pertussis in all appropriate clinical presentations, and not be falsely reassured by vaccination history. While it certainly is encouraging that vaccination offers significant protection from severe disease and routinely should be recommended for our patients, it underscores that we all need to recognize the limitations of our efforts and the need for continued vaccine research and development.

The effect on posttussive vomiting was independent of antibiotic treatment timing, which further underscores the value of both rapid treatment and completion of the pertussis vaccination schedule, Dr. McNamara commented.

Dr. McNamara reported having no disclosures.

sworcester@frontlinemedcom.com

DATA WATCH: Spending up for the most costly medical conditions

BY RICHARD FRANKI
Frontline Medical News

Spending for each of the five most costly medical conditions rose by at least 21% from 2002 to 2012, the Agency for Healthcare Research and Quality reported.

That smallest-of-the-five increase of 21% belonged to the most expensive of the five, heart conditions, which rose from $83.5 billion in 2002 (in 2012 dollars) to $101 billion in 2012.

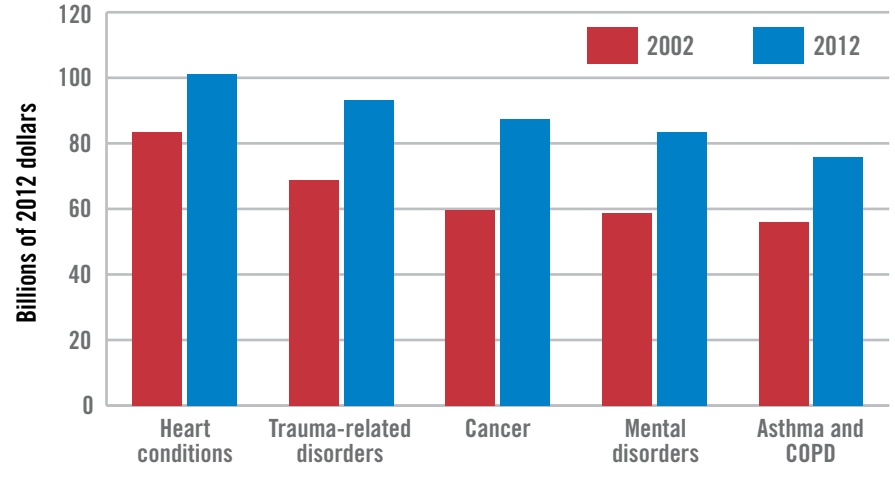
The largest-of-the-five increase went to cancer, which jumped 46% from $59.8 billion to $87.5 billion, with mental disorders showing the next-largest increase as costs rose 43% from $58.6 billion to $83.6 billion, according to data from the Medical Expenditure Panel Survey. The same conditions made up the top five in both 2002 and 2012.

The average expenditure per person affected actually went down slightly for mental disorders – from $1,887 to $1,849 – but the number of persons affected rose 45%, from 31.1 million in 2002 to 45.2 million in 2012, which was the largest increase among the five most costly conditions.

The number of people affected went down 1% for trauma-related disorders and 10% for asthma and chronic obstructive pulmonary disease and rose almost 18% for heart conditions and 42% for cancer, the AHRQ said.

rfranki@frontlinemedcom.com

Total medical spending for the five most costly conditions



Notes: Based on data from the Medical Expenditure Panel Survey. COPD = chronic obstructive pulmonary disease.

Source: Agency for Healthcare Research and Quality

What if your PAH patient may not have PAH?

A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.[1]

If you know what to look for, a V/Q scan makes it relatively easy to spot.[1]

1 in 25*

As many as **1 out of every 25** of your previously treated PE patients (>3 months of anticoagulation[2]) may develop CTEPH.[3,4*]

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

VISIT **scan4CTEPH.COM** FOR MORE INFORMATION

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100 Bayer Boulevard, Whippany, NJ 07981 USA

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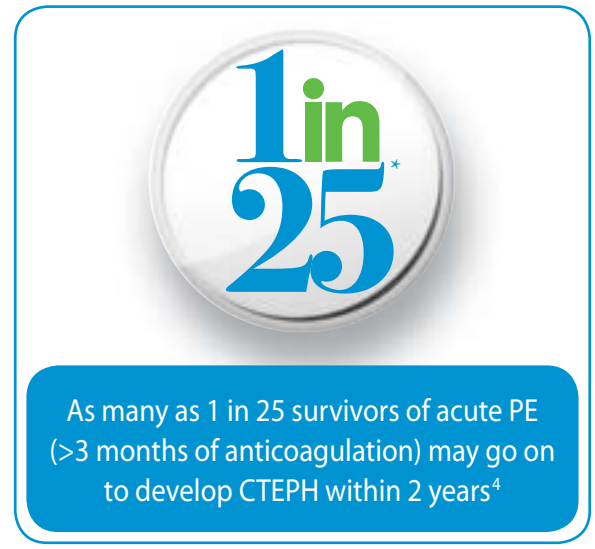
Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

RICHARD CHANNICK, MD

Richard N. Channick, MD, is Associate Professor of Medicine at Harvard Medical School, Boston, Massachusetts, and has been Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital in Boston since 2009.



CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH[1]:

1: Pulmonary arterial hypertension

2: PH due to left heart disease

3: PH due to lung diseases and/or hypoxia

4: CTEPH

5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term "post-pulmonary embolism syndrome" to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity.[2] The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH.[2,3] As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.[4]

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.[5]

Symptoms of CTEPH are nonspecific[6] and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema.[7] Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.[7]

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH.[8-10] It is this potential to effect a curative treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries.[11] The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH.[12] Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR).[11] Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH.[13] If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.[13]

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event.[3,13] A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH.[14] Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.[15]

The absence of prior acute PE does not exclude a diagnosis of CTEPH[9,16,17]

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE.[9,16,17] The true incidence of CTEPH may, therefore, be underestimated, because postembolism observational studies do not include patients who have no history of venous thromboembolism.[13]

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.[6] If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.[18,19]

As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.[9, 16,17]

If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening[17]

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out.[19] Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH.[8] Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.[8] Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH.[20] Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied.[20] Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.[5,8,21-23] Though it can detect chronic thromboembolic disease in segmental, lobar, or main pulmonary arteries, CTPA may miss disease that is

confined to very distal segmental or subsegmental pulmonary arteries.[8,24]

The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.[8] It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. V/Q scanning also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings.

PTE surgery is the first-line treatment of choice for surgical candidates who have CTEPH[15]

Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.[25] This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that "underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH."[8] Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.[6,26] If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

CONFIRMATION OF CTEPH DIAGNOSIS

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.[8] CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.[5,8]

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient's surgery. Operability assessment must consider the patient's risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.[8] If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.[8] This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well be deemed operable by another experienced CTEPH team.

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.[5] Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.[8-10] Rather than reserving PTE surgery as a "last-ditch" treatment option, patients who have operable CTEPH should be referred for surgery without delay.[8] Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,[8] anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.[7] About two-thirds of patients have normal hemodynamics following PTE.[27]

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*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).[4]

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100 Bayer Boulevard, Whippany, NJ 07981 USA

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Surveillance program IDs enterovirus early

BY DEEPAK CHITNIS
Frontline Medical News

ATLANTA – Implementing surveillance programs at area hospitals is an effective tool for health care providers and public health officials to identify severe acute respiratory illness (SARI) and enterovirus specifically early.

"We do surveillance for respiratory illness [at] three sentinel sites that participate in the Minneapolis–St. Paul metro area," explained Hannah Friedlander, an epidemiologist with the Minnesota Department of Health in St. Paul, who presented the study. "[But] our surveillance didn't actually actively look for enterovirus, it looked for rhinovirus, which is known to cross-react with enterovirus on PCRs [polymerase chain reactions]," she said at the International Conference on Emerging Infectious Diseases.

To remedy that, the surveillance program – which involves the participation of one pediatric hospital, one hospital serving both children and adults, and one primarily serving adults – added testing for enterovirus to PCRs of all SARI specimens collected from Sept. 1 through Oct. 31, 2014. In total, 363 SARI specimens were collected over that time frame, of which 100 (28%) were found to be pan-EV positive and underwent further evaluation for EV-D68. Ultimately, 64 of the EV-positive specimens were found to be EV-D68 strains.

The vast majority of cases identified as being caused by the EV-D68 strain (73%) were collected between Sept. 6 and Sept. 20. This indicates that starting surveillance of SARI cases when enteroviruses traditionally become more frequent could allow for faster determination of which strain is most prevalent and what the optimal treatment should be. "It's hard to say if this was surprising because we hadn't previously been looking for enterovirus, so we don't have another year to compare [these] data to," Ms. Friedlander explained. "But I think it's surprising that we saw as much of [enterovirus] as we did."

Most cases of EV-D68 (64, or 36%) were in patients between the ages of 5 and 11 years, with a median age of 6 years. A total of 52 (81%) EV-D68 cases presented with shortness of breath, and 31 cases (48%) presented with wheezing or cough. Hospital stays of 4 days or fewer occurred in 73% of cases, with a median stay length of 3 days; 33% of EV-D68 patients required admittance to the ICU, and 13% of EV-D68 patients were placed on a mechanical ventilator at some point during treatment.

"This fall is our third year doing this type of surveillance, so at the time the data for this [were] collected, we only had 1 year of surveillance under our belt," she explained. "We now look prospectively for enterovirus, not EV-D68 specifically, so it'll be interesting to see as the years go on if this was an outlier year."

'We now look prospectively for enterovirus.'

MS. FRIEDLANDER

Ms. Friedlander and her coinvestigators implore hospital systems to not only have surveillance programs in place, but also for them to have the flexibility to include additional testing should the need for it arise. That flexibility is what proved crucial in the early identification of EV-D68 in her own study population.

This study was funded by the Council of State and Territorial Epidemiologists, and the Centers for the Disease Control and Prevention. Ms. Friedlander did not report any relevant financial disclosures.

dchitnis@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The development and performance of the surveillance program in this study illustrate the importance of having a system like this in place – both for the early detection of known pathogens, and also to respond to emerging or new disease processes that have the potential to cause significant harm. This study demonstrates the importance of agility and the benefits of being able to adapt an existing process to monitor a previously unrecognized viral strain or other deadly disease that unexpectedly may traverse the world.

USPSTF: Ask about smoking, urge quitting

BY KATIE WAGNER LENNON
Frontline Medical News

The U.S. Preventive Services Task Force has issued a final, grade A recommendation calling on all clinicians to ask all adults whether they smoke, advise them to quit if they do, and provide cessation aids to adults who use tobacco.

The guideline also includes two grade I (insufficient evidence) statements, one on the balance of benefits versus harms of pharmacotherapy interventions for tobacco cessation in pregnant women and the other on electronic nicotine delivery systems for tobacco cessation in all adults (Ann Intern Med. 2015 Sep 22. doi: 10.7326/M15-2023).

The guideline reaffirms the 2009 USPSTF recommendation, which urges clinicians to ask all adults about tobacco use and provides tobacco cessation interventions to help them quit.

The new recommendations differ from the 2009 recommendation in that it calls for more evidence on the use of e-cigarettes for smoking cessation in adults and the use of medications to help pregnant women stop smoking.

"A large body of evidence on interventions for smoking cessation already exists, and the overall benefit of pharmacotherapy and behavioral counseling to promote smoking is well established," according to the recommendations.

"Tobacco is the leading preventable cause of disease, disability, and death in the United States," with cigarette smoking, specifically, causing more than 480,000 premature deaths annually and accounting for one in every five deaths, according to the recommendations.

"In pregnant women, smoking increases the risk of congenital anomalies; perinatal complications, such as preterm birth, fetal growth restriction, and placental abruption; miscarriage and stillbirth; and neonatal or pediatric complications, such as sudden infant death syndrome and impaired lung function in childhood," the recommendations say.

According to a 2013 systematic review of 28 studies, rates of smoking abstinence at 6 months or more were 8% in groups that received physician advice, compared with 5% in groups that received no advice or usual care.

Pharmacotherapy was effective at stopping nonpregnant smokers from continuing to smoke; a 2012 systematic review of 117 nicotine replacement therapy (NRT) studies found that 17% of participants who took any form of an NRT drug abstained from smoking for 6 months or more, compared with 10% of participants who received placebo or did not take an NRT drug, the review says.

Combinations of behavioral counseling and pharmacotherapy for smoking cessation also were effective; "a 2012 good-quality systematic review" found the abstinence rate of participants who received combination pharmacotherapy and intensive behavioral counseling was 14.5%, at 6 months or more, compared with 8% among control participants who received "usual care, self-help materials, or brief advice on quitting (which was less intensive than the counseling or support given to the intervention groups)."

For pregnant women, "a good-quality systematic review of 86 studies done in 2013" found that behavioral interventions were effective at improving rates of smoking cessation.

Compared with control participants, pregnant women who received any type of behavioral intervention before the third trimester had higher cessation rates late in pregnancy.

Responding to pubic comments, USPSTF said that "both intervention types (pharmacotherapy and behavioral intervention) are effective and recommended," with combinations of interventions being the most effective way to help patients to stop smoking.

"Further research is still needed to elucidate specific features of complex behavioral counseling interventions, benefits of pharmacotherapy in specific populations [such as pregnant women and adults with mental health conditions], and the efficacy of newer technology-based interventions … such as Internet-based programs, mobile or smartphone applications, and text-messaging programs."

The document also called for investigations into the safety, benefits, and harms of electronic nicotine delivery systems.

The authors of the recommendations stated they had nothing to disclose.

klennon@frontlinemedcom.com

Hypothyroidism associated with IPF mortality

BY AMY KARON
Frontline Medical News

FROM CHEST

Hypothyroidism affected almost 17% of patients with idiopathic pulmonary fibrosis and was independently associated with their mortality, according to a report in the September issue of CHEST.

"We report, to our knowledge for the first time, an association between hypothyroidism and idiopathic pulmonary fibrosis," wrote Dr. Justin Oldham of the pulmonary and critical care section of the University of Chicago and his associates. "Hypothyroidism, a largely autoimmune process, is common among patients with IPF and may represent an additional feature of autoimmunity in this patient population." The retrospective study could not assess causality, but raises questions about whether autoimmune abnormalities contribte to or exacerbate IPF, and whether hypothyroidism and IPF share common underlying causes, they added.

Recent years have seen a "paradigm shift" away from immunologic or inflammatory causes of IPF in favor of alveolar injury and abnormal cellular repair mechanisms, but some studies point to autoimmunity in IPF, said the investigators. To further explore the question, they studied hypothyroidism – which in developed countries is most often autoimmune – among 196 patients with IPF, with an equal number of age-and sex-matched controls with COPD (Chest 2015;148:692-700).

Nearly 17% of IPF patients – including 13% of women and 28% of men – reported using thyroid replacement therapy with no history of thyroidectomy or radioactive iodine ablation. In contrast, only 7% of COPD controls had a recorded diagnosis of hypothyroidism (odds ratio, 2.7; 95% confidence interval, 1.3-5.5; $P = .01$). Men and women with IPF and comorbid hypothyroidism had significantly shorter survival than did patients who had IPF only ($P = .001$). Hypothyroidism also independently predicted mortality in the multivariable analysis (hazard ratio, 2.1; 95% CI, 1.3-3.4), as did sequential increases in gender,

Continued on following page

VITALS

Key clinical point: Hypothyroidism was common among patients with idiopathic pulmonary fibrosis and was independently associated with mortality.

Major finding: Hypothyroidism predicted mortality in the multivariable analysis (hazard ratio, 2.1).

Data source: A retrospective hospital-based study of 392 patients with IPF (cases) or COPD (controls).

Disclosures: The National Institutes of Health funded the study. Dr. Oldham and five coauthors declared no competing interests. Senior author Dr. Imre Noth and one coauthor reported grant support and honoraria from NIH, Brystol-Myers Squibb, Gilead Sciences, Intermune, Medimmune, and several other pharmaceutical companies.

Continued from previous page

age, and physiology (GAP) stage, the investigators said. "These conclusions held when transplant-free, transplant-excluded, and transplant-as-a-competing-event Cox regression models were constructed," they reported. Furthermore, multivariable analyses of data from two IPF clinical trials (ACE-IPF and PANTHER) revealed similar associations among hypothyroidism, GAP stage, and mortality, they said.

Exactly how hypothyroidism contributes to IPF and IPF-related mortality is unclear, said Dr. Oldham and his associates. Because the study did not examine longitudinal changes in thyroid stage, they could not relate those trends to IPF progression, they noted.

Although they excluded patients whose thyroid disease was known not to be autoimmune, they could not specifically confirm that all remaining patients with hypothyroidism had autoimmune thyroiditis, because most had been diagnosed years before.

Future longitudinal studies should examine whether IPF and hypothyroidism share underlying causes, and should examine why hypothyroidism seems to increase IPF-related mortality, they concluded.

IASLC aims to reduce smoking, lung cancer

BY SUSAN LONDON
Frontline Medical News

DENVER – The International Association for the Study of Lung Cancer released an updated Tobacco Control and Smoking Cessation declaration that outlines a set of measures aimed at reducing smoking and lung cancer.

The declaration could be viewed as a vaccine of sorts, according to Kenneth Michael Cummings, Ph.D., a professor at the Hollings Cancer Center, Medical University of South Carolina, and co-chair of IASLC's Tobacco Control and Smoking Cessation Committee.


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"How about a vaccine to prevent 80% of lung cancer deaths worldwide? We have it: Get rid of cigarettes," he said in a press conference at the World Congress on Lung Cancer, where the declaration was released.

The previous declaration, released in 2008, focused heavily on giving the Food and Drug Administration the authority to regulate tobacco in the United States, which it now has. Since then, the economics of tobacco have evolved rapidly, and new products such as e-cigarettes have become available.

Also, 180 countries have ratified the World Health Organization's Framework Convention on Tobacco Control (FCTC) treaty, allowing them to implement evidence-based policies such as smoke-free environments, warning labels, advertising bans, and taxation.

Nevertheless, lung cancer still accounts for nearly 2 million cases and 1.6 million lives lost each year. And at least 80% of those deaths are directly attributable to smoking, Dr. Cummings said.

In some parts of the world, cigarette consumption has declined, but "that's not happening everywhere," he said. "In parts of Asia, such as China, Japan, and Southeast Asia, and in Latin America, we are still seeing a rapid increase in lung cancer deaths. And in parts of the world which have not taken up smoking but are the targets of the industry, such as Africa and Indonesia, we are likely going to see an epidemic there, which can be prevented, which is really the point of our new statement."

The 2015 declaration has five components that address tobacco control and smoking cessation.

The first component calls for forceful implementation of the FCTC treaty, especially through higher cigarette prices via taxation. "This is…the most important component of our 'vaccine,' for every member of this organization to really advocate for raising the cigarette prices to a level where it makes it unaffordable for young people to take up the behavior," Dr. Cummings said. In low- and middle-income countries, where cigarettes remain relatively inexpensive, imposing a tax of at least 70% of the retail price would immediately cut consumption by about a third (N Engl J Med. 2014;370:60-8).

Trade policies and tobacco interference are related issues, he noted. "Our organization has been strong in trying to keep tobacco out of trade agreements." Some countries, such as Malaysia, have refused to allow tobacco to be part of the Trans-Pacific Partnership agreement now under negotiation. "We need to support that [stance] because if tobacco is in there, we have countries being sued under trade agreements for doing the right things in terms of implementing policies."

The declaration's second component calls for holding cigarette companies civilly and criminally accountable for their actions. While Philip Morris International has stated that it supports evidence-based regulation of tobacco, "I think our organization can help [by taking] cigarettes off the shelf today," Dr. Cummings said. Holding manufacturers accountable in courts is another way to raise the price of cigarettes and thereby reduce consumption, he added.

The third component of the declaration is to support policies that keep young people from starting to smoke, such as raising the legal age of use to 21. "The neurobiology is very clear: The younger you are when you get exposed to an addictive substance, the more likely it is you are going to find it hard to quit at the end. So, raising the legal age is certainly something we ought to do," Dr. Cummings asserted, adding that 21 "is sort of a compromise" as the brain continues to develop until the age of 25.

Ensuring provision of tobacco-cessation services to all smokers, the declaration's fourth component, is important no matter a patient's status. "Even in our cancer patients, it's not too late. It has a big effect on their outcomes," he said.

The fifth component is support for policies that address alternatives for nicotine delivery that are likely safer than cigarettes. "I don't really care if companies make money selling something, but they don't have to kill one out of two of their consumers to do it," Dr. Cummings commented.

These alternatives might include e-cigarettes, provided evidence supports their inclusion. "I think that's the problem we have with e-cigarettes today," he said, noting that much less is known about them as compared with standard cigarettes, and that the products and manufacturers change monthly.

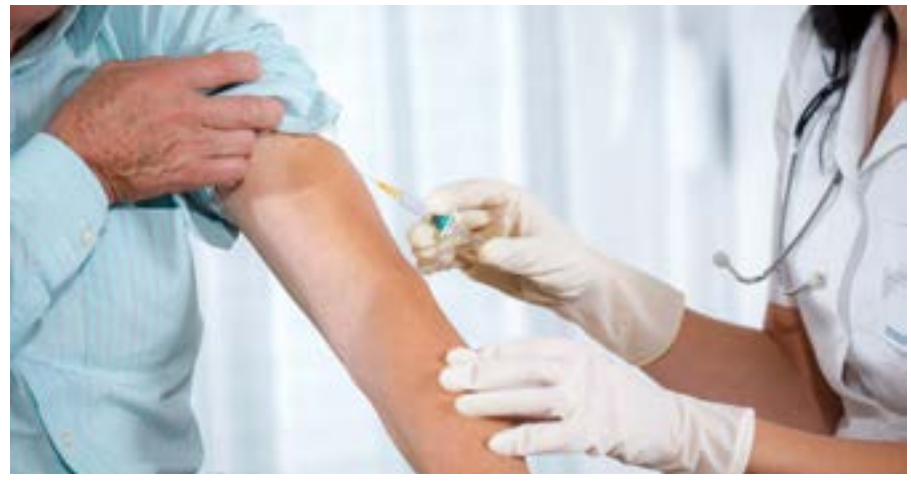
Mandates raise flu shot uptake in health care setting

BY MIKE BOCK
Frontline Medical News

Overall, 77% of health care personnel reported receiving an influenza vaccination during the 2014-2015 season, with the highest vaccination coverage reported in work sites with employer requirements for vaccination, according to an investigation published in the Morbidity and Mortality Weekly Report (2015 Sep 18;64[36]:993-9).

Vaccination data came from an opt-in Internet panel survey conducted by Abt Associates for the Centers for Disease Control and Prevention, and included questions on demographic characteristics, occupation, work setting, self-reported influenza vaccination, and employer vaccination policies. Results from 1,914 survey responses were analyzed. The overall health care personnel influenza vaccination coverage estimate for the 2014-2015 season was 77%, compared with 75% for the 2013-2014 season. When compared with the 2013-2014 season, coverage in 2014-2015 was higher among pharmacists (95% vs. 86%), assistants/aides (64% vs. 58%), and nonclinical personnel (75% vs. 69%). Coverage among other clinical personnel decreased from 87% in 2013-2014 to 81% in 2014-2015, while other categories experienced little change between the two time periods.

The researchers, led by Carla L. Black, Ph.D., of the National Center for Immunization and Respiratory Diseases, CDC, noted that among health care personnel whose employers did not require vaccination, coverage among those whose employer made vaccination available on-site at no cost for more than 1 day was 84%, compared with 74% among those whose employer made vaccination available at no cost for 1 day only, and 60% among those whose employer did not provide influenza vaccination on-site at no cost but instead actively promoted vaccination through other mechanisms.


JOVANMANDIC/THINKSTOCK

"These findings support recommendations for a comprehensive strategy that includes easy access to vaccination at no cost on multiple days, along with promotion of vaccination, to increase [health care personnel] influenza vaccination coverage," Dr. Black and her colleagues wrote.

mbock@frontlinemedcom.com

For the long-term, once-daily, maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)

Prescribe INCRUSE ELLIPTA one inhalation, once daily

& help patients add more breath to their day

Indication

- INCRUSE ELLIPTA is an anticholinergic 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 Safety Information for INCRUSE ELLIPTA

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

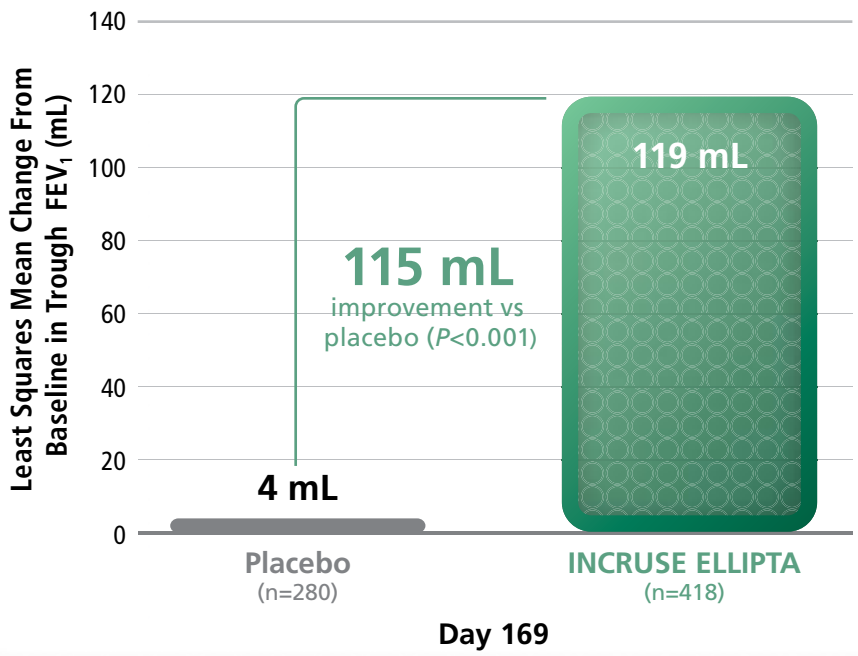
- INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- If paradoxical bronchospasm occurs, discontinue INCRUSE ELLIPTA and institute alternative therapy.
- 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.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in one 12-week and one 24-week clinical trial with INCRUSE ELLIPTA (and placebo) were: nasopharyngitis, 8% (7%); upper respiratory tract infection, 5% (4%); pharyngitis, 1% (<1%); viral upper respiratory tract infection, 1% (<1%); cough, 3% (2%); arthralgia, 2% (1%); myalgia, 1% (<1%); upper abdominal pain, 1% (<1%); toothache, 1% (<1%); contusion, 1% (<1%); tachycardia, 1% (<1%). Other adverse reactions with INCRUSE ELLIPTA observed with an incidence <1% but more common than placebo included atrial fibrillation.

Once-daily INCRUSE ELLIPTA
Helps Improve Breathing in Patients With COPD

Primary Endpoint: Trough (Predose) FEV_1 at Day 169[1,2]



- Results from a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that compared the efficacy and safety of INCRUSE ELLIPTA and placebo, each administered once daily by the ELLIPTA Inhaler. The primary endpoint was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168[1]

Provided improvement in health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)

- In the same 6-month study, INCRUSE ELLIPTA demonstrated an improvement in health-related quality of life, as measured by a decrease in mean SGRQ total score of 4.69 units, compared with placebo at Day 168
- The proportion of patients with a clinically meaningful decrease (defined as a decrease of at least 4 units from baseline) at Week 24 was greater for INCRUSE ELLIPTA (42%; 172/410) compared with placebo (31%; 86/274)
- These endpoints were not adjusted for multiple comparisons
- The SGRQ is a respiratory disease-specific, patient-reported instrument that measures symptoms, activities, and impact on daily life[3]

Important Safety Information for INCRUSE ELLIPTA (cont'd)

ADVERSE REACTIONS (cont'd)

- In addition to the two placebo-controlled clinical trials with INCRUSE ELLIPTA, a 12-month trial evaluated the safety of umeclidinium 125 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and exceeded that in placebo) in subjects receiving umeclidinium 125 mcg were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

DRUG INTERACTIONS

- Avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

References: 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. **2.** Data on file, GSK. **3.** Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 (suppl B):25-31.

Please see Brief Summary of Prescribing Information for INCRUSE ELLIPTA on the following pages.

www.GSKSource.com

INCRUSE® ELLIPTA®
(umeclidinium 62.5 mcg inhalation powder)

BRIEF SUMMARY

INCRUSE® ELLIPTA®
(umeclidinium inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
INCRUSE ELLIPTA is an anticholinergic 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.

4 CONTRAINDICATIONS
The use of INCRUSE ELLIPTA is contraindicated in the following conditions: severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium or any of the excipients *[see Warnings and Precautions (5.3), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Disease and Acute Episodes
INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. INCRUSE ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of INCRUSE ELLIPTA in this setting is not appropriate.
INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. INCRUSE 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.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INCRUSE 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 INCRUSE ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.2 Paradoxical Bronchospasm
As with other inhaled medicines, INCRUSE ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with INCRUSE ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; INCRUSE ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

5.3 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of INCRUSE 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 INCRUSE ELLIPTA *[see Contraindications (4)]*.

5.4 Worsening of Narrow-Angle Glaucoma
INCRUSE 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 if any of these signs or symptoms develops.

5.5 Worsening of Urinary Retention
INCRUSE 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 if any of these signs or symptoms develops.

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.2)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.4)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.5)]*

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.
A total of 1,663 subjects with COPD across 8 clinical trials (mean age: 62.7 years; 89% white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind, placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to 52 weeks *[see Clinical Studies (14) of full prescribing information]*.
The incidence of adverse reactions associated with INCRUSE ELLIPTA in Table 1 is based upon 2 placebo-controlled efficacy trials: one 12-week trial and one 24-week trial.

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

Adverse Reaction	INCRUSE ELLIPTA (n = 487) %	Placebo (n = 348) %
Infections and infestations		
Nasopharyngitis	8%	7%
Upper respiratory tract infection	5%	4%
Pharyngitis	1%	<1%
Viral upper respiratory tract infection	1%	<1%
Respiratory, thoracic, and mediastinal disorders		
Cough	3%	2%
Musculoskeletal and connective tissue disorders		
Arthralgia	2%	1%
Myalgia	1%	<1%
Gastrointestinal disorders		
Abdominal pain upper	1%	<1%
Toothache	1%	<1%
Injury, poisoning, and procedural complications		
Contusion	1%	<1%
Cardiac disorders		
Tachycardia	1%	<1%

Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than 1% but more common than placebo included atrial fibrillation.
In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109 placebo) were treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the efficacy trials described above. Adverse reactions that occurred with a frequency greater than or equal to 1% in subjects

receiving umeclidinium 125 mcg that exceeded that in placebo in this trial were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

7 DRUG INTERACTIONS

7.1 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.4, 5.5), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of human response, INCRUSE 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 INCRUSE ELLIPTA.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of INCRUSE ELLIPTA during labor and delivery. INCRUSE ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

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

8.4 Pediatric Use

INCRUSE 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 INCRUSE ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.
Clinical trials of INCRUSE ELLIPTA included 810 subjects aged 65 years and older, and, of those, 183 subjects were aged 75 years 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

Patients with severe renal impairment (creatinine clearance less than 30 mL/min) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with severe renal impairment and their healthy controls. 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 INCRUSE ELLIPTA.
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.
Treatment of overdosage consists of discontinuation of INCRUSE ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 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).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
Not for Acute Symptoms: Inform patients that INCRUSE 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 INCRUSE ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.
Paradoxical Bronchospasm: As with other inhaled medicines, INCRUSE ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue INCRUSE ELLIPTA.
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 if any of these signs or symptoms develops.
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 if any of these signs or symptoms develops.

GSK
Research Triangle Park, NC 27709

Revised: 6/2014 INC:3BRS

Flu shots decrease severity, duration of illness

BY DEEPAK CHITNIS
Frontline Medical News

ATLANTA – Individuals who neglect to get their annual influenza vaccinations will likely experience more-severe symptoms and a longer duration of the illness if they contract the disease, specifically the A/H_3N_2 strain.

In a study of 155 influenza patients between 2009 and 2014, 138 (89%) were positive for influenza A virus, 111 (72%) of whom were vaccinated against influenza.

"We know that flu vaccines are about 60% effective, but of that remaining 40%, do they still get severe flu? The data from our study say no," explained Dr. Eugene V. Millar of the Uniformed Services University of the Health Sciences in Bethesda, Md.

Sixty-six (48%) individuals contracted the A/H_3N_2 strain of the influenza virus; of these patients, those who did not get vaccinated reported higher average severity scores for upper respiratory symptoms (7 vs. 3), lower respiratory symptoms (7 vs. 3), systemic

'If you didn't get that vaccination, you'd be on your back.'

DR. MILLAR

symptoms (9.5 vs. 6), and total symptoms (22 vs. 12) than did subjects who did get vaccinated (P less than .01).

"People ask me all the time why I bother getting a flu vaccine if it never works," Dr. Millar said at the International Conference on Emerging Infectious Diseases.

"I tell them that if you're walking around and talking to people, then it did work, even if you feel a little lousy; if you didn't get that vaccination, you'd be on your back," he continued.

Such disparity in the severity and duration of symptoms was not noted in 69 (50%) of the 155 influenza patients who contracted the A/H_1N_1 strain of the virus, nor in the 3 (2%) subjects who had an "untyped" form of influenza A. However, Dr. Millar cautioned that results regarding H_1N_1 may have been confounded by a couple of factors.

"As we've seen with the [H_1N_1] pandemic, it was just a pandemic of the sniffles, so it's very hard to assess symptom severity when the differences are moderate to none," Dr. Millar explained, adding that the variant strain of H_3N_2 which became prevalent during the 2014-2015 respiratory season proved to be the far more severe disease.

Furthermore, patients found with A/H_1N_1 were more likely to be put on antivirals, making it impossible to look at vaccine effect.

In total, 884 patients with influenza-like illness were screened for inclusion in the study, from which the sample of 155 subjects was eventually derived.

Median age of the 155 subjects was 30.6 ($P = .61$), mean body mass index was 27.6 kg/m^2 ($P = .07$), males outnumbered females 88 to 67, and 106 subjects were active-duty military at the time they had influenza.

"These are healthy people presenting to outpatient [clinics], it's very interesting to see if the same thing would hold true for the elderly or people with underlying medical conditions, since those are the people we're really trying to protect not only from influenza, but its complications, as well, such as secondary bacterial pneumonia," Dr. Millar said.

Nine subjects (6%) had influenza during the 2009-2010 season, 56 (36%) were sick during the 2010-2011 season, 16 (10%) had influenza during the 2011-2012 season, 38 (25%) were sick during the 2012-2013 season, and 36 got the flu (23%) during the 2013-2014 season.

dchitnis@frontlinemedcom.com

VITALS

Key clinical point: Although not entirely effective at outright preventing A/H3N2 disease, influenza vaccination can significantly decrease the length and severity of disease.

Major finding: Unvaccinated individuals reported significantly higher severity scores for upper respiratory, lower respiratory, systemic, and total symptoms than did subjects who received influenza vaccinations.

Data source: Retrospective cohort study of 155 individuals between 2009 and 2014.

Disclosures: The Infectious Disease Clinical Research Program and the National Institute of Allergy and Infectious Diseases supported the study. Dr. Millar did not report any relevant financial disclosures.

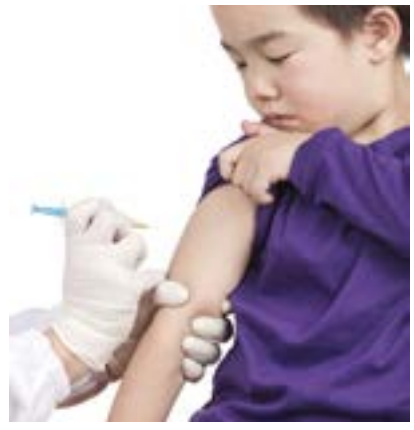
Population-level data support flu vaccine recs

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Expanded influenza vaccination coverage among children between 2002 and 2012 appears to have provided direct benefit with respect to influenza-related hospitalizations among vaccinated children, according to an analysis of vaccination and hospitalization data.

Additionally, the coverage among children appears to have provided indirect benefits in adults, Cecile Viboud, Ph.D., of the National Institutes of Health, Bethesda, Md., reported at the International Conference on Emerging Infectious Diseases.

Between 2006-2007 and 2010-2011, the Advisory Committee on Immunization Practices (ACIP) broadened vaccination recommendations to include not only children



YANGNA/THINKSTOCK

aged 6-23 months, but also those aged 24-59 months, then those aged 5-18 years, and eventually all those over age 6 months. Consequently, the vaccine coverage rate increased from less than 5% in 2002 to about 52% in 2012 (and to about 70% in those under age 5 years).

Modeling of weekly influenza-related hospitalization outcomes (pneumonia and influenza outcomes and respiratory and circulatory outcomes) provided solid evidence of a direct and significant protective effect of vaccination both in children under age 5 years and in those aged 5-19 years. This finding was consistent across disease outcomes, and remained significant in those under age 5 after adjusting for state, but the association was weaker with stratification by season, Dr. Viboud noted.

Further, hospitalization rates among working-age adults and seniors aged 65-74 years declined with increasing pediatric vaccine coverage, suggesting an indirect protective effect in that population, she said, noting that the vaccination rate among older adults remained stable across the study period.

No evidence was seen for an indirect protective effect among adults over age 74 years, she said.

Dr. Viboud and her colleagues used age-specific annual vaccination rates derived from the National Immunization Survey and the Behavioral Risk Factor Surveillance System.

Age-specific rates of influenza-associated hospitalizations were estimated for each season during 1989-2012 by modeling weekly pneumonia and influenza outcomes plus respiratory and circulatory outcomes from the State Inpatient Databases of the Agency for Healthcare Research & Quality.

"In a nutshell, we see strong statistical evidence for the direct protective effects of the influenza vaccination program in children on the basis of analyses of population-level hospitalization data, which supports the expansion of the ACIP flu vaccine recommendations in the past decade," Dr. Viboud said in an interview. "We also find weak evidence of herd immunity effects, whereby hospitalization rates are reduced in adults. That the evidence is weak is perhaps not surprising given that vaccine uptake in children remains moderate (60% in most highly vaccinated states) and vaccine effectiveness is modest at 40%-60% depending on the season."

The indirect effects may become clearer with increasing vaccine uptake, she added.

sworcester@frontlinemedcom.com

VITALS

Key clinical point: Expanded influenza vaccination coverage in children provided direct benefits with respect to hospitalizations.

Major finding: Vaccine coverage rate increased from less than 5% in 2002 to about 52% in 2012.

Data source: An analysis of vaccination and hospitalization data.

Disclosures: Dr. Viboud reported having no disclosures.

Surveillance data uphold early flu vaccination

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Influenza vaccine effectiveness during the 2010-2011 through 2013-2014 flu seasons was moderate for up to 6 months post vaccination – about the duration of the average flu season, according to surveillance data.

Vaccine effectiveness in 1,720 non–active-duty U.S. Department of Defense beneficiaries ranged from 40% to 69% across the flu seasons, and after adjusting for age group, calendar season, and flu season, significant and fairly consistent protection was provided for up to 180 days, Dr. Jennifer M. Radin and her colleagues at the Naval Health Research Center, San Diego, reported in a poster at the International Conference on Emerging Infectious Diseases.

The adjusted vaccine effectiveness was 61% during the first 2 weeks after vaccination, 62% from days 15 through 90, and 60% during days 91 through 180. After that, the effectiveness dropped to –11%, they said.

Vaccine effectiveness in this study was assessed using outpatient febrile respiratory illness surveillance among a convenience sample of individuals of all ages, 75% of whom were under age 25 years, who presented with fever, cough, or sore throat at outpatient facilities in California and Illinois. Case patients were those who tested polymerase chain reaction–positive for influenza; those who were PCR negative for influenza served as controls.

"Previous studies have found that protection from contracting influenza declines over time following influenza vaccination due to decreasing antibody levels. However, we found ... moderate, sustained protection up to 6 months post vaccination," Dr. Radin said in a statement, explaining that at this level of effectiveness, vaccination reduces the risk of a doctor's visit by 50%-70%.

The findings suggest that vaccine administration close to the start of flu season is associated with slightly increased vaccine effectiveness, but the start of flu season varies each year, thus optimal timing is hard to predict.

"Consequently, early flu vaccination may still offer the best overall protection," Dr. Radin and her colleagues wrote. The finding of a dramatic drop in effectiveness after 6 months also underscores the importance of yearly vaccination.

sworcester@frontlinemedcom.com

Asthma exacerbations seen often after meds stopped

BY SHANNON AYMES
Frontline Medical News

Nearly a third of patients have asthma exacerbation in the 2 years after medication step-down, according to a new study.

With the goal of using the least amount of medication to control asthma, guidelines recommend considering medication step-down after 3 months of stabilized asthma. However, there is limited evidence backing these recommendations, especially when it comes to understanding the long-term outcomes after asthma medication step-down.

Dr. Matthew A. Rank of the division of allergy, asthma, and clinical immunology at the Mayo Clinic in Scottsdale, Ariz., and colleagues analyzed the long-term outcomes of patients after asthma medication step-down.

The investigators conducted a

retrospective claims-based analysis using data obtained from the Optum Labs Data Warehouse which contains information from more than 100 million de-identified patients with Medicare Advantage or commercial insurance plans (Chest. 2015;148[3]:630-39).

Data was extracted on patients who had an asthma diagnosis code between 2000 and 2012 with continuous medical and pharmacy coverage for 3 or more years during the study period and with a history of medication step-down.

A medication step-down was greater or equal to 50% decrease in asthma controller medication between evaluations. Stability was defined as not having an asthma exacerbation requiring care in the hospital or ED, or systemic corticosteroids and claiming fewer than two rescue inhalers prescriptions in the 4-month study period.

The study cohort was divided into four asthma stability groups: 0-3 months, 4-7 months, 8-11 months, and greater to or equal to 12 months of stability. Of the 26,292 individuals included in the study, 32% developed an asthma exacerbation during the 2 years after medication step-down. There was a strong association between the risk of developing an asthma exacerbation during the 2-year study period and the length

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of asthma stability prior to medication step-down. For instance, 44% in participants with less than 4 months of stability, 34% with 4-7 months of stability, 30% with 8-11 months of stability, and 21% with more than 12 months of stability (*P* less than .001).

In addition, study participants who were women, were black, were younger than 19 years old, had a Charlson comorbidity index great than or equal to 1, and had at least two outpatient visits for asthma were significantly associated with a shorter interval to asthma exacerbation (*P* less than .001 for all variables).

Finally, most study participants had a hospital or ED visit, systemic corticosteroids, two rescue inhalers in a 4-month period, or needed to return to baseline asthma controller treatment. The authors suggest that this is evidence that most of the cohort continued to have underlying asthma during the 2-year study period.

Furthermore, 33% of participants with less than 4 months of stability required return to baseline treatment versus 8%, 13%, and 15% for more than 12 months of stability, 8-11 months, and 4-7 months, respectively.

Among the limitations noted by the authors: Data were from insured patients, data did not indicate if step-

down involved consultation with a health care provider, and the cohort did not include patients who did not step down as a comparison.

"Individuals and their providers can cautiously apply the data from this study to decisions about stepping down asthma medications. The novel insights from this analysis that contribute to this decision making process are consideration to the length of stability prior to step-down and the rate of asthma exacerbations in the 24 months following step-down," they said.

The study was funded by the Mayo Foundation for Medical Education and Research. The authors reported no disclosures.

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1 in 20 students using e-cigarettes for cannabis

BY BIANCA NOGRADY
Frontline Medical News

Significant numbers of high school students are using e-cigarettes to vaporize cannabis, new research data suggest.

An anonymous survey of 3,847 Connecticut high school students found that, overall, 5.4% of the total sample reported using e-cigarettes or vaporizers to vaporize cannabis, either in the form of hash oil, THC-infused wax, or dried leaves.

Among students who had ever used an e-cigarette, 18% said that they had used it for cannabis, while 18.4% of cannabis users reported using e-cigarettes for cannabis.

More than one-quarter of students who reported using both cannabis and e-cigarettes said they had used e-cigarettes as a delivery mechanism for cannabis, according to a study published online Sept. 7 in Pediatrics.

Males and younger students were significantly more likely than females or older students to use e-cigarettes for cannabis, and the researchers found that the students' socioeconomic status (SES) was not related to their tendency to use e-cigarettes to vaporize cannabis. The study did find significantly different rates of cannabis e-cigarette use between the five schools included in the study.

"These results indicate that factors such as the acceptability of cannabis use within a school (i.e., 'cannabis culture') or the extent to which a school has explicit policies prohibiting e-cigarette use may play a more important role in encouraging or deterring vaporizing cannabis than students' SES," wrote Meghan E. Morean, Ph.D., of Oberlin College,

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VIEW ON THE NEWS

E-cigarettes a new drug gateway

We have previously studied the process by which a child or adolescent becomes a regular smoker or binge drinker, but in our work we extended the gateway hypothesis on teen use to suggest that learning how to smoke or inhale drug vapors was the critical gateway event.

A young person who learns to inhibit a natural aversion to smoke or smoke-filled environments and suppress his or her cough reflex to inhale cigarettes has learned a particularly dangerous behavior, and as the gateway drugs have shifted from tobacco and alcohol to cannabis, it is deja vu for experts who trained and worked in the 1960s and 1970s.

Dr. Mark S. Gold is an adjunct professor of psychiatry at Washington University in St. Louis and is the former chairman of the department of psychiatry at the University of Florida, Gainesville. No conflicts of interest were declared.

Inpatient mortality has dropped for pneumonia

BY RICHARD FRANKI
Frontline Medical News

Inpatient mortality for pneumonia, acute MI, heart failure, and stroke each fell significantly from 2002 to 2012, the Agency for Healthcare Research and Quality reported.

Over that period, mortality among adults hospitalized with pneumonia went from 65 per 1,000 admissions to 35.8 per 1,000 for a drop of 45% – largest of the four high-volume conditions. Corresponding declines for the others were 41% for acute MI, 29% for heart failure, and 27% for stroke, the AHRQ noted.

Since "death following discharge from a hospital is not reflected in these data," the report said, measures of inpatient mortality "can reflect both improvements in health care and shifts in where end-of-life care takes place over time."

The estimates in the report are based on data from the Nationwide Inpatient Sample (2002-2011) and State Inpatient Databases (2012).

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Ohio, and her coauthors.

Dried cannabis leaves were the most popular form of cannabis used in portable vaporizers, and hash oil was more commonly used with e-cigarettes than THC-infused wax (Pediatrics. 2015 Sept. 7. doi: 10.1542/peds.2015-1727).

While acknowledging that the results might be an underestimation of true figures because of the limitations of self-reporting, the authors said that further research is needed to determine whether e-cigarette use might serve as a gateway to cannabis use and the health impact of vaporized cannabis.

"At this time, the relative safety of using e-cigarettes for vaping cannabis versus smoking combustible cannabis is not well established," Dr. Morean and her coauthors wrote. "However, a recent study indicated that adults who vaporize hash oil experience greater subjective tolerance and evidence of dependence compared with those smoking combustible cannabis."

Cannabis consumed through e-cigarettes is challenging for parents, teachers, and police to detect because the device does not produce the characteristic pungent aroma of smoked cannabis, the researchers noted.

"As e-cigarettes and related devices continue to gain popularity among youth, it will be important to monitor rates of using these products to vaporize cannabis."

When asked about the findings, Dr. Robert L. DuPont said in an interview that American drug markets are changing rapidly, making more drugs available through highly potent routes of administration such as vaporization.

"This effective and convenient way of delivering THC has much appeal, especially to youth, being new, cool, and smoke-free, as the rate of cannabis passes cigarettes for youth," said Dr. DuPont, president of the Institute for Behavior and Health in Rockville, Md., and the first director of the National Institute on Drug Abuse.

The National Institutes of Health funded the study. No conflicts of interest were declared.

Novel apnea therapy not helpful, possibly harmful

BY MARY ANN MOON
Frontline Medical News

VIEW ON THE NEWS

Adaptive servo-ventilation should not be used outside of clinical trials in heart failure patients who have predominantly central sleep apnea, at least until the reason for the unexpected 34% increase in cardiovascular mortality is understood.

The issue is important because at least one new technique to abolish Cheyne-Stokes respiration that doesn't use positive pressure therapy – phrenic-nerve stimulation – has already been developed and is being assessed in a clinical trial. If Cheyne-Stokes respiration is actually beneficial in HF, this strategy may prove harmful.

Dr. Ulysses J. Magalang is in the division of pulmonary, allergy, critical care, and sleep medicine at Ohio State University Wexner Medical Center, Columbus. Dr. Allan I. Pack is at the Center for Sleep and Circadian Neurobiology at the University of Pennsylvania, Philadelphia. Dr. Magalang reported grants support from the Rudi Schulte Family Foundation, Hill-Rom, and the Tzagournis Medical Research Endowment; Dr. Pack reported having no relevant financial disclosures. They made these remarks in an editorial accompanying the SERVE-HF report (N Engl J Med. 2015 Sep 1. doi:10.1056/NEJMe1510397Th).

Adaptive servo-ventilation is not beneficial and may even be harmful for patients who have predominantly central sleep apnea accompanying heart failure with reduced ejection fraction, Dr. Martin R. Cowie reported at the annual congress of the European Society of Cardiology.

The noninvasive therapy did control central sleep apnea in a large international randomized controlled trial, but nevertheless did not affect the composite endpoint of death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening HF. Moreover, it unexpectedly raised the risk of cardiovascular death by 34%, and significantly increased all-cause mortality as well, said Dr. Cowie of Imperial College London.

Adaptive servo-ventilation delivers servo-controlled inspiratory pressure on top of expiratory positive airway pressure during sleep, to alleviate central sleep apnea. This form of sleep-disordered breathing, which may manifest as Cheyne-Stokes respiration in patients who have HF with reduced ejection fraction, is reported to affect up to 40% of this patient population. Its prevalence rises as the severity of HF increases, and it is an independent risk marker for poor prognosis and death in HF.

A recent trial showed that continuous positive airway pressure (CPAP) did not improve morbidity or mortality in patients who had HF with central sleep apnea, but suggested that a treatment that could reduce the apnea-hypopnea index (AHI) – the number of apnea or hypopnea events per hour of sleep – to below 15 might be effective. Adaptive servo-ventilation can accomplish this, and small studies and meta-analyses have shown that the treatment improves surrogate markers including plasma concentration of brain natriuretic peptide, left ventricular ejection fraction (LVEF), and functional outcomes in heart failure.

It unexpectedly raised the risk of cardiovascular death by 34%.

DR. COWIE

Dr. Cowie and his associates conducted the SERVE-HF trial, assessing the effect of adding adaptive servo-ventilation to guideline-based medical therapy on survival and cardiovascular outcomes. He presented the trial results at the meeting, and they were simultaneously published online (N Engl J Med. 2015 Sep 1 [doi: 10.1056/NEJMoa1506459]).

The industry-sponsored study comprised 1,325 patients aged 22 and older treated and followed at 91 medical centers for a median of 31 months (range, 0-80 months). They were randomly assigned to receive medical therapy plus adaptive servo-ventilation delivered through a face mask for at least 5 hours every night (666 intervention subjects) or medical therapy alone (659 control subjects).

Central sleep apnea was well controlled only in the intervention group. At 1 year, their mean AHI was 6.6 events per hour, and the oxygen desaturation index – the number of times per hour that the blood oxygen level dropped by 3 or more percentage points from baseline level – was 8.6.

Yet the primary composite endpoint was not significantly different between the two study groups: The rate of death from any cause, lifesaving cardiovascular intervention, and unplanned hospitalization for worsening HF was 54.1% with adaptive servo-ventilation and 50.8% without it.

The treatment also had no significant effect on a broad spectrum of secondary measures such as symptoms and quality of life. Six-minute walk distance gradually declined in both groups, but that decline was significantly more pronounced in the intervention group, the investigators said.

Even more worrisome was the significant increase in mortality associated with adaptive servo-ventilation. Cardiovascular mortality was 29.9% with the treatment, compared with 24.0% without it, for a hazard ratio of 1.34. All-cause mortality was 34.8% with the treatment and 29.3% without it, for an HR of 1.28.

The reason for this unexpected result is not yet known. One explanation is that central sleep apnea may be a compensatory mechanism with potentially beneficial effects in patients who have HF. Attenuating those effects with adaptive servo-ventilation may then have been detrimental. For example, central sleep apnea, and particularly Cheyne-Stokes breathing, may beneficially activate the respiratory muscles, increase sympathetic nervous system activity, induce hypercapnic acidosis, increase end-expiratory lung volume, and raise intrinsic positive airway pressure.

Another possibility is that applying positive airway pressure with adaptive servo-ventilation may impair cardiac function in at least a portion of patients who have HF by decreasing cardiac output and stroke volume during treatment.

ResMed, maker of the AutoSet adaptive servo-ventilator, sponsored SERVE-HF, which was also supported by the National Institute for Health Research and the National Institutes of Health. Dr. Cowie disclosed ties with Servier, Novartis, Pfizer, St. Jude Medical, Boston Scientific, Respicardia,Medtronic, and Bayer; his associates reported ties to numerous industry sources.

Oropharyngeal exercises significantly cut snoring

BY AMY KARON
Frontline Medical News

After 3 months, the intervention group had significantly improved on both the snore index and the total snore index. The intervention group also improved significantly on perceived intensity and frequency of snoring.

Eight minutes of oropharyngeal exercises performed three times a day significantly reduced snoring, according to a report in the September issue of CHEST.

At 3 months, the snore index and the total snore index dropped significantly for the exercise group but not the control group, said Vanessa Ieto. Ph.D., of the Sleep Laboratory of the University of São Paulo in Brazil and her associates.

The regimen improved snoring symptoms among primary snorers as well as patients with mild to moderate obstructive sleep apnea, although the apnea-hypopnea index only improved among patients with moderate OSA, the researchers added.

"This set of oropharyngeal exercises is a promising treatment of large populations suffering from snoring who are currently largely ignored by the medical community," they said.

Snoring is embarrassing and disruptive, and can exacerbate pharyngeal neurogenic lesions and carotid artery atherosclerosis, but few studies have objectively exam-

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ined interventions for primary snorers or patients with mild OSA, the researchers said.

In their randomized trial of 39 such patients, the intervention group performed six oropharyngeal exercises three times daily, while the control group patients practiced breathing exercises and wore nasal dilator strips at night. Both groups performed nasal lavage with saline solution three times a day.

Average age was 46 years, and mean body-mass index was 28.2 kg/m^2. A blinded researcher evaluated data from computerized polysomnography and a snoring recorder (Chest 2015;148:683-81).

Nasopharyngeal exercises used in the study were as follows:

- Push tip of tongue against hard palate and slide tongue backward (20 times).
- Suck entire tongue up against palate (20 times).
- Force back of tongue against floor of mouth while touching tip of tongue to bottom incisors (20 times).
- Elevate soft palate and uvula while intermittently saying "A" (20 times).
- Place finger in mouth while pressing buccinator muscle outward (10 times per side).
- Chew and deglutinate on both sides of mouth whenever eating. Avoid perioral contraction.

After 3 months, the intervention group had significantly improved on both the snore index (snores per hour; $P = .041$ for change from baseline) and the total snore index (the total sound intensity of snores per hour; $P = .033$), the researchers said. The intervention group also improved significantly on several subjective measures, including perceived intensity and frequency of snoring and sleep quality. The control group only improved in terms of subjective snore frequency, the researchers said.

The apnea-hypopnea index did not drop significantly for the overall intervention group, but did improve significantly among patients with moderate OSA, they added. "The most likely explanation is that a 'floor effect' in the AHI prevented the observation of any effect on this metric among patients with mild or no OSA at study entry," Dr. Ieto and her associates said.

"Our results point out that snoring, rather than AHI, is probably the best metric to follow patients with mild forms of OSA in whom the most significant complaint is snoring," they said.

The study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The researchers declared they had no competing interests.

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Obstructive sleep apnea often complicates heart failure

BY MITCHEL L. ZOLER
Frontline Medical News

LONDON – The majority of patients with severe heart failure had sleep-disordered breathing and, in most affected patients, this manifested as obstructive sleep apnea, in an analysis of more than 1,000 German heart failure patients enrolled in a multicenter registry.

"The vast majority of heart failure patients with sleep-disordered breathing [SDB] have obstructive sleep apnea, which differs from previous results," said Dr. Olaf Oldenburg at the annual congress of the European Society of Cardiology. Possible reasons why this German registry had different findings, compared with prior reports, were its inclusion of heart failure patients with milder symptoms, inclusion of patients with preserved ejection fraction, and in-

'You need to look at the effect of SDB and not just the apnea-hypopnea index.'

DR. OLDENBURG

clusion of more women, suggested Dr. Oldenburg, director of the sleep laboratory at the Heart and Diabetes Center of Ruhr University of Bochum in Bad Oeynhausen, Germany.

His finding that nearly two-thirds of the heart failure patients with SDB in this registry had obstructive sleep apnea and that one-third had moderate or severe obstructive sleep apnea was notable because this remains a form of sleep-disordered breathing that can be treated, he said.

"There is still enough evidence to treat obstructive sleep apnea" in heart failure patients when it has a moderate or severe presentation, which is defined as causing 15 or more apnea-hypopnea events/hour during sleep. "Obstructive sleep apnea is definitely not a compensatory mechanism in heart failure," he said.

He highlighted the ongoing need to treat more severe obstructive sleep apnea in heart failure patients because this form of SDB sharply contrasts

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with the results of the SERVE-HF trial, also reported at the congress, which showed that in patients with advanced heart failure and central sleep apnea nocturnal treatment with adaptive servo-ventilation failed to provide benefit and also appeared to boost patient mortality (N Engl J Med. 2015 Sep 17;*373*[12]:1095-105).

Following that report "we need to think about which heart failure patients to treat" with nocturnal ventilation, and differentiate between heart failure patients with obstructive sleep apnea and those with central sleep apnea, Dr. Oldenburg said.

The data he reported came from the SchlaHF-XT (Sleep Disordered Breathing in Heart Failure) registry, which enrolled patients with heart failure and reduced or preserved ejection fraction and any New York Heart Association functional class treated either at German hospitals or in physician offices. He reported data for 1,186 fully assessed and classified patients, who averaged 68 years old and two-thirds of whom were men. Slightly more than half had heart failure with reduced ejection fraction, and about half had New York Heart Association class II heart failure, a quarter had class III heart failure, with the remaining patients divided rough-

ly equally between class I and IV.

Screening for SDB showed that 24% had no SDB, 37% had mild SBD, 21% had moderate SDB, and 19% had severe SDB (percentages total 101% because of rounding). Among those with SDB, 64% had obstructive sleep apnea, 22% had central sleep apnea, and the remaining 14% had either a mixed form of sleep apnea or were not classifiable.

The analysis also showed that moderate and severe SDB, the forms that require treatment, occurred more often (43%) among patients with heart failure and reduced ejection fraction, compared with patients with heart failure and preserved ejection fraction, who had a 36% prevalence of SDB requiring treatment. Moderate or severe central sleep apnea occurred in 15% of patients with reduced ejection fraction and in 9% of patients with preserved ejection fraction.

A second report at the congress by Dr. Oldenburg showed that the duration of time when a patient's oxygen saturation fell below 90% was a better gauge of the severity of SDB than was the traditional measure of the apnea-hypopnea index (AHI), the average number of apnea-hypopnea episodes a patient has during an hour of sleep. For this analysis, he used data collected on 963 patients with chronic, stable heart

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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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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, post menopausal 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 SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSAGE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications 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.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg N =124 %	80 mcg N =121 %	160 mcg N = 109 %	4.5 mcg N = 237 %	N = 400 %
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	160/4.5 mcg N = 771 %	160 mcg N = 275 %	4.5 mcg N = 779 %	N = 781 %
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

More post-adenotonsillectomy in kids with OSA

BY MIKE BOCK
Frontline Medical News

Respiratory compromise and secondary hemorrhage were the most common early side effects in children who had adenotonsillectomies; children with obstructive sleep apnea (OSA) have nearly five times more respiratory complications after surgery than children without OSA, a multistudy review concluded.

Graziela De Luca Canto, Ph.D., of the Federal University of Santa Catarina, Brazil, and her associates performed a data review by identifying 1,254 different citations found via electronic database searches; after eliminations, only 23 studies were included in the final analysis.

Although children with OSA have nearly five times more respiratory complications after adenotonsillectomy than their peers, (odds ratio, 4.90), they are less likely to have postoperative bleeding, compared with children without OSA (OR, 0.41).

Among both groups, the most frequent complication was respiratory compromise (9.4%), followed by secondary hemorrhage (2.6%).

Because children with OSA are more likely to require supplemental oxygen, oral or nasal airway insertion, or assisted ventilation in the immediate postoperative period than their peers, the authors suggested that anesthesiologists would be wise to screen patients for snoring, airway dysfunction, and other airway anatomic disorders before performing surgery.

mbock@frontlinemedcom.com

Continued from previous page

failure with reduced ejection fraction who underwent a comprehensive sleep study with pulse oximetry measurements during 2002-2013.

The results showed that while the measured AHI significantly linked with the 5-year mortality rate of these patients, the relationship became statistically insignificant after researchers adjusted for age, sex, body mass index, heart failure severity, ejection fraction, medications, and other clinical variables.

In contrast, the average time a patient spent with an oxygen saturation level below 90% overnight strongly linked with 5-year mortality even after adjusting for all these covariables.

The analysis showed that each hour of sleep a heart failure patient spent with an oxygen saturation level below 90% linked with a relative 16% reduction in 5-year survival. Patients in the quartile with the greatest amount of time spent with an oxygen saturation level below 90% had a 50% 5-year mortality rate, while those in the quartile with the least amount of time spent with severely depressed oxygen saturation had a 30% 5-year mortality rate.

Based on this finding "you need to look at the effect of SDB and not just the apnea-hypopnea index" when assessing SDB in patients with heart failure, Dr. Oldenburg said.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Nighttime caffeine delayed circadian clock

BY AMY KARON
Frontline Medical News

A double espresso–sized dose of caffeine consumed 3 hours before bedtime delayed the normal onset of the melatonin rhythm by about 40 minutes, researchers reported in Science Translational Medicine.

"In addition to increasing daytime exposure to sunlight and reducing evening exposure to electrical light, avoiding evening caffeine may help treat problematic delayed sleep timing," according to Tina Burke of the University of Colorado Boulder and her associates.

The results also could support consuming caffeine in the morning to help recover from jet lag, but further

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studies would need to test that possibility, the researchers added.

Caffeine is known to affect circadian rhythms in rats and flies, but its circadian effects in humans were unknown, the investigators said.

Their 49-day, double-blinded study included five healthy, normal-weight adults who averaged 24 years of age. For a week before each scheduled laboratory visit, participants slept 8 hours a night as verified with the help of sleep logs, wrist actigraphy, and time-stamped voice mail reminders. In the laboratory, they received caffeine or placebo 3 hours before their normal bedtime and were exposed to either bright or dim (control) light at bedtime (Sci Transl Med. 2015;7:1-9).

Caffeine plus dim light was associated with about a 40-minute longer phase delay than placebo and dim light ($P = .011$), the investigators reported.

Bright light with placebo led to about an 85-minute phase delay ($P = .0007$), while bright light plus caffeine caused a 105-minute shift ($P = .0003$).

Experiments with cultured human cells also showed that caffeine competitively bound to adenosine receptors, which disrupted signaling of cyclic adenosine monophosphate (cAMP), a key part of the circadian clock, the researchers said.

The study was funded by the National Institutes of Health, the National Center for Advancing Translational Sciences, and the Howard Hughes Medical Institute in collaboration with the University of Colorado.

Ms. Burke reported no relevant financial conflicts.

Youth with chronic diseases use alcohol, marijuana

BY SHANNON AYMES
Frontline Medical News

Alcohol and marijuana use is common in youth with chronic disease, and alcohol use is associated with nonadherence to treatment, according to a new study published in Pediatrics.

Approximately one in four American youths are living with a chronic medical condition. The most common substance abused by young people is alcohol, which can lead to adverse medication interactions and difficulty with treatment adherence and self-care. As with healthy youth, alcohol abuse may be associated with poor sleep, smoke exposure, and unprotected or unplanned sex. Marijuana use can lead to airway inflammation, treatment nonadherence, and sleep disturbances. Currently, there are no studies that indicate marijuana has therapeutic utility in young people.

Elissa Weitzman of Harvard Medical School in Boston, and colleagues sought to fill in knowledge gaps on the prevalence of substance use in chronically ill youths, which may lead to development of preventative strategies.

The investigators conducted a cross-sectional web-based assessment of youth aged 9-18 years who were being treated for cystic fibrosis, asthma, arthritis, type 1 diabetes, or inflammatory bowel disease (IBD). The questionnaire assessed alcohol use, behaviors, marijuana use, and health care interactions (Pediatrics 2015. doi: 10.1542/peds.2015-0722).

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Of the 532 youths invited to participate in the study, 403 consented to participate; 51.6% were female, and 75.1% where white. The average age of participants was 15.6 years, and overall they were in good mental health.

Alcohol use within the past year was reported in 30.8%, and older age correlated to alcohol use (*P* less than .001).

Binge drinking was reported in 37.7% of respondents who reported alcohol use within the past year, and 10.4% in the total group. Binge drinking was reported more often in older (*P* less than .001) and white (*P* less than .01) chronically ill youth. Better mental health scores were associated with binge drinking (*P* less than .01).

Marijuana use was reported in 17.2% of the study group and 20.6% of the high school–aged group. Furthermore, marijuana use in chronically ill youth was associated with males, older age, lower socioeconomic status (*P* less than .01), and poorer mental health (*P* less than .01). Participants with IBD had higher rates of marijuana use than participants with arthritis or asthma. Almost all youth who reported past-year marijuana use also reported past-year alcohol use, the investigators noted.

Knowledge of alcohol's potential effects with medications and laboratory results was low, with only 53.1% and 37.2% of high school students answering correctly, respectively. Those who answered incorrectly were 8.53 and 4.46 times more likely to drink and binge drink (*P* less than .001).

Approximately 8.3% and 32% of the high school–aged participants reported skipping or forgetting to take prescription medications within the past 30 days, respectively. Intentional nonadherence was associated with lower mental health scores (*P* less than .001).

High school–aged youth who admitted to alcohol use within the past year were 1.61 times and 1.79 times more likely to skip and forget their medications, respectively.

Ms. Weitzman and her associates noted that the association of better mental health scores with binge drinking may be related to the social aspect, whereas the association of poorer mental health scores with marijuana may be related to its possible use to improve symptoms.

The authors also pointed out that although nonadherence was associated with alcohol use and poorer mental health scores, it also may be related to health-risking behaviors, poor self-regulation, and the feeling of invulnerability associated with adolescent development.

"Alcohol and marijuana use are prevalent among youth with chronic medical conditions, and drinking is associated with treatment nonadherence. Education and screening of medically vulnerable youth are warranted to ameliorate risk," they concluded.

The authors reported no disclosures, and the study was supported by a National Institutes of Health grant.

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: This study highlights how important it is for subspecialists to have a transition plan for their young adolescents and young adults. This plan should include interviewing the patient without the presence of the parents to allow more probing questions and anticipatory guidance for our patients.

First-time youth tobacco users turning to e-cigarettes

BY GREGORY TWACHTMAN
Frontline Medical News

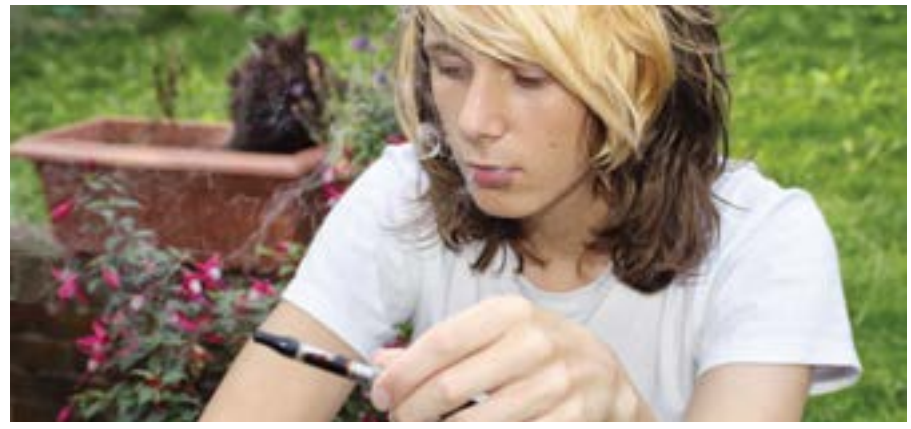
First-time youth tobacco users are turning to e-cigarettes, a survey showed.

Researchers examining the results of the survey of 2,084 11th- and 12th-grade participants in the Southern California Children's Health Study during the spring of 2014 found that e-cigarettes were enjoying a "favorable social environment" among this group.

"This finding is a cause for concern because e-cigarettes were the dominant tobacco product used, and a substantial portion of e-cigarette users had no history of tobacco use," Jessica L. Barrington-Trimis, Ph.D., a researcher at the University of Southern California's department of preventive medicine, and her colleagues said in the August issue of Pediatrics (doi:10.1542/peds.2015-0639).

Twenty-four percent of teens reported any lifetime e-cigarette use; 10% were current users (past 30 days) and 14% were past users. "Notably, a lower proportion of adolescents (n = 390, 18.7%) had ever smoked a cigarette; 5.7% (n = 119) were current cigarette users and 10.0% (n = 271) were past cigarette smokers," Dr. Barrington-Trimis and her associates reported.

The investigators suggested that because of a more favorable perception of e-cigarettes (for example, 43% of the adolescents predicted that their friends would react positively to their own e-cigarette use), they "could contribute to the 'renormalization' of tobacco products generally," and called for more research in this area.



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Research was funded by a grant from the National Cancer Institute and the Food and Drug Administration Center for Tobacco Products. The authors reported no relevant financial conflicts of interest.

gtwachtman@frontlinemedcom.com

‘David technique’ may enhance aortic repair

BY RICHARD MARK KIRKNER
Frontline Medical News

Many techniques for repair of aortic dissection have evolved, but no trials have compared those techniques to determine which is the best.

However, a study team has attempted to evaluate a surgical approach (the “David technique”) that includes three specific steps – no aortic cross clamp, the use of deep hypothermic circulatory arrest (DHCA), and the antegrade resumption of cardiopulmonary bypass. They found that this approach yielded significantly better long-term outcomes than did other approaches tried.

The study investigators, led by Dr. Jennifer S. Lawton of Washington University in St. Louis, reported their findings in the Journal of Thoracic and Cardiovascular Surgery (2015 Aug;150(2):294-301.e1).

“We hypothesized that a surgical strategy to prevent cross-clamp injury or false lumen pressurization would be associated with reduced morbidity, mortality, persistent false lumen patency, and improved survival,” Dr. Lawton and her coauthors wrote.

At 5 years, the predicted survival was 86% for Group 1 (the ‘David technique’) and 56% for Group 2 (a variety of techniques); and at 10 years, 72% and 37%, respectively.

“This study was designed to determine the differences in outcomes between operative techniques,” they said.

VITALS

Key clinical point: An operation to repair type A aortic dissection that involves three specific steps achieves better outcomes than do other surgical approaches.

Major finding: Survival rates at 5 years were 86% for the group that had operations in which the surgeons used the three specific steps vs. 56% for the other group.

Data source: Retrospective analysis of single-center population of 146 patients who had repairs for type A aortic dissection.

Disclosures: None of the study coauthors had any relationships to disclose.

The study evaluated 196 patients who had surgery for acute type A aortic dissection over 17 years. Group 1, comprising 49 patients, had the operation according to the protocol that involved the three specific steps, as Dr. Tirone David of the University of Toronto first reported in 1999 (Ann. Thorac. Surg. 1999;67:1999-2001) — the “David technique,” as the study authors called it.

Group 2 consisted of patients whose repair involved a variety of techniques, including one or two steps of the David technique but not all three.

Study endpoints were 30-day mortality rate, postoperative adverse events, presence of a false aortic lumen, and overall survival, the latter defined as the time from the date of surgery to the date or death or last follow-up.

The evaluation included examination of patients’ latest CT scan or MRI that was at least 6 months after the operation for false lumen, but only 78 patients had imaging at that interval.

Patients in Group 1 had a higher rate of persistent false lumen – 74% vs. 68% in Group 2.

Thirty-day mortality was 6.1% in Group 1 and 15.7% in Group 2, but Dr. Lawton and her coauthors said this difference was not statistically significant.

Survival rates at 1, 5, and 10 years among both groups were “consistent with published ranges,” the authors said.

At 5 years, the predicted survival was 86% for Group 1 and 56% for Group 2; and at 10 years, 72% and 37%, respectively.

The study authors acknowledged the controversy that surrounds the use of retrograde resumption of cardiopulmonary bypass after replacement of the ascending aorta and that there’s no consensus on which method is best for resuming cardiopulmonary bypass after repair of a type A aortic dissection.

The study also found no difference in the incidence of false lumen between the two groups, but again, this is a source of controversy.

“Persistence of a false lumen following repair for type A aortic dissection has been reported to be associated with poor prognosis and reduced long-term survival,” Dr. Lawton and her study colleagues said.

“Others have reported a patent false lumen was not an independent predictor of late reoperation, but was a predictor of aortic growth following repair of type A aortic dissection,” the investigators commented.

The study authors said one limit of their findings is its retrospective nature, but they also said that a prospective, randomized trial would be difficult to conduct.

None of the study coauthors had any relationships to disclose. They presented their original data at the American Association for Thoracic Surgery Aortic Symposium, April 24-25, 2014, in New York.

VIEW ON THE NEWS

Whether or not to use a cross-clamp in type A aortic dissection repair is a critical question, but a major concern of this study was the wide variability of techniques used in the comparison group, Dr. Richard J. Shemin said in his invited commentary (J. Thorac. Cardiovasc. Surg. 2015 [doi:10.1016/j.jtcvs.2015.04.038]). “The variety of approaches attests to the lack of institutional agreement on the surgical principles tested in the study,” he said. “The large variety of techniques in the control group makes the comparison and interpretation of this study difficult.”

“There are more questions to consider from this study than answers derived from the data about the clamp strategy,” he said

But, Dr. Shemin said, using the cross-clamp with axillary antegrade perfusion is “not a major issue.” And the use of clamping during the cooling period can save overall cardiac arrest time during the operation.

“If one does use femoral cannulation, then not applying the cross-clamp until achieving circulatory arrest is prudent,” he said. “With axillary cannulation, one achieves antegrade perfusion so early cross-clamping can be safely performed with the advantages of saving operative time.”

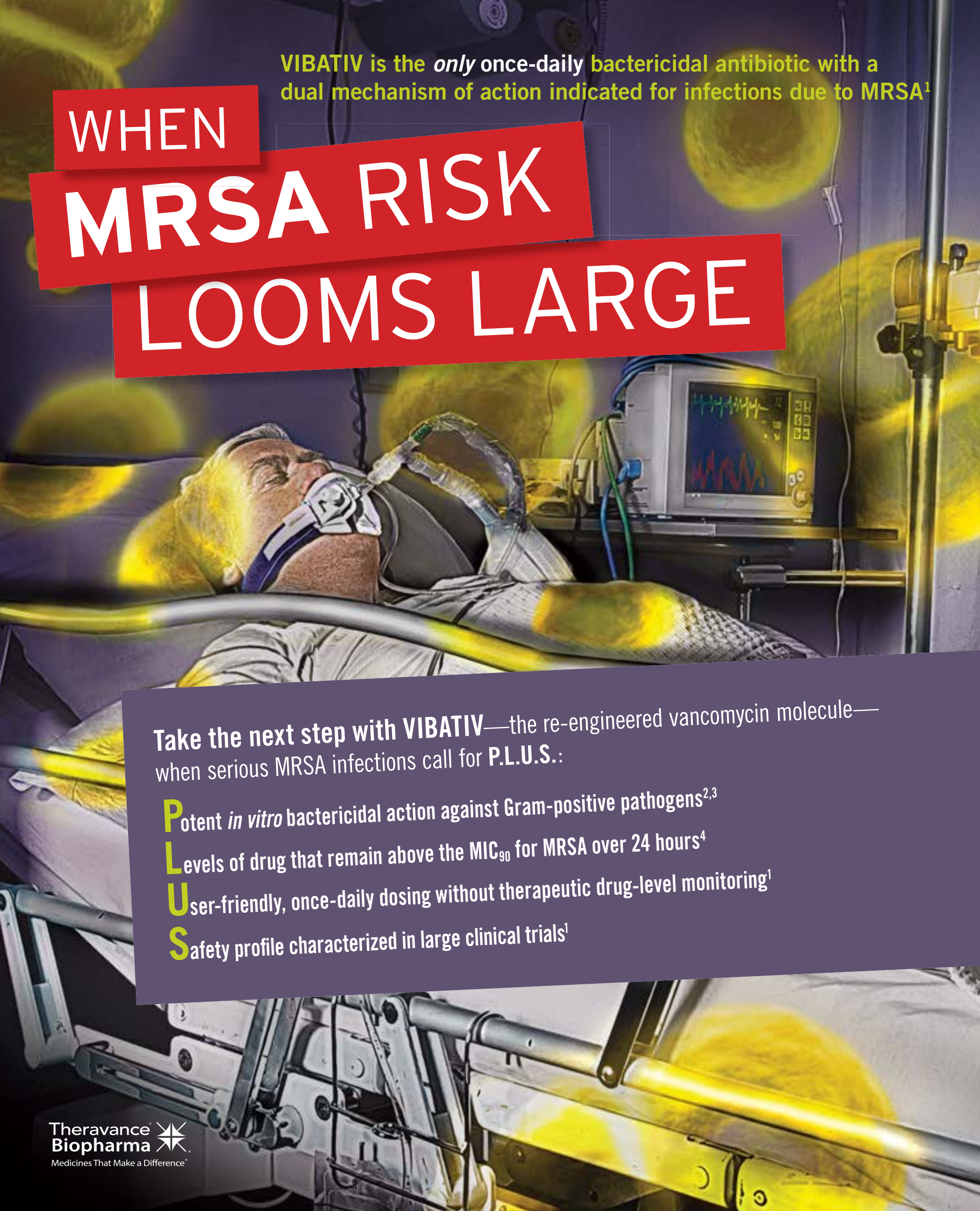
The clamp site must be inspected during circulatory arrest. Antegrade cerebral perfusion is proven to be an excellent technique and is facilitated by right axillary cannulation, Dr. Shemin said. “Most importantly, establishing antegrade CPB [cardiopulmonary bypass] perfusion after circulatory arrest is mandatory in all cases to minimize distal aorta trauma,” he said.

Dr. Richard J. Shemin is a cardiothoracic surgeon at UCLA Medical Center, Santa Monica, Calif.

VIEW ON THE NEWS

Dr. G. Hossein Almassi, FCCP, comments: The goal of repair of Type A aortic dissection is to repair the ascending aorta expeditiously and to establish antegrade perfusion in the aorta to prevent pressurization of the false channel. This is usually accomplished by establishment of antegrade perfusion through a right axillary artery cannulation for cardiopulmonary bypass, avoidance of aortic cross clamping, and the use of deep hypothermic circulatory arrest, the so called David technique (not to be confused with David procedure for aortic root repair). The authors of this study reviewed 196 patients with type A aortic dissection at their institution that underwent repair with a variety of techniques over a 17-year period. They found improved 5- and 10-year patient survival with the David technique. There were only 49 patients in the David technique group, indicating a more recent adoption of this technique with more refinements of surgical and perioperative care techniques. The comments of Dr. Shemin on clamping the ascending aorta during the cooling period to reach the desirable temperature for the establishment of DHCA – and, thus, shortening the operative time in these emergent operations – are germane.

With application of a well-defined institutional protocol for repair of this devastating aortic pathology, good surgical outcomes with acceptably low mortality rates are to be expected.



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INDICATION

VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). VIBATIV should be reserved for use when alternative treatments are not suitable.

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- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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References: 1. VIBATIV® (telavancin) Prescribing Information. Theravance Biopharma Antibiotics, Inc. March 2014. **2.** Draghi DC, et al. Comparative surveillance study of telavancin activity against recently collected Gram-positive clinical isolates from across the United States. *Antimicrob Agents and Chemother.* 2008;52:2383-2388. **3.** Draghi DC, et al. *In vitro* activity of telavancin against recent Gram-positive clinical isolates: results of the 2004-05 Prospective European Surveillance Initiative. *J Antimicrob Chemother.* 2008;62:116-121. **4.** Data on file. Theravance Biopharma Antibiotics, Inc.

IMPORTANT SAFETY INFORMATION

Mortality
Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity
New onset or worsening renal impairment occurred in patients who received VIBATIV. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function.

Monitor renal function in all patients receiving VIBATIV prior to initiation of treatment, during treatment, and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.

Fetal Risk
Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

Contraindication
VIBATIV is contraindicated in patients with a known hypersensitivity to the drug.

Hypersensitivity Reactions
Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin.

Geriatric Use
Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

Infusion Related Reactions
VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause “Red-man Syndrome”-like reactions including: flushing of the upper body, urticaria, pruritus, or rash.

QTc Prolongation
Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, VIBATIV prolonged the QTc interval. Use of VIBATIV should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Most Common Adverse Reactions
The most common adverse reactions (greater than or equal to 10% of patients treated with VIBATIV) were taste disturbance, nausea, vomiting, and foamy urine.

VBT 00046-04 August 2014

Post-CABG stroke risk same with one or two clamps

BY RICHARD MARK KIRKNER
Frontline Medical News

When performing on-pump coronary artery bypass grafting (CABG), cardiac surgeons can control very few factors to reduce the risk of stroke – with the exception of which method of aortic manipulation they use. Debate and controversy, however, have surrounded which aortic manipulation technique is best: single- or double-clamp occlusion.

A large retrospective study of almost 8,500 patients who had CABG at the Mayo Clinic in Rochester, Minn., over a 17-year period showed that, while use of the single-aortic cross-clamp (SC) technique steadily increased, the risk of stroke is virtually the same as it is with the partial aortic cross-clamp (PC), or double cross-clamp, technique. The study authors, led by Dr. Juan C. Araque, published their results online in the Journal of Thoracic and Cardiovascular Surgery (2015. doi: 10.1016/j.jtcvs.2015.04.010).

"It is intuitive that less aortic manipulation would result in less risk of stroke," Dr. Araque and colleagues said, but even off-pump CABG, which requires no aortic manipulation, is not without stroke risk.

"It is conceivable that there is

Continued on following page

VIEW ON THE NEWS

Dr. G. Hossein Almassi, FCCP, comments: Stroke is one of the most devastating complications of CABG dreaded by patients and surgeons alike. Efforts at minimizing stroke have been primarily focused on the manipulation of the ascending aorta during aortic cannulation and subsequent aortic clamping, and, thus, the recommendations for routine epiaortic ultrasonography before any manipulation. The study is a retrospective review of 8,500 patients at the Mayo clinic over 17 years comparing a single aortic cross clamping (SC) for the performance of both the distal coronary and the proximal aortic anastomoses of the bypass grafts vs. the release of the aortic cross clamp following the completion of distal coronary anastomoses and the application of a partial occlusion clamp (side-biting clamp) to the ascending aorta for the performance of the proximal anastomoses (PC). The stroke rate was similar between the two groups (1.2% SC vs. 1.5% PC). On propensity matching, both groups had a stroke rate of 1.2%.

The study suffers from its retrospective nature and lack of pre- and postoperative examination by a neurologist. However, it indicates that with careful attention to details and tailoring the procedure to the patient rather than tailoring patient to the procedure, one can obtain good patient outcomes.

White board in the OR adds a layer of safety

BY ALICE GOODMAN
Frontline Medical News

NEW YORK – Displaying a low-tech, low-cost white board in the operating room during the "time out" before surgery can significantly improve memory retention among members of the surgical team, a new study suggests.

"We found that providing a white board that you can buy at any office supply store gives a visual stimulus on top of the verbal stimulus [that] improves retention of important information," Dr. Aryan Meknat, the study author, said at the annual Minimally Invasive Surgery Week.

A surgical pause or "time out" performed before any operative procedure is a major component of the Joint Commission's Universal Protocol to prevent wrong site, wrong procedure, and wrong person surgery.

Retention of information presented during the surgical pause is essential, at the beginning of the case and for the duration of the procedure, he said.

During the study, surgical teams were randomly divided into two groups: In the first group, 30 team members were given information verbally during the surgical pause; while a second group of 29 team members was provided with verbal information that was read from the white board. The white board was displayed in the operating room throughout the surgical procedure for the second group.

After the conclusion of the procedure, the white board was removed and both groups were given a short written questionnaire.

Each team was tested only once in order to keep the study blinded. Also, participants had no prior knowledge that they would be tested after the procedure.

Study participants were asked to recall several facts about the patient, including the patient's first and last name, age, sex, weight, site of IV placement, allergies, medications, relation of accompanying guardian, and the signature on the consent form.

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Team members in the first study group answered a total of 300 questions, and 200 questions (66.7%) were correctly answered. Participants in the second group – which used the white board – answered 290 questions, and 239 (82.4%) were correctly answered. The white board group had a 23.6% overall increase in correctly answered questions.

The difference between retention in the two groups was statistically significant (*P* less than .05) in every category tested.

"These findings apply to operating rooms everywhere, especially in cases where there may be long delays before starting the procedure, changes in anesthesia midcase, situations where two procedures are scheduled in one patient, or in intraoperative emergency situations. "We need to be sure that the surgical team retains information, as well as [listens] to verbal instructions," said Dr. Meknat of MobiSurg, a mobile surgical unit based in Laguna Hills, Calif.

Dr. Meknat reported having no relevant financial disclosures.

Continued from previous page

some inherent risk of stroke associated with any cardiac operation, and that risk may increase with manipulation of the ascending aortic with the aortic cross clamp," they wrote. "Our data would suggest, however, that the risk does not increase further with the additional aortic manipulation of the partial occlusion clamp."

The study comes on the heels of a 2008 meta-analysis that found no benefit of SC in comparison to PC (Interact Cardiovasc Thorac Surg. 2008;7:500-3), while another study in 2011 suggested that less aortic manipulation carried a significantly lower stroke risk (Heart Lung Circ. 2011;20:318-24).

The Mayo study evaluated the SC technique in 2,051 patients and PC in 6,446 patients who had isolated on-pump CABG between 1993 and 2010. The rate of stroke was 1.2% in the SC group and 1.5% among those who had PC.

In two propensity-matched cohorts of 1,333 patients each, the stroke rate was 1.2% in each group. The investigators used the Society of Thoracic Surgeons' risk calculator variables to create the propensity-matched cohorts.

The study group excluded high-risk patients, including those who had off-pump operations or previous cardiac surgeries or required replacement of a cross clamp during an unplanned operation.

The goal of the study was not to compare outcomes with the off-pump technique. "It is only to bring attention to the associated non-zero stroke rate with both techniques," Dr. Araque and colleagues said.

Their findings are significant because on-pump CABG is the preferred operation of cardiac surgeons, accounting for more than 80% of the CABG operations in the SYNTAX study (N Engl J Med. 2009;360:961-72). "The 'anaortic' off-pump technique may be a more specialized technique, representing less than 15% of operations in one large series," Dr. Araque and coauthors said.

They acknowledged a few limitations resulting from the observational nature of the study, including that surgeons may have missed some strokes because they did not use a routine, standardized procedure for evaluating stroke signs along with the lack of documented assessment of the descending aorta. But they also stated that the large number of patients in the study, along with the use of propensity matching, addresses some of the bias inherent in an observational study.

The authors said they had no relevant financial disclosures.

VIEW ON THE NEWS

A randomized trial is needed to answer the question, 'Can CABG [coronary artery bypass grafting] be safely performed with either one or two aortic clamps in all patients?' " Dr. Jennifer S. Lawton said in her invited commentary (J Thorac Cardiovasc Surg. 2015. doi:10.1016/j.jtcvs.2015.05.002).

Dr. Lawton acknowledged the positions that advocates of both techniques have staked out: Advocates of the single-clamp (SC) technique prefer the ability to perform the proximal anastomoses without the added space constraints and reduced visibility of the partial clamp and moving heart; proponents of the partial-clamp (PC) method cite advantages in the ability to determine graft length with the full heart and the likelihood to reanimate the heart earlier to reduce the risk of a heart attack.

The PC technique required longer cardiopulmonary bypass time, 88.2 minutes vs. 73.7 minutes, but the SC group had longer cross-clamp times, 54.5 vs. 50.7 minutes. "The longer clamp time did not alter the outcomes reported (stroke and mortality) – although specific outcomes of myocardial injury including need for inotropes, troponin levels, myocardial infarction, etc. were not reported," Dr. Lawton said. "Thus, the question for the surgeon is, 'What is more important, the brain or the heart?' "

The results from Dr. Araque's study "are valuable" because of the large patient cohort and the suggestion that "the use of a second clamp is not likely to significantly alter outcomes of stroke and mortality," she wrote.

But the study leaves a few questions remaining, Dr. Lawton said. "What is the best treatment of high-risk patients who may benefit from limited aortic manipulation the most? Can two clamps be safely applied to all types of aortas? And does the risk of dissection go up with the use of two clamps?"

Although a randomized trial would be difficult because of the low risk of stroke in on-pump CABG, such a trial could answer those questions if it involved routine epiaortic ultrasound, Dr. Lawton said.

Dr. Lawton is professor of surgery in the division of cardiothoracic surgery at Washington University, St. Louis.

CRITICAL CARE COMMENTARY: Intestinal microbiome: Friend or foe?

BY DR. LEE MORROW, FCCP

The term 'intestinal microbiome' vaguely refers to the ecological community of commensal, symbiotic, and potentially pathogenic microbes living within the human alimentary tract. These organisms play various key roles in energy uptake, vitamin synthesis, epithelial homeostasis, and immunity development. In recent years, there has been an ever-increasing interest in the intestinal microbiome and its potential implications for critically ill patients. A simple PubMed.gov search shows a more than 25-fold increase in the number of publications on this topic over the past decade, from 63 papers in 2004 to 1,716 articles in 2014.


DR. MORROW

While accumulating data suggest that the density and diversity of the bowel flora are of central importance in maintaining homeostasis, our understanding of host-microbe interactions is in its relative infancy. We know that the gut microbiota typically contains hundreds of trillions of microorganisms, including over 1,000 different species and more than 3 million genes. Because the average adult human contains around 37 trillion cells and 30,000 genes, we are literally visitors in our own bodies with the microbes outnumbering us ten to one – cells or genes. It is estimated that about a third of the microbiota is common to all humans but that the remaining two-thirds is as specific to each person as his or her fingerprints. However, unlike our fingerprints, the gut flora is a malleable entity affected by diet, medications, acute illness, and a host of other factors.

The potential clinical utility of alterations in the intestinal microbiome is not an entirely novel frontier for intensivists. Rather, there have long been various levels of speculation and/or evidence regarding the role of the GI microbes in the pathogenesis of such diverse ICU entities as antibiotic-associated diarrhea, sepsis, ventilator-associated pneumonia, and *Clostridium difficile* diarrhea. Conflict arises because in some scenarios, obliteration of the normal gut microbiome appears to be causative (*C difficile* diarrhea being the classic example), while in other instances, the same flora are implicated as the culprit (sepsis and ventilator-associated pneumonia).

This juxtaposition of yin and yang lies at the heart of one unique dilemma in managing critically ill patients: Are the intestinal microbiota friends or foes? Should we be sterilizing the gut or constantly replenishing this ecosystem? Selective oral decontamination (SOD) and selective digestive decontamination (SDD) are strategies that view the gut microbiome as enemies and are used to prevent ventilator-associated pneumonia. SOD attempts to sterilize the upper aerodigestive tract through the use of topical broad-spectrum antibiotics while SDD extends the zone of combat to include the entire alimentary tract by adding several doses of systemic antibiotics to the topical oral agents. Presumably through the reduction of the density of the gut flora, these strategies have repeatedly been shown to be effective in preventing pneumonia. More importantly, this remarkably low-cost strategy significantly reduces mortality, as well.[1] It should be noted that SOD and SDD are not currently endorsed by existing pneumonia guidelines in the United States, given significant concerns for potential adverse effects of widespread use on local antibiograms if incorporated into routine practice.

A diametrically opposite strategy – one that views the flora as the solution and not the problem – is the concept of probiotic administration. Probiotics are microorganisms of human origin that survive when ingested, colonize the intestines, and subsequently confer health benefits upon the host. Related concepts include prebiotics (nondigestible products that promote growth of beneficial microbes) and symbiotics (combinations of prebiotic and probiotic agents). Probiotic species have a variety of theoretic mechanisms whereby they may have effects on the host including probiotics' direct competition with pathogens, release of factors to create a locally hostile environment for pathogens, and immunomodulation.[2] Of these, immunomodulation appears to be of increasing importance and significance. Briefly, immunomodulation involves complex interactions between probiotic species and intestinal dendritic cells to polarize T cells, a sequence of events that ultimately optimizes mucosal integrity, as well as local and systemic immunity.[3]

To date, existing studies viewing the microbiota as a friendly entity – the probiotic approach – are relatively few in number and have limitations due to sample size and/or methodologic issues. Current systematic reviews and meta-analyses have concluded that probiotics generally appear to confer benefits for selected indications but that extensive further study is needed before definitive conclusions can be made.[4] The probiotic strategy also has the added potential safety concern inherent to treating critically ill patients with living microbes. Critics of the probiotic strategy point to the PROPATRIA trial, a randomized, controlled study in patients with predicted severe pancreatitis that showed increased mortality in probiotic-treated patients.[5] While this study appears to be an outlier and the increased mortality may have been due to study-specific issues, this finding reiterates the need for meticulous attention to safety when prescribing probiotics.

So, we return to the fundamental question: is the intestinal microbiome our friend or is it our foe? Not surprisingly, the answer appears to be both. Given the immense diversity of the normal adult gut flora, we should expect both beneficial and harmful effects ultimately depending on the relative balance of the microbiome's beneficial and potentially harmful constituents. Maintaining this balance, then, becomes an important therapeutic target. However, the aforementioned microbial variability between individuals and the propensity for the flora to change over time within an individual present challenges when attempting to therapeutically alter the microbiome and improve outcomes. Moreover, might there be select populations that might disproportionately benefit from manipulations of the gut flora? Thinking outside the box, maybe the microbiota dysbiosis seen with obesity confers protection – the so-called obesity paradox.

While accumulating data suggest that the density and diversity of the bowel flora are of central importance in maintaining homeostasis, our understanding of host-microbe interactions is in its relative infancy.

At present, there are no widely available commercial tests to assess a given patient's microbiome – and there are no well-defined 'targets' for manipulation. In our critically ill patients, the flora's eternal evolution rapidly accelerates with abrupt changes brought on by dietary changes, various medications, and acute illness itself, turning our ill-defined target into a *moving* ill-defined target. Adding further insult to injury, there is a host of unknowns when we consider probiotic therapy as a means to rebalance the intestinal microbiota. What are the optimal probiotic species to use? What are the threshold densities that must be achieved to effect change? Is colonization important or is ingestion of nonviable organisms equally effective? What are the optimal routes of probiotic administration? What are the implications of ICU nutrition and/or medications?

Perhaps in the end, these fundamental questions are more important than determining 'friends' and 'foes.' Ideally, evidence-based nutritional guidelines (including the anticipated upcoming revisions to the ASPEN nutrition guidelines) will continue to highlight the potential for, as well as the knowledge gaps, surrounding microbiome manipulation therapy. Ideally, such attention to this inexpensive and widely available therapeutic option will pressure funding sources and regulatory agencies to further exploration of these issues and to help ICU care evolve in this novel direction.

Dr. Morrow is Section Editor for Critical Care Commentary.

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Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist 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.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Once-daily ANORO ELLIPTA significantly improved lung function by 167 mL (*P*<0.001) vs placebo at Day 169[1]*

*As measured by the primary endpoint, trough (predose) FEV_1 at Day 169 (mean of the FEV_1 values at 23 and 24 hours after dosing on Day 168), in a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Least squares mean change from baseline of 171 mL for ANORO ELLIPTA (n=413) and 4 mL for placebo (n=280).

Important Safety Information for ANORO ELLIPTA

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.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this advertisement.

Theravance

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

Lung function comparison studies with tiotropium

Indications

- ANORO ELLIPTA is a combination anticholinergic/LABA indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD.
- SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[2]

Description of Studies[3-5]

Design: Three 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies that evaluated the efficacy and safety of ANORO ELLIPTA (administered once daily by the ELLIPTA inhaler) and other treatment arms, including tiotropium 18 mcg (administered once daily by the HandiHaler).

Treatment arms: In the 1st study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or VI 25 mcg.† In the 2nd study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or UMEC 125 mcg.* In the 3rd study, patients were randomized to treatment with ANORO ELLIPTA or tiotropium 18 mcg.

Patients: Studied in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted, a mean reversibility range of 11.7% to 15.6%, and a mean postbronchodilator FEV_1/FVC ratio range of 0.46 to 0.48.

Primary endpoint: 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).

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; UMEC=umeclidinium; VI=vilanterol.

*UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg are not approved strengths.

†Vilanterol is not approved as monotherapy.

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

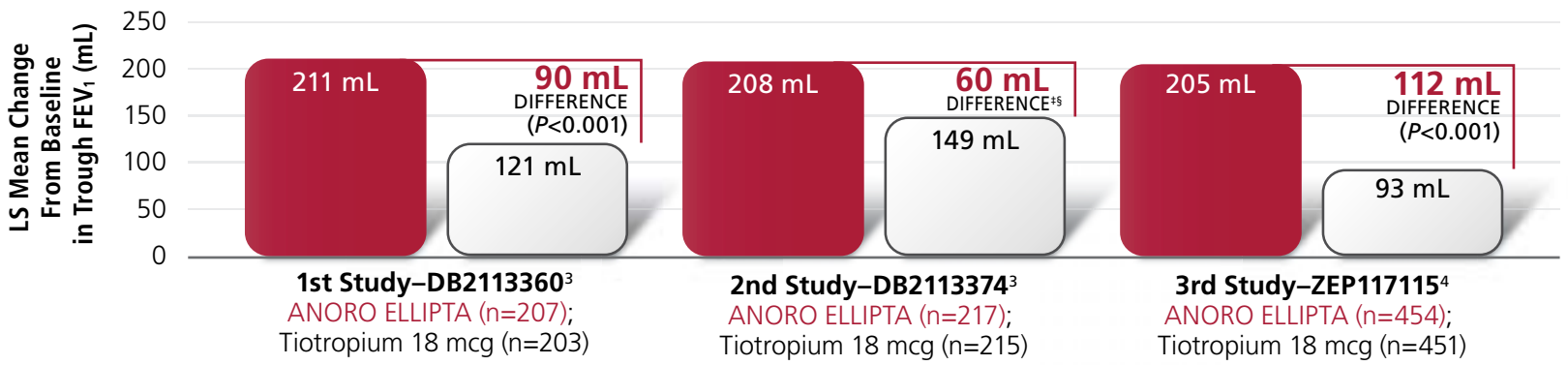
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled 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.
- 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.

Once-daily ANORO ELLIPTA demonstrated superior lung function improvement compared with tiotropium in 2 studies

PRIMARY ENDPOINT: TROUGH (PREDOSE) FEV_1 AT DAY 169[3,4]



‡The comparison of UMEC/VI 125 mcg/25 mcg with UMEC 125 mcg preceded that of ANORO ELLIPTA with tiotropium as part of a predefined hierarchy of treatment comparisons and did not achieve statistical significance. Therefore, results of the comparison of ANORO ELLIPTA with tiotropium were descriptive only and statistical significance could not be inferred.[3]

§Reflects rounding.

LS=least squares.

Adverse events (AEs) occurring in ≥3% of subjects in any of the 3 studies[3-5]

Safety data were descriptive only. The studies were not powered to compare the safety profile of ANORO ELLIPTA with that of tiotropium. The range of AEs across the 3 studies for ANORO ELLIPTA (n=883) and tiotropium 18 mcg (n=874), respectively, were: headache (9-10%, 4-7%), nasopharyngitis (6-10%, 7-8%), back pain (2-5%, 2-5%), lower respiratory tract infection (0-4%, <1-1%), upper respiratory tract infection (<1-4%, <1-7%), COPD (<1-3%, <1-2%), cough (2-3%, 2-3%), gastritis (0-3%, <1%), pain in extremity (<1-3%, <1-2%), hypertension (<1-2%, <1-3%), and urinary tract infection (0-<1%, <1-3%).

Important Safety Information for ANORO ELLIPTA (cont'd)

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.

References: 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, Appendix A. **2.** SPIRIVA HandiHaler [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. **3.** Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med.* 2014;2(6):472-486. **4.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014;108(12):1752-1760. **5.** Data on file, GSK.

Please see additional Important Safety Information for ANORO ELLIPTA on preceding pages.

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

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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 if any of these signs or symptoms develops.
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 if any of these signs or symptoms develops.
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 develops.

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 if any of these signs or symptoms develops.

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 if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Scoring tool may reveal ventilator dependence risk

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – A new preoperative risk scoring tool may help identify patients at high risk for requiring mechanical ventilation for more than 48 hours in the 30 days after surgery, a study suggests.

The risk score is based on seven measures: whether patients have had a small bowel procedure, have had an esophageal procedure, are current smokers, have severe chronic obstructive pulmonary disease, have hypoalbuminemia, are older than age 60 years, or have signs of systemic inflammatory response syndrome or sepsis.

The score was validated via the American College of Surgeons (ACS)/National Surgical Quality Improvement Program (NSQIP) database to identify patients who underwent nonemergent general or vascular surgery at Thomas Jefferson University Hospital between 2006 and 2013, Dr. Adam P. Johnson, study coauthor, reported at the ACS/NSQIP National Conference.

The risk score assigned 1 point each for a small bowel procedure, current smoking, severe chronic obstructive pulmonary disease, and hypoalbuminemia (less than 3.5 mg/dL); 2 points each for age over 60 years and signs of systemic inflammatory response syndrome or sepsis; and 3 points for esophageal procedures. Total risk scores ranged from 0 to 7 points for the population.

The median score was 2 for patients who did not need a ventilator after surgery and 3 for those who did.

Notably, patients with a risk score of more than 3 comprised the 20%-30% of patients who experienced 60%-70% of adverse events.

A cutoff value of 3 identified the top 20% of patients at highest risk for ventilator dependence, with a ventilator dependence rate of 5.4% (*P* less than .01).

The risk factors and scoring system are specific to Thomas Jefferson University Hospital. However, other institutions should be able to use the methodology and framework to identify ventilator risk factors in their own patients, Dr. Johnson suggested.

Future steps include evaluating how the risk tool performs when compared with risk scores derived from national datasets, automating the best performing risk score, and using the score in the preadmission testing of every patient undergoing elective general surgery or vascular operations. Once identified, high-risk patients would then be entered into an aggressive pre-, intra-, and postoperative pulmonary optimization pathway.

"The pathway might be resource intensive for all patients, but we might be able to hone in and use it more effectively for patients at greatest risk," Dr. Johnson said in a statement.

Although ventilator dependence occurs in only about 1%-3% of patients, the consequences are nonetheless significant, increasing mortality and health care costs, said Dr. Scott W. Cowan, senior study author and Jefferson's NSQIP Surgeon Champion.

pwendling@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Ventilator dependence after surgery is generally low, but the contributions to health care resource utilization are great. This scoring system is easy to use and predicted which patients have 60%-70% of the adverse events after surgery and the top 20% of patients who had the highest risk for ventilator dependence. The scoring system does not require additional testing above what is traditionally done for preoperative evaluation, which makes it desirable. Of note, two of the criteria were directed at gastrointestinal procedures in an institution where a high volume of GI procedures occurred. The score was calculated on elective and nonemergent general and vascular surgery patients. In my opinion, the utility of this scoring system is not to discourage surgery in high-risk patients, but to quickly identify the high-risk patient for ventilator dependence preoperatively. These high-risk patients can then be triaged into a more-aggressive preoperative, intraoperative, and postoperative pulmonary education program that is patient specific and largely patient centered. This not only allows physician awareness and vigilance, but also puts patients in the driver's seat to take control and actively participate in their comprehensive care plan for a good outcome.

Resuscitation type had no laparotomy impact

BY SHARON WORCESTER
Frontline Medical News

LAS VEGAS – Choice of damage control resuscitation – plasma:platelet:red blood cell ratio of either 1:1:1 or 1:1:2 – did not affect whether severely injured patients required an emergency laparotomy, nor did it affect time to laparotomy or survival following laparotomy, according to findings from the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial.

"We were unable to detect significant effects of damage control resuscitation on the frequency and time to emergency laparotomy, outcomes, disposition at 30 days, or main endpoint survival," said Dr. Vicente J. Undurraga Perl of the Oregon Health and Science University, Portland.

The lack of a difference between the treatment groups with respect to emergency laparotomy and 30-day survival may be a result of the low overall mortality of 23% and to the study being underpowered to detect a difference between the groups.

'We were unable to detect significant effects of damage control resuscitation on the frequency and time to emergency laparotomy [or] outcomes.'

The PROPPR trial demonstrated that damage control resuscitation, defined as "a massive transfusion strategy targeting a balanced delivery of plasma:platelet:RBC in a ratio of 1:1:1," allows earlier achievement of hemostasis in a greater number of severely injured patients than does a 1:1:2 ratio.

A corresponding reduction in deaths because of exsanguination was observed in the study subjects, who were enrolled from 12 level-1 trauma centers in North America, where they presented with severe injuries.

VITALS

Key clinical point: Choice of damage control resuscitation – plasma:platelet:red blood cell ratio of either 1:1:1 or 1:1:2 – does not affect whether severely injured patients require an emergency laparotomy, time to laparotomy, or survival following laparotomy.

Major finding: 52% of patients in the 1:1:1-ratio emergency resuscitation group and 50% in the 1:1:2-ratio group underwent emergency laparotomy, and 30-day survival was 82% and 77%, respectively.

Data source: An analysis of data for 680 patients from the PROPPR trial.

Disclosures: Dr. Perl reported having no relevant disclosures.

Of 680 patients who had severe injuries and were predicted to require massive transfusions, 613 underwent a surgical procedure and 397 underwent a laparotomy. Of the latter, 346 were emergency laparotomies.

Of those who received damage control resuscitation using the 1:1:1 ratio, 52% underwent emergency laparotomy (defined as laparotomy within 90 minutes of arrival at a trauma center).

Of those who received the 1:1:2 ratio, 50% underwent emergency laparotomy. The difference between the groups was not statistically significant, Dr. Perl reported at the annual meeting of the American Association for the Surgery of Trauma.

The median time to laparotomy was 28 minutes in both groups, and the proportions of patients who survived to 3 hours, 6 hours, 24 hours, and 30 days also were similar in the two groups. For example, 88% and 85% of those in the 1:1:1 and 1:1:2 groups, respectively, survived to 24 hours; 82% and 77%, respectively, survived to 30 days, he said.

There was no overall difference in mortality between the groups (hazard ratio, 0.78), nor was there a difference in survival by study site, he noted.

sworcester@frontlinemedcom.com

Lung adenocarcinomas you don't want to miss

BY SUSAN LONDON
Frontline Medical News

SEATTLE – Many advanced non–small cell lung cancer adenocarcinomas can now be managed with therapies that target driving mutations, but these mutations must be identified and tracked as they can change over time, Dr. Mark A. Socinski said at a joint meeting by Global Biomarkers Consortium and World Cutaneous Malignancies Congress.

The 2013 College of American Pathology guideline for the molecular testing of lung cancer "was a monumental publication and a beachhead, if you will, for establishing a standard of care [for NSCLC], much like we have in breast cancer for ER, PR, and HER2 measurement," he said. Furthermore, "we are now in an era where doing subsequent or sequential biopsies with repeat molecular testing is a standard of care in this population."

Although lung adenocarcinomas are homogeneous histologically, they are diverse with respect to oncogenic drivers (JAMA. 2014;311[19]:1998-2006), noted Dr. Socinski, director of the lung cancer section at the University of Pittsburgh Medical Center; clinical associate director of the University of Pittsburgh Lung Cancer SPORE; codirector of the UPMC Lung Cancer Center of Excellence; and coleader of the lung cancer program at the University of Pittsburgh.

"Our major nemesis is KRAS. We still don't have a good answer for that," he said. But roughly a third of lung adenocarcinomas have actionable mutations in the genes for EGFR [epidermal growth factor receptor], ALK, ROS1, BRAF, MET, or RET.

"In the year 2015, these are what I look for in our patient population. … We test routinely to identify these populations," he said. "In my clinic this week, I might have had almost all of these patients on targeted TKIs [tyrosine kinase inhibitors] with these sorts of things, getting clinical benefit in this particular setting."

Common mutations

"The EGFR mutation story really transformed lung cancer," Dr. Socinski said. In patients whose adenocarcinomas harbor these mutations, targeted therapy with an EGFR inhibitor commonly nets a dramatic response. "If you see this a number of times and you're a lung cancer doc, you become addicted to oncotype testing. And you certainly don't want to ever miss this," he said.

The IPASS trial (First-Line Iressa Versus Carboplatin/Paclitaxel in Asia) comparing the targeted agent gefitinib (Iressa) with chemotherapy in advanced NSCLC adenocarcinoma among never or light smokers was "a transformational trial in lung cancer," according to Dr. Socinski (N Engl J Med. 2009;361[10]:947-57).

"The lesson from IPASS: Phenotype we threw out the door; it's really about genotype. And if you didn't have the genotype [EGFR mutation], a TKI was very poor treatment. And if you had the genotype, the TKI was superior to chemotherapy," with a 52% reduction in the risk of progression or death.

Trials testing the EGFR inhibitors erlotinib (Tarceva) and afatinib (Gilotrif) have likewise shown a progression-free survival benefit in this patient population.

"One of the issues that we struggled with for some time was whether there is any survival benefit," Dr. Socinski said. A recent combined analysis of two afatinib trials has answered that question affirmatively (Lancet Oncol. 2015;16(2):141-51), and these agents have therefore become standard of care for EGFR-mutant adenocarcinoma.

"Interestingly, as we say, all EGFR mutants are not created equal, because in the exon 21[–mutated tumors], actually there was no difference relative to chemotherapy, and that survival advantage is really driven by exon 19. So the nature of your mutation is important in this particular analysis," he cautioned.

When patients on EGFR targeted therapy develop resistance, the cause in about half of cases is emergence of a secondary mutation in exon 20, the T790M mutation (Sci Transl Med. 2011;3(75):75ra26).

"The standard of care is to biopsy at the time of progression," Dr. Socinski maintained. "The reason why rebiopsy is important and it's important to diagnose that [new mutation] is that we have a couple of drugs close to [Food and Drug Adminis-

Continued on following page

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tration] approval that are highly active in patients with T790M-positive disease after a first- or second-generation TKI."

Specifically, the investigational third-generation TKIs rociletinib (ASCO 2015. Abstract 8001) and AZD9291 (ASCO 2014. Abstract 8009) have response rates of about 48% and 53%, respectively, in this setting. "This looks quite promising. And these drugs will likely be commercially available between now and the holidays at the end of the year," he predicted.

The T790M mutation can appear at different times, he said.

"I've even got several patients whom we've rebiopsied three or four times, and there has been T790M negativity and then emergence of positivity on subsequent biopsy. Given the activity of these drugs, that's important to know."

Another fairly common actionable mutation in lung adenocarcinoma is ALK, for which oncologists now have crizotinib (Xalkori). Crizotinib has likewise been tested against combination chemotherapy in a phase III trial in which it yielded superior progression-free survival in patients with advanced nonsquamous NSCLC harboring ALK mutations (ASCO 2014. Abstract 8002).

"This is now a second example with a molecular biomarker in which we've replaced the standard of care chemotherapy with a molecularly targeted agent," Dr. Socinski noted.

Second-generation ALK inhibitors such as the investigational agent alectinib are showing promise (ASCO 2015. Abstract 8008). "Even in previously crizotinib-exposed patients, these have a great deal of activity and allow another option for sequential therapy in this population of patients," he said.

Uncommon mutations

Driving mutations of ROS1 are found in about 1%-2% of lung cancers, most often in younger never smokers with adenocarcinomas, according to Dr. Socinski.

'The EGFR mutation story really transformed lung cancer. ... you certainly don't want to ever miss this.'

DR. SOCINSKI

These tumors respond to crizotinib, which is also a ROS1 inhibitor. "In fact I think it may actually be a better ROS1 drug than an ALK drug," he said.

The drug yields an impressive median progression-free survival of 19.2 months and overall response rate of 72% in this setting (N Engl J Med. 2014;371[21]:1963-71), "so ROS1 is another biomarker that we go hunting for in this population, even though you won't see it very commonly."

Mutations of BRAF are found in about 2% of metastatic adenocarcinomas (Cancer. 2015;121[3]:448-456). The large majority, about fourth-fifths, are of the V600E type.

The BRAF inhibitor dabrafenib (Tafinlar) has been associated with an overall response rate of 32% in patients with this specific mutation (abstract LBA38, Ann Oncol. 2014;25[Suppl 4]. doi: 10.1093/annonc/mdu438.46). And preliminary data suggest efficacy increases when it is combined with the Mek inhibitor trametinib (Mekinist) (ASCO 2015. Abstract 8006), as has been seen in melanoma.

About 4% of lung cancers have an intermediate or high level of MET amplification.

In a small sample of patients with these tumors, treatment with crizotinib appeared to be active (ASCO 2014. Abstract 8001). In addition, this agent has efficacy against lung cancers having exon 14 splice mutations in MET (ASCO 2015. Abstract 8021). "So this is another genotype not to miss," Dr. Socinski said.

Finally, mutation of RET is seen about 1%-2% of unselected NSCLCs, also typically in young never smokers or former smokers with adenocarcinoma.

Cabozantinib (Cometriq), a multitargeted TKI having activity against RET, yields a 28% response rate in RET-rearranged adenocarcinomas (ASCO 2015. Abstract 8007).

A controversial topic for these uncommon mutations in lung adenocarcinomas is how much evidence should be required for new targeted agents to gain FDA approval, Dr. Socinski said.

"For instance, the ROS1 experience: Do we really need a randomized trial in a rare genotype to approve this drug [crizotinib] for ROS1-positive patients? I would say, absolutely not," he concluded.

Dr. Socinski disclosed that he receives fees from Celgene and Genentech, and performs contracted research for Celgene, Clovis, Genentech, GlaxoSmithKline, Pfizer, and Synta.

Advances drive staging, classification changes

BY NEIL OSTERWEIL
Frontline Medical News

DENVER – The term "precision medicine" can be applied to both clinical care and to pathology, as newly updated staging and classification systems for lung cancer show.

The proposed revised (8th) edition of the TNM staging system for lung cancer gives more weight to tumor size as a prognostic factor, reclassifies some primary tumor (T) descriptors, validates current nodal status (N) descriptors, modifies the definition of some types of metastases (M), and includes additional stages for better prognostic stratification, reported Dr. Ramón Rami-Porta from the Universitari Mútua Terrassa in Barcelona, at a conference on lung cancer sponsored by the International Association for the Study of Lung Cancer.

Similarly, the updated World Health Organization (WHO) Classification of Lung Tumors, described by Dr. William D. Travis from the Memorial Sloan Kettering Cancer Center in New York, incorporates knowledge gained from immunohistochemistry and molecular testing for common genetic mutations into recommendations for treating the specific clinical circumstances of patients with lung cancer.

WHO's Next

"The 2015 WHO Classification captures a remarkable decade of advances in every lung cancer specialty, from pathology – including histology, cytology, immunohistochemistry, genetics – to oncology, surgery, radiology, and epidemiology. The rapid expansion of immunohistochemical and molecular tools has had a profound impact on how we were able to reclassify a number of tumors, in addition to how we were able to contribute to improvement of subtyping of lung cancers, particularly non–small cell lung cancer," Dr. Travis said at a media briefing following his discussion of the new classification at a plenary session.

The changes are expected to improve clinical management of patients with advanced lung cancer by clarifying criteria and terminology for small biopsies and cytology, establishing more accurate histologic subtyping, suggesting strategic management of small tissues, and streamlining the work flow for molecular testing. The classification also emphasizes the need for multidisciplinary cooperation among myriad clinicians, he said.

For surgically resected patients, the classification officially recognizes for the first time subsets of non–small cell lung cancer of adenocarcinoma histology with survival rates of 100% (adenocarcinoma in situ), or nearly 100% (minimally invasive adenocarcinoma).

Among the major changes that will affect the diagnosis of surgically resected patients are the adoption of the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification, restriction of a diagnosis of large cell carcinoma to tumors lacking clear differentiation by both immunohistochemistry and morphology, reclassifying of squamous cancers into keratinizing, nonkeratinizing, and basaloid subtypes with elimination of clear cell, small cell, and papillary subtypes. Neuroendocrine subtypes are grouped together, but their classification otherwise remains largely unchanged.

'The 2015 WHO Classification captures a remarkable decade of advances.'

DR. TRAVIS

The revised classification is expected to improve prediction of survival and recurrence, predict whether a patient is likely to have a survival benefit with platinum-based chemotherapy, allow radiologic pathologic correlations, and affects TNM staging by emphasizing solid tumor size (vs. whole tumor size), Dr. Travis said.

TNM Changes

The proposed changes to the TNM tumor staging have been submitted for approval to the American Joint Committee on Cancer and the Union for International Cancer Control.

If adopted, they would represent the first significant changes since the 7th edition's publication in 2009. The changes are based on data on more than 77,000 patients diagnosed with lung cancer from 1999 through 2010.

The proposed changes are not intended, however, to alter clinical practice, and instead "imply a taxonomic refinement rather than new indications of already established treatment protocols," Dr. Rami-Porta said.

In some cases, the proposed changes would result in an upgrading of the T stage, while others would result in downgrading. For example, tumors that range in size between 1 and 2 cm, designated T1a in the 7th edition, would be T1b in the 8th edition. Similarly, tumors larger than 2 cm and up to 3 cm would be upgraded from T1b to T1c, those larger than 4 up to 5 would go from T2a to T2b, those larger 5 and up to 7 cm would rise from T2b to T3, and those larger than 7 cm would be reclassified from T3 to T4. Tumors invading the diaphragm would also be upgraded from T3 to T4 under the proposed revisions.

The changes 'imply a taxonomic refinement rather than new indications' of established protocols.

DR. RAMI-PORTA

In contrast, tumors with limited invasion of the trachea (bronchus less than 2 cm from the carina) would be downgraded from T3 to T2, as would tumors associated with total atelectasis and/or pneumonitis.

The current N descriptors are adequate for predicting prognosis, the investigators determined, prompting the recommendation to retain them in the new edition.

The investigators propose slight changes to the M descriptors of metastases. Although they found no significant differences in survival among patients with M1a (metastases within the chest cavity) descriptors, when distant metastases outside the chest cavity (M1b) were assessed by the number of metastases, they found that patients with tumors with one metastasis in one organ had significantly better outcomes than those who had multiple metastases in one or more organs.

The proposed revision would continue to group in the M1a category cases with pleural/pericardial effusions, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or a combination of multiple parameters. However, single metastatic lesions in a single distant organ would be reclassified as M1b, and multiple lesions in a single organ or multiple lesions in multiple organs would be reclassified as M1c.

Recent quitters win big in lung screening trials

BY NEIL OSTERWEIL
Frontline Medical News

DENVER – It's never too late to quit smoking, results of lung cancer screening trials confirmed.

Among more than 3,300 heavy smokers over age 50 who took part in two low-dose CT (LDCT) screening programs, former smokers had a 37% reduction in all-cause mortality, compared with current smokers, and those who were active smokers at the time of randomization but quit during the follow-up period had a 43% lower risk for death, compared with those who continued to smoke, reported Dr. Ugo Pastorino of the Instituto Nazionale dei Tumori in Milan.

The take-home message is, 'Help people stop smoking, because you cure lots of people and save many lives.'

DR. YAMAGUCHI

He noted that the U.S. National Lung Screening Trial (NLST) showed that screening with low-dose helical CT was associated with a nearly 7% reduction in all-cause mortality over a 7-year follow-up period, compared with patients screened with chest x-ray.

"But we have to keep clear in our minds that the benefit achieved by this trial of early detection in terms of mortality reduction is only 1% per year, so it's a not a major improvement.

"It's a start, but we have to aim to improve this mortality reduction," Dr. Pastorino said at a conference sponsored by the International Association for the Study of Lung Cancer.

Neither the NLST nor other randomized screening trials currently underway have examined in detail the effects of smoking status on screening outcomes, prompting Dr. Pastorino and his colleagues to investigate the matter in two cohorts of smokers assigned to LDCT in screening trials.

VITALS

Key clinical point: Quitting smoking results in a significant reduction in all-cause mortality among heavy smokers taking part in screening programs.

Major finding: Compared with current smokers, the relative risk for all-cause mortality among ex-smokers or recent quitters was 0.74

Data source: Data on two cohorts totaling 3,381 current or ex-smokers assigned to low-dose CT lung screening.

Disclosures: The study was supported by the Italian Ministry of Health.

The study included 3,381 heavy smokers with a median follow-up of 9.7 years and a total follow-up of 32,858 person-years.

Men comprised 69% of the combined cohorts, who had a median age of 58 and a median smoking history of 40 pack-years.

The investigators divided the participants into current smokers – those who continued to smoke throughout the screening period, or if they quit did so within 1 year of the end of follow-up or death – and former smokers, subdivided into early quitters, who had stopped smoking by the time of accrual, and late quitters, who were active smokers at the time of accrual or randomization but stopped smoking at least 1 year before the end of the follow-up period or at least 1 year before death.

In an analysis of the effects of smoking on mortality, controlled for sex, age, body mass index, lung function, and pack-years smoked, the investigators found that the relative risk for death from any cause among both early and late quitters, compared with current smokers, was 0.74.

When they excluded 239 quitters who had kicked the habit less than 2 years before the end of follow-up or death, the benefits of not smoking were even greater, with a relative risk of 0.61.

Interestingly, when they looked at the early quitters, compared with current smokers, the RR for quitting was 0.63, and the effect appeared even stronger among more recent (late) quitters, who had an RR for all-cause mortality of 0.57, compared with current smokers. (All comparisons were significant as shown by 95% confidence intervals.)

Former smokers had a 37% reduction in all-cause mortality, compared with current smokers in the trials.

DR. PASTORINO

Also of note was the fact that lung cancer accounted for fewer than 30% of deaths, Dr. Pastorino noted.

Dr. Nise H. Yamaguchi of the Hospital Israelita Albert Enstein in Sao Paolo applauded Dr. Pastorino and his colleagues for the study, and succinctly summarized the take-home message.

"If you came here from all around the world to see all these fancy treatments and everything that you can't do, go back home and help people stop smoking, because you cure lots of people and save many lives for sure," she said.

Share of lung cancer patients who never smoked is rising

BY SUSAN LONDON
Frontline Medical News

DENVER – An increasing share of patients with lung cancer report that they have never smoked, according to a pair of retrospective cohort studies reported at a world conference on lung cancer.

At three U.S. institutions serving geographically and racially diverse populations, the proportion of never smokers rose from 9% to 15% over a 24-year period among patients with non–small cell lung cancer (NSCLC), but did not change among those with small-cell lung cancer (SCLC). At a U.K. tertiary care institution, the proportion of never smokers rose from 13% to 27% over a 7-year period among patients undergoing surgery for lung cancer.

Data further suggested that these trends were due at least in part to an increase in the absolute number of never smokers with lung cancer, and not simply to a decline in the proportion of smokers with lung cancer, or to earlier, incidental detection of tumors resulting from better imaging technology.

More research will be needed to determine the specific factors driving this increase, according to Dr. Everett E. Vokes, cochair of the conference, moderator of a related press conference, and the John E. Ultmann Professor and Chair, department of medicine, University of Chicago.

"What is causing this, for me, would be very, very speculative," Dr. Vokes said. "Secondhand smoke is still there, and radon is mentioned. That shouldn't necessarily justify an increase, because those are either constant or also decreasing [like smoking]. And of course it could be pollution and factors that have to do with small particles and carcinogens in the air."

More research will be needed to determine the specific factors driving this increase.

DR. VOKES

In the first study, investigators led by Dr. Lorraine Pelosof of the University of Texas Southwestern Medical Center in Dallas used registries at three institutions – Southwestern Medical Center, Parkland Hospital in Dallas, and Vanderbilt University in Nashville, Tenn. – to identify patients who were diagnosed with lung cancer between 1990 and 2013.

Analyses were based on 10,593 patients with NSCLC and 1,510 patients with SCLC.

The latter serve as an internal control given cancer's tight link with smoking, Dr. Pelosof noted.

In adjusted analyses, the proportion in the NSCLC group who reported never smoking increased from 9% to 15% during the study period (*P* less than .0001). In contrast, the proportion in the SCLC group held steady at roughly 2%.

Among patients with NSCLC, never smokers were on average younger and more likely to be female, compared with smokers, Dr. Pelosof reported at the conference, which was sponsored by the International Association for the Study of Lung Cancer.

In teasing out the cause for the rise in never smokers with NSCLC, analyses showed that the absolute numbers of patients with NSCLC increased during the study period.

Preliminary data suggested that earlier, incidental detection did not explain the trend, as rates of

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stage I, II, and III disease in never smokers were stable or decreased, while the rate of stage IV disease increased.

In addition, the trend did not appear to be explained by an influx to the institutions of patients with mutations seeking targeted therapies on clinical trials, as the trend persisted after adjustment for race/ethnicity, which was used as a surrogate for mutational status.

The investigators plan several avenues of additional research to sort this out, Dr. Pelosof said.

"We want to look at possibly other institutions that are geographically and demographically diverse. Additional institutions would be helpful," she said. "And then to get at some of the mechanisms, [looking at] mutational status and biology I think would be very important."

In the second study, Dr. Eric Lim, a consultant thoracic surgeon at Royal Brompton Hospital, and a senior lecturer and reader in thoracic surgery at the National Heart and Lung Institute, Imperial College, London, and his colleagues assessed smoking status among 2,170 pa-

'To get at some of the mechanisms, [looking at] mutational status and biology I think would be very important.'

DR. PELOSOF

tients who underwent surgery for lung cancer at the hospital between 2008 and 2014.

Overall, 20% of the patients in the cohort were never smokers. Their mean age at presentation was 60 years, and two-thirds were women.

The predominant tumor types were adenocarcinoma, seen in 54%, and carcinoid, seen in 27%.

The proportion who were never smokers more than doubled during the study period, from 13% to 27%. The absolute annual number of such patients also rose, from about 60 to nearly 100.

Fully 52% of the never smokers presented with only nonspecific symptoms of cough or chest infection, while 11% had hemoptysis.

In the remaining 36%, the cancer was identified as an incidental finding on imaging done for other reasons.

"Nonsmoking lung cancer is increasing and now a significant proportion of the workload for surgeons across the United Kingdom," concluded Dr. Lim. "Early detection in this group is challenging because they have no clear-cut symptoms, and serious symptoms were only present in a minority," he said.

'Early detection in this group [of nonsmokers] is challenging because they have no clear-cut symptoms.'

DR. LIM

"Clearly it's not going to be cost effective to screen the entire population of nonsmokers for lung cancer," he added. Since these patients "do not have established risk factors, research into early detection, ideally by noninvasive or molecular screening, is urgently required to identify early lung cancer in nonsmokers."

Dr. Pelosof and Dr. Lim reported having no relevant financial conflicts of interest.

IOM: Teamwork key to reducing diagnostic errors

BY JULIE APPLEBY
Kaiser Health News

WASHINGTON – Almost every American will experience a medical diagnostic error, but the problem has taken a back seat to other patient safety concerns, an Institute of Medicine panel said in a report calling for widespread changes.

Diagnostic errors – defined as inaccurate or delayed diagnoses – account for an estimated 10% of patient deaths, hundreds of thousands of adverse events in hospitals each year, and are a leading cause of paid medical malpractice claims, according to the report.

Such errors can occur with very rare conditions, such as the Liberian man with undetected Ebola who was sent home from a Dallas hospital last September; or more common problems, such as acid reflux being

mistaken for a heart attack or a pathology report showing cancer that is never communicated to a patient.

Still, reducing the number won't be easy, in part because there is no required way to track such errors. Reversing current trends will require better teamwork, training, and computer systems, according to the report.

"Some people go to their graves with a diagnostic error that is never detected," said committee member Robert A. Berenson, a research fellow at the Urban Institute in Washington. "It's much more difficult to measure than a medication error."

The report, called "Improving Diagnosis in Health Care," is the latest in a series launched 15 years ago with "To Err Is Human: Building a Safer Health System," which fueled the patient-safety movement with its estimate that as many as 98,000 patients die each year because of medical errors.

This report has a role for just about everyone in the health system, from computer programmers to clinicians to patients. It recommends better teamwork among health care providers, patients, and families. Citing the dearth of data about diagnostic errors, the report calls for voluntary efforts to report such problems. Dedicated funding is needed for research, the report says, and hospitals and doctors need to

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develop better ways to identify, reduce, and learn from "near misses."

The report notes that computerized health records, which can help track and coordinate care, can also become a barrier to efficient and correct diagnoses. The systems, it says, often aren't compatible from one physician's office to another or among hospitals, "auto-fill" functions sometimes result in the wrong information being entered, and the sheer volume of inputs and alerts can overwhelm medical staff.

'Some people go to their graves with a diagnostic error that is never detected. It's much more difficult to measure than a medication error.'

It cites a study of emergency department staff that found clinicians spent more time inputting information into computers than taking care of patients. Another study found that while EHR systems provide alerts in response to abnormal test results, 70% of medical staff said they receive more alerts than they can manage.

Making the systems more efficient and allowing patients more timely access to their own medical records to check for and correct errors "could be a game changer," said Berenson.

Indeed, patients "are going to be critical to the solution," said Dr. Michael Cohen, another report author and a professor of pathology at the University of Utah, Salt Lake City. "There's a real opportunity for patients to advocate for themselves and at the same time to challenge the health care providers about the diagnosis being made."

Helen Haskell, who formed Mothers Against Medical Error after her 15-year-old son died as the result of a medical error, said she was pleased the report focused on better teamwork and communication. She also said patients need better access to their records – particularly hospital records – and said consumers should always ask questions.

"What else can it be? Does this diagnosis match all my symptoms?" are two of the best questions to ask, said Haskell. "If there is any question, people should get a second opinion."

Kaiser Health News is a nonprofit national health policy news service that is part of the Henry J. Kaiser Family Foundation.

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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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, post menopausal 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 SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSAGE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications 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.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg N =124 %	80 mcg N =121 %	160 mcg N = 109 %	4.5 mcg N = 237 %	N = 400 %
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	160/4.5 mcg N = 771 %	160 mcg N = 275 %	4.5 mcg N = 779 %	N = 781 %
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

ICU care improves survival without increasing costs

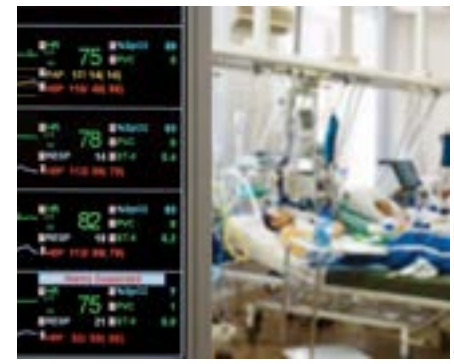
BY MARY ANN MOON
Frontline Medical News

Compared with care on a general hospital ward, ICU care improved survival without raising costs significantly in a study of more than 1 million Medicare patients hospitalized with pneumonia.

The retrospective cohort study involved older patients whose condition was considered "borderline" – not one that would clearly benefit from ICU admission but also not one for which ICU admission could clearly be ruled out.

The decision of whether to admit these study participants to a general ward or an ICU was deemed discretionary. "Contrary to [our] prespecified hypothesis, [our] findings suggest that ICU admission for borderline patients … is associated with reduced mortality without a considerable increase in costs," said Dr. Thomas S. Valley of the division of pulmonary and critical care medicine, University of Michigan, Ann Arbor, and his associates.

The investigators analyzed data from the American Hospital Association's annual surveys and the Healthcare Cost Reporting Information Systems regarding 1,327,370 Medicare patients admitted to 2,988 hospitals across the country during a recent 2-year period. A total of 328,404 patients (29.5% of the study population) were admitted to ICUs and the remainder to general hospital wards.



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After the data were adjusted to account for numerous patient, disease, and hospital variables, ICU admission was associated with significantly lower 30-day mortality (14.8%), compared with general ward admission (20.5%) – an absolute reduction of 5.7%. Yet the differences between the two groups were nonsignificant regarding payments by Medicare ($9,918 for ICU vs. $11,238 for general ward care) and hospital costs ($14,162 for ICU vs. $11,320 for general ward care).

These findings were consistent across numerous sensitivity analyses, including some that compared urban against rural hospitals, white against nonwhite patients, small against large ICUs, and severely ill against less severely ill patients, Dr. Valley and his associates said (JAMA. 2015 Sep 22;314[12]:1272-79. doi: 10.1001.jama.2015.11068).

There are several reasons why ICU care might be beneficial for "borderline" patients with pneumonia: Greater attention from nurses and other clinicians could allow for more timely recognition of decompensation, more aggressive care is more likely to head off the development of sepsis, better adherence to guide-

Continued on following page

Value-based care poses new legal risks for doctors

BY ALICIA GALLEGOS
Frontline Medical News

The government's push toward value-based care aims to fix a broken reimbursement system and improve quality of care for patients. But the new payment models also bring new legal risks for physicians, experts and antifraud officials warned.

"Novel payment methodologies may present new program integrity vulnerabilities," Dr. Shantanu Agrawal, director of the center for program integrity at the Centers for Medicare & Medicaid Services, said at an American Bar Association meeting. "As they assume financial risk, providers are also assuming program integrity risk. Without adequate controls, provider-run systems may be relatively vulnerable."

The Department of Health & Human Services plans to have 30% of Medicare payments in value-based payment structures by the end of 2016, and 50% by the end of 2018. The transition will be driven through investments in alternative payment models such as Accountable Care Organizations (ACOs), advanced primary care medical home models, bundled payments models, and integrated care demonstrations for Medicare and Medicaid patients.

At the end of 2014, value-based payments represented 20% of Medicare fee-for-service payments to providers, according to CMS data. The rate was fueled by government programs such as the Medicare Shared Savings Program (MSSP), Pioneer ACOs, the Bundled Payments for Care Improvement Initiative, and the Comprehensive Primary Care Initiative. Meanwhile, HHS is encouraging private payers, marketplace plans, Medicare Advantage plans, and state Medicaid programs to move in the same value-based direction.

With so many new regulations, mandates, and programs coming down the pipeline, physicians are likely not thinking about the legal dangers that may arise with alternative payment structures, said Mark S. Kopson, a health law attorney in Bloomfield Hills, Mich., and chair of the American Health Lawyers Association's Payers, Plans, and Managed Care Practice Group.

Fee-for-service models can involve claims "about excess treatments and unnecessary services to drive up reimbursement," Mr. Kopson said in an interview. "When you get into these [value-based] types of programs, it's the exact opposite. The real threat is the withholding of necessary care in order to reduce expenses and therefore drive up those margins for the providers."

To avoid such claims, physicians should ensure that their charts include the reasoning behind treatment decisions and a thorough record of why certain treatments were chosen and diagnoses were made, Mr. Kopson advised.

"Going forward, your charting better be completely accurate and detailed so that you don't leave room for the government to make an argument that you should have provided this or that additional treatment," he said.

Inaccurate reporting of enrollment data or financial information within new payment models could also land doctors in legal trouble, according to CMS officials.

Problematic reports, enrollee data, or other information physicians are required to submit to the government could be considered falsification and lead to False Claims Act violations.

"Providers are responsible for the information reported and should ensure that the appropriate checks and balances are in place that verify data is reported timely and accurately," Tony A. Salters, a CMS spokesman, said in an interview. "For some models, providers must attest to the accuracy of this data. [To] report inaccurately could result in violations of federal laws."

ALICIA GALLEGOS/FRONTLINE MEDICAL NEWS

Dr. Shantanu Agrawal, director of the CMS center for program integrity, said, "Without adequate controls, provider-run systems may be relatively vulnerable."

Physician-run payment models, such as doctor-led ACOs, may also draw legal scrutiny if physicians fail to prevent bad behavior by de facto partners. Physicians must ensure that all costs claimed by subcontractors, other providers, and suppliers who are paid from or authorized by the provider-run system, have been validated, Mr. Salters said.

"Doctors need to be aware that other entities who become new partners should hold themselves to the same high standards," he said. "Providers should have basic financial mechanisms in place, with more sophisticated systems requiring more sophisticated methods," to ensure validation.

CMS officials recommend doctors conduct independent audits of their accounts, manual validation of record system accuracy, and periodic verification of subcontractor claims to confirm the accuracy of claims and costs within new payment models.

These are "all routine steps that practitioners can take in their own offices but which are even more important when the doctor assumes responsibility for a larger scope of services," Mr. Salters said.

Gaps in documentation surrounding bundled payments can be another legal land mine, Mr. Kopson noted. Adequate records of the care spectrum are essential to prevent accusations that care was not provided during a single episode of care, or over a specific period of time.

"You have to capture and document all the services you are delivering, and have accurate tracking in place for the entire continuum of care," Mr. Kopson said.

The CMS recommends that physicians establish a strong compliance program to assist with antifraud controls of new payment systems. When creating or updating a compliance program, government officials said providers should consider the unique characteristics of the model in which they participate.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Continued from previous page

line-based treatment is known to improve mortality, and a greater likelihood of being managed by a pulmonary or critical care specialist with greater expertise in pneumonia care should improve outcomes, the researchers noted.

Their study findings have important implications for health care reform. "In order to contain U.S. health care costs, it has been suggested that reducing critical care bed supply would result in more efficient admission decisions and cost savings with minimal mortality decrements," Dr. Valley and his associates said. This "presumes that ICU admission for discretionary patients provides minimal benefit but substantially increases costs." The results of this study clearly refute that assumption, they said.

VIEW ON THE NEWS

This study provides important empirical evidence that ICU admission can benefit "low-risk" patients. It demonstrates that the value of intensive care extends beyond mere life support for patients with an acutely failing organ and instead includes all the organizational and human resources that comprise an ICU.

It would be tempting to use these results to justify more liberal ICU admission, but that would be untenable in this era of constrained health care resources. Rather than increasing ICU use, we should make general wards function more like ICUs. The task at hand is to study why intensive care saves lives, then use that information to make hospital care safe and effective for all patients, regardless of where in the hospital they are cared for.

Dr. Ian J. Barbash is in the division of pulmonary, allergy, and critical care medicine at the University of Pittsburgh. Dr. Jeremy M. Kahn is in the department of health policy and management at the university's Graduate School of Public Health. Both Dr. Barbash and Dr. Kahn are also at the university's Clinical Research, Investigation, and Systems Modeling of Acute Illness Center. *Both authors reported having no relevant financial disclosures. They made these remarks in an editorial accompanying Dr. Valley's report (JAMA. 2015;314:1240-41. doi: 10.1001/jama.2015.11171).*

Reduce lung function decline

Delay IPF progression with Esbriet

Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had ≥10% decline in %FVC, $P<0.001$). Treatment effect was evident at 13 weeks ($P<0.001$) and increased through trial duration[1,2,*,†]
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)[2,*,‡]
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet[2]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[3]

Learn more about Esbriet and how to access medication at Esbriet.com.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.
‡Stable was defined as no decline in lung function.

References: 1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

Genentech
A Member of the Roche Group

Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

ESBRIET® (pirfenidone)

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information],* which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

INTERMUNE®

Medicare hospital-related mortality down

BY RICHARD FRANKI
Frontline Medical News

Several measures of mortality declined among hospitalized Medicare fee-for-service beneficiaries from 1999 to 2013, a study showed.

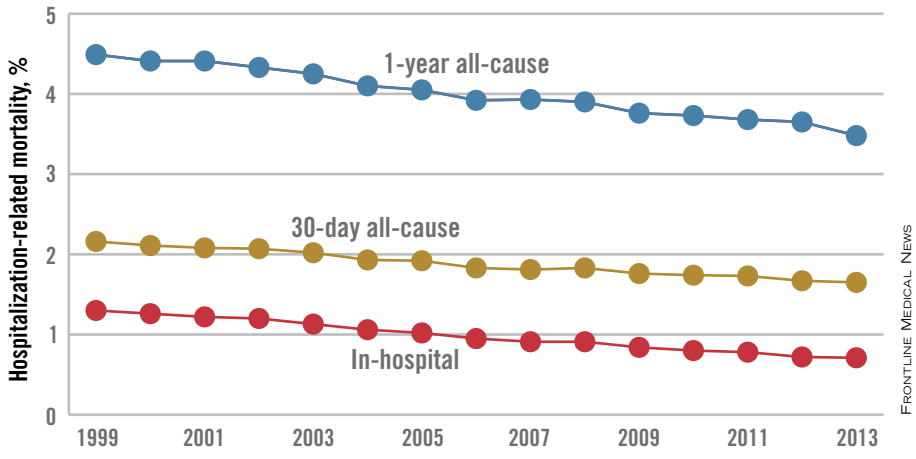
Over that time period, in-hospital mortality dropped from 1.3% to 0.71%. Meanwhile, 30-day mortality declined from 2.16% in 1999 to 1.65% in 2013, and 1-year mortality slipped from 4.49% to 3.48% among 60,056,069 individuals aged 65 years or older who were enrolled in a Medicare fee-for-service plan for at least 1 month over the study period, reported Dr. Harlan M. Krumholz of Yale University, New Haven, Conn., and his associates.

The decline in mortality was accompanied by a drop in the number of hospitalizations, which went from more than 35,000/100,000 person-years of enrollment in 1999 to just under 27,000 in 2013. The number of beneficiaries admitted to the hospital at least once went down as well, from almost 22,000/100,000 person-years to more than 17,000, as did the number of hospitalizations that involved major surgery: 3,784/100,000 person-years in 1999 and 3,105 in 2013 (JAMA 2015;314:355-65).

Dr. Krumholz is supported by a grant from the National Heart, Lung, and Blood Institute.

rfranki@frontlinemedcom.com

Mortality among hospitalized Medicare beneficiaries, 1999-2013



Note: Based on data for 60,056,069 beneficiaries aged 65 years or older who were enrolled in the Medicare fee-for-service program for at least 1 month from 1999 to 2013.
Source: JAMA 2015;314:355-65

Most physicians still work in small practices

BY RICHARD FRANKI
Frontline Medical News

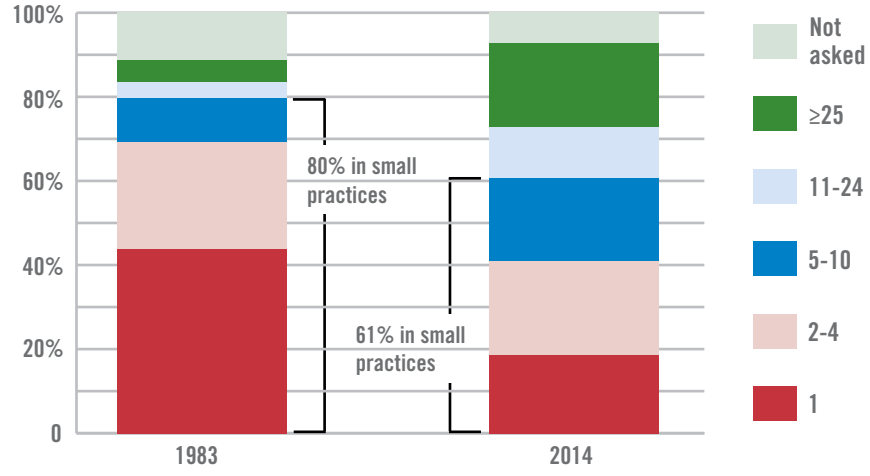
While medical practice arrangements seem to have changed dramatically over the last 30 years, the majority of physicians still work in small practices, the American Medical Association reported.

In a 2014 AMA survey, almost 61% of respondents worked in practices of 10 or fewer physicians. That's down from the 80% reported by the AMA in 1983, but it still qualifies as a majority. Over that same period, the proportion of physicians working in practices of 25 or more increased from 5% to 20%.

These changes in practice size were related to changes in practice ownership, the AMA noted. In 1983, the percentage of physicians who were the owners of their practices was 76%. In 2014, that number was 51%.

Looking at short-term data comparing the 2014 survey with one from 2012, the AMA found that the "share of physicians who worked directly for a hospital or in practices that were at least partially owned by a hospital increased from 29% in 2012 to 32.8% in 2014. Over that 2-year period, the share of physicians who were directly employed by a hospital increased from 5.6% to 7.2%, while the percentage of physicians who were in solo practice decreased from 18.4% to 17.1%."

Physician distribution by practice size (number of physicians)



Note: Based on data from the AMA's Physician Practice Benchmark Survey (2014) and Socioeconomic Monitoring System Survey (1983).
Source: American Medical Association

Task force proposes to replace ABIM's 10-year MOC exam

BY ALICIA GALLEGOS
Frontline Medical News

A task force convened by the American Board of Internal Medicine has proposed replacing the board's 10-year Maintenance of Certification exam with more meaningful assessments and exploring certification in specialized areas.

The Assessment 2020 Task Force, which convened in 2013 to evaluate the ABIM Maintenance of Certification (MOC) program, released its proposals in a report that aims to inform ongoing redesign of ABIM's Certification and MOC programs, according to Dr. Richard J. Baron, ABIM president and CEO.

The independent task force includes representatives from ABIM leadership and experts in assessment, education, health care, and consumer advocacy. The task force recommends that ABIM focus MOC assessments on cognitive and technical skills, recognize specialization, and consider certification in specialized areas without requiring maintenance of underlying certificates. On that final recommendation, ABIM has already started such changes. In July, the board announced that no disciplines within its MOC program will require underlying certification and that all diplomates can choose the certifications they wish to maintain.

The task force also recommends that ABIM replace its 10-year secure exam with more frequent assessments. The assessments could be taken in a secure setting – possibly at home with remote authentication – with the potential for some portion to be open book but still timed.

"The Assessment 2020 Task Force members provided useful insights and recommendations that will be instrumental as we reshape certification to meet physicians' and society's changing needs," Dr. Clarence H. Braddock III, chair of the ABIM board of directors, said in a statement. "We now need to hear constructive feedback from the internal medicine community on these recommendations, begin to determine their feasibility and develop implementation plans where needed."

Dr. Wayne J. Riley, president of the American College of Physicians, said the college is hopeful that the new report will lead to positive changes that raise the MOC's relevance and value to physicians and patients. "We remain committed to advocating for substantial and meaningful reforms to the ABIM MOC program," he said in an interview.

agallegos@frontlinemedcom.com
On Twitter @legal_med

BREO ELLIPTA 100/25—Improves lung function, and also reduces exacerbations in patients with a history of exacerbations

Indications

- BREO 100/25 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 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 is the only strength indicated for COPD.
- BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information for BREO 100/25 for COPD

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

CONTRAINDICATIONS

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO 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.

Please see additional Important Safety Information for BREO 100/25 throughout this advertisement.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO 100/25 on the pages following this advertisement.

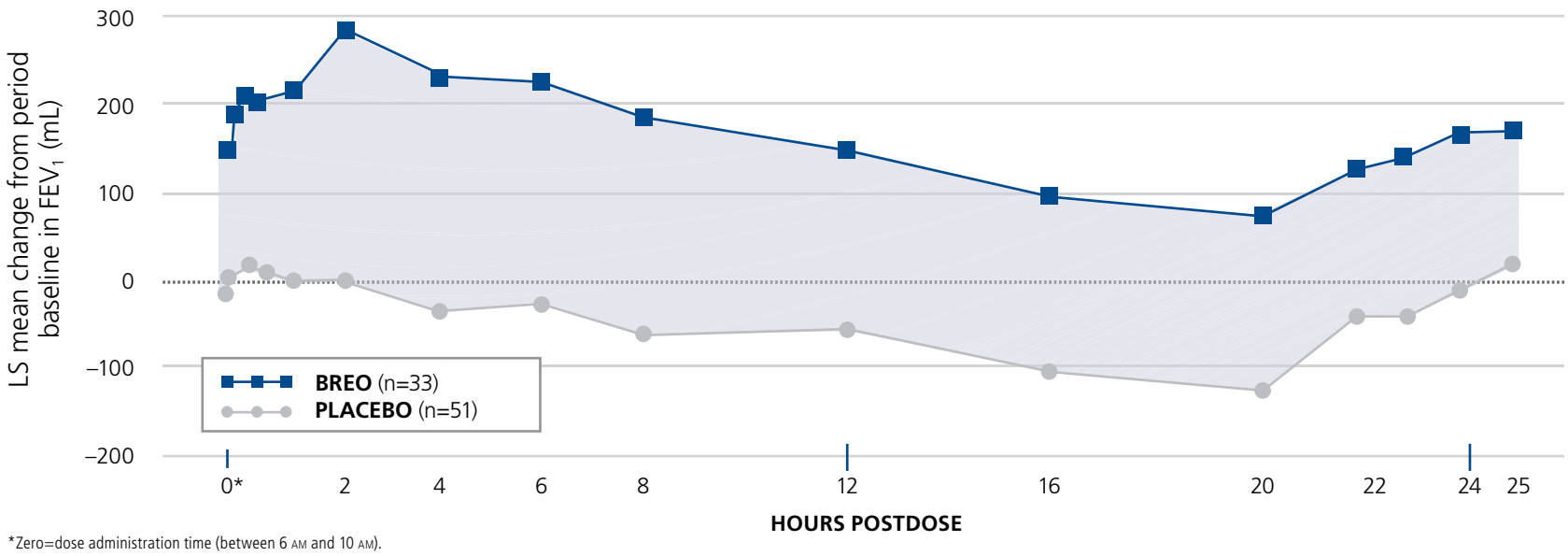
gsk | Theravance

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

24-hour BREO 100/25 provided sustained improvement in lung function

Primary endpoint: BREO 100/25 provided a 220 mL improvement in weighted mean FEV_1 (0-24 hours) from period baseline vs placebo ($P<0.001$) at end of the 28-day treatment period[1]

SECONDARY ENDPOINT: SERIAL FEV_1 (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29[1,2]



*Zero=dose administration time (between 6 AM and 10 AM).
FEV_1=forced expiratory volume in 1 second; LS=least squares.

A multicenter, randomized, double-blind, placebo-controlled, crossover study evaluated the effect of 28 days of treatment with BREO 100/25 on lung function over 24 hours in 54 patients (mean age: 57.9 years) with COPD.† The primary endpoint was weighted mean FEV_1 (0-24 hours) at the end of the 28-day treatment period (period Days 28 and 29). This was calculated from predose FEV_1 (mean of –30- and –5-minute measurements) and postdose FEV_1 after 5, 15, 30, and 60 minutes and 2, 4, 6, 8, 12, 16, 20, 22, 23, and 24 hours. The secondary endpoint was serial FEV_1 (0-25 hours) at period Days 28 and 29.

†At screening, patients had a mean postbronchodilator % predicted FEV_1 of 49.8%, a mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio of 52.9%, and a mean % reversibility of 8.8%.

In a separate 6-month lung-function study: a multicenter, randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs fluticasone furoate (FF) 100 mcg and vs placebo (each administered once daily by the ELLIPTA inhaler) on lung function in 1030 patients (mean age: 62.7 years) with COPD.‡ For the co-primary endpoints, BREO significantly improved weighted mean FEV_1 (0-4 hours) postdose on Day 168 by 120 mL vs FF§ and 173 mL vs placebo ($P<0.001$ for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV_1 at Day 169 of 115 mL vs placebo (95% confidence interval [CI]: 60, 169; $P<0.001$); the 48 mL difference vs vilanterol (VI) 25 mcg‖ did not achieve statistical significance (95% CI: –6, 102; $P=0.082$).[2,3]

‡At screening, patients had a mean postbronchodilator % predicted FEV_1 of 48.3%, a mean postbronchodilator FEV_1/FVC ratio of 47.6%, and a mean % reversibility of 15.9%.
§The weighted mean comparison of BREO with FF, the ICS component, was assessed to evaluate the contribution of VI to BREO. ICSs are not approved as monotherapy for COPD.
‖The trough FEV_1 comparison of BREO with VI, the LABA component, was assessed to evaluate the contribution of FF to BREO. Vilanterol is not approved as monotherapy.

Important Safety Information for BREO 100/25 for COPD (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications 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 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. Advise patients to rinse the mouth with water 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. 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 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (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 100/25 and in 7 subjects receiving BREO 200/25 (<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.

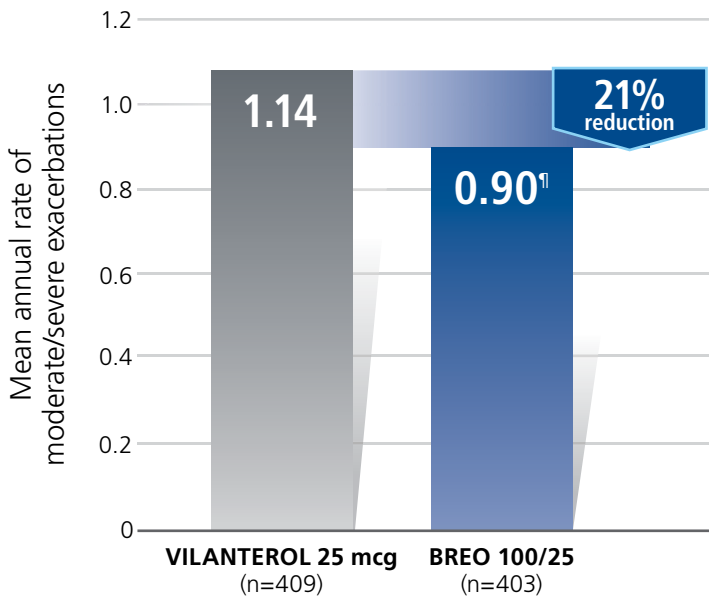
WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- 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 slowly.
- Caution should be exercised when considering the coadministration of BREO 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 and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- 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 may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

In patients with a history of exacerbations

BREO 100/25 significantly reduced the annual rate of moderate/severe COPD exacerbations

PRIMARY ENDPOINT: ANNUAL RATE OF MODERATE/SEVERE EXACERBATIONS[2,4]



¶*P*=0.024

Study description

Design: 12-month, multicenter, randomized, double-blind, parallel-group study that evaluated the effect of BREO 100/25, BREO 200/25,# FF/VI 50/25, and VI 25 mcg** (each administered once daily by the ELLIPTA inhaler) on the rate of moderate/severe exacerbations. Patients were randomized to treatment following a 4-week run-in on fluticasone propionate 250 mcg/salmeterol 50 mcg twice daily.

Patients: 1633 patients (mean age: 63.7 years) with COPD and a history of one or more moderate or severe exacerbations in the previous year. At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 45.7% and a mean postbronchodilator FEV_1/FVC ratio of 45.5%.

COPD exacerbation criteria: exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or 1 major symptom together with 1 minor symptom: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days.

Exacerbation severity criteria: exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required, and were considered to be severe if hospitalization was required.

#BREO 100/25 is the only strength approved for COPD.
**Vilanterol is the LABA component of BREO and is not approved as monotherapy.

Important Safety Information for BREO 100/25 for COPD (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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 and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma 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

- In subjects with COPD, the most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO 100/25 (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 100/25 in two 1-year COPD studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO 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 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 or asthma.
- 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 with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

References: 1. Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther.* 2012;34(8):1655-1666. **2.** Data on file, GSK. **3.** Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. *Respir Med.* 2013;107(4):560-569. **4.** Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med.* 2013;1(3):210-223.

Please see additional Important Safety Information for BREO 100/25 throughout this advertisement.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO 100/25 on the pages following this advertisement.

www.BREO-copd.com

BREO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the COPD indication. See full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, 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. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. *[see Warnings and Precautions (5.1) of full prescribing information]*.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease BREO 100/25 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 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.

Important Limitation of Use

BREO is NOT indicated for the relief of acute bronchospasm

4 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 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 reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO 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, 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, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists BREO 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 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. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may need to be interrupted. Advise the patient to rinse his/her mouth with water 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 BREO 100/25 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 fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 6% (51 of 806 subjects); or BREO 200/25: 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 BREO 100/25 and in 7 subjects receiving BREO 200/25 (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 may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe COPD exacerbation, or a severe asthma attack, 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, a severe COPD exacerbation, or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma 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 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, 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 doses of BREO. 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 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 should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO 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)]*.

5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions, Including Anaphylaxis Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO *[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 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. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, 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 and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma 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.

5.15 Coexisting Conditions BREO, 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 clinical trials evaluating BREO in subjects with COPD or asthma, 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, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA *[See Warnings and Precautions (5.1) of full prescribing information.]*

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*

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.

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease The clinical program for BREO 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 with COPD received at least 1 dose of BREO 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- 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 100/25 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 white. 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 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 1. Adverse Reactions with BREO 100/25 with ≥3% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BREO 100/25 (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 oral candidiasis, oropharyngeal candidiasis, candidiasis, and fungal oropharyngitis.

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 white. 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 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions shown in Table 1, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO 100/25 (n = 806) for 12 months included back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

6.3 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.

Cardiac Disorders Palpitations, tachycardia.

Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

Musculoskeletal and Connective Tissue Disorders Muscle spasms.

Nervous System Disorders Tremor.

Psychiatric Disorders Nervousness.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO 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), 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, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma 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 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 reproduction studies are not always predictive of human response, BREO 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.

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 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 4 and 1 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 1 time 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 during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, BREO 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 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 in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of BREO 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 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 less than 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.

BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO 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 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., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, 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.

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 with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death.

Not for Acute Symptoms

Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

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

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting $Beta_2$-Agonists

Instruct patients not to use other LABA for COPD and asthma.

Local Effects

Inform patients 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, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects

Inform patients that long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

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.

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Docs could face faster false-payments return demands

BY ALICIA GALLEGOS
Frontline Medical News

In a novel decision, the U.S. District Court for the Southern District of New York has ruled that the 60-day clock to return overpayments to the government begins ticking when a health provider receives notice a potential overpayment exists, not when an overpayment is conclusively ascertained.

Doctors should be concerned about the ruling, said Houston health law attorney Michael E. Clark, immediate past chair for the American Bar Association Health Law Section.

"This is a very troubling development because the judge has embraced the theory that certainty is not required as to what constitutes an identified overpayment," Mr. Clark said in an interview. "Rather, knowledge can be established by recklessness under the facts. In short, practitioners must set up systems to alert them about potential overpayments so they can move quickly to avoid potentially ruinous False Claims Act liability."

The Aug. 3 ruling in *Kane v. Healthfirst* is the first published decision to address the 60-day overpayment rule imposed under the Affordable Care Act and the Fraud Enforcement and Recovery Act (FERA). The rule requires that an overpayment be reported and returned by health providers within 60 days of the "date on which the overpayment was identified." Health providers who retain an overpayment beyond that point are subject to liability under the False Claims Act (FCA).

In the *Kane* case, the federal government contends that three hospitals operated by Continuum Health Partners failed to report and return overpayments to Medicaid within 60 days of identification. Because of a computer glitch, Continuum billed both the government and a managed care organization for the same services, according to court documents. After the New York State Comptroller's Office alerted Continuum to a possible overbilling, Continuum hired an employee, Robert P. Kane, to conduct an internal investigation into its billing. Mr. Kane – who was later fired – allegedly found 900 potentially improper Medicaid claims totaling $1 million, according to court documents. The government claims Continuum failed to repay the overpayments within 60 days and instead repaid only "small batches" of the affected claims over the next 2 years. Mr. Kane filed a whistleblower suit against Continuum, and the government intervened as a plaintiff.

The judge ruled 'that certainty is not required as to what constitutes an identified overpayment.'

MR. CLARK

But Continuum argued that the hospitals did not knowingly conceal the overpayments from the government, and that the overbillings had not been officially "identified." The defendants were provided only notice of potential overpayments and did not identify actual overpayments so as to trigger the 60-day report and return clock, Continuum said in court documents. The health system requested the court throw out the government's suit for lack of merit.

District Judge Edgardo Ramos agreed with the federal government and allowed the lawsuit to continue. Judge Ramos said the legislative history indicates that Congress intended for FCA liability to attach in circumstances where there is an established duty to pay money to the government, even if the precise amount due has yet to be determined.

Defendants can no longer complain that they were confused by the 60-day overpayment rule.

MR. ANDROPHY

"After the comptroller alerted defendants to the software glitch and approached them with specific wrongful claims, and after Kane put defendants on notice of a set of claims likely to contain numerous overpayments, defendants had an established duty to report and return wrongly collected money," Judge Ramos said. "To allow defendants to evade liability because Kane's email did not conclusively establish each erroneous claim and did not provide the specific amount owed to the government would contradict Congress's intentions."

In an email, a spokesperson for the defendants said the hospitals are disappointed with the judge's decision and will continue to vigorously defend their case in court. Attorneys for the government did not return messages seeking comment.

The judge's ruling is encouraging to the federal government and for plaintiffs who wish to sue health providers for overbilling violations, said Joel M. Androphy, a Houston plaintiffs' attorney.

"This is going to open the floodgates for lawyers now as part of their false claim and reporting practices to let the courts know about overpayment issues," Mr. Androphy said in an interview.

Defendants can no longer complain they were confused by the 60-day overpayment rule and the meaning of "identification," he added. The judge's ruling makes the regulation more clear and provides guidance to health providers about how the rule will be enforced, he said.

Washington health law attorney Robert T. Rhoad, however, disagreed that the opinion clarifies application of the 60-day overpayment rule. The decision does not provide the bright lines for compliance that providers expect and need. To protect themselves from litigation, physicians should take prudent steps to conduct an appropriate investigation if faced with actual or constructive notice of a possible overpayment, Mr. Rhoad said. Showing that they acted with due diligence could help doctors withstand future governmental or judicial scrutiny.

agallegos@frontlinemedcom.com

Medicare hospital costs down over last 6 months of life

BY RICHARD FRANKI
Frontline Medical News

Inpatient costs for Medicare patients over the last 6 months of life dropped 23% per death from 2009 to 2013, a study showed.

After adjustment for inflation, the average inpatient cost for patients aged 65 years and older who died was over $17,400 in 2009.

By 2013, Medicare spending in the last 6 months of life had dropped to just under $13,400.

The trend in spending was similar over the last 3 months of life and over the last month, but the declines – 18% for the last 3 months and 14.5% for the last month – were not as great, reported Dr. Harlan M. Krumholz of Yale University in New Haven, Conn., and his associates (JAMA. 2015;314(4):355-65).

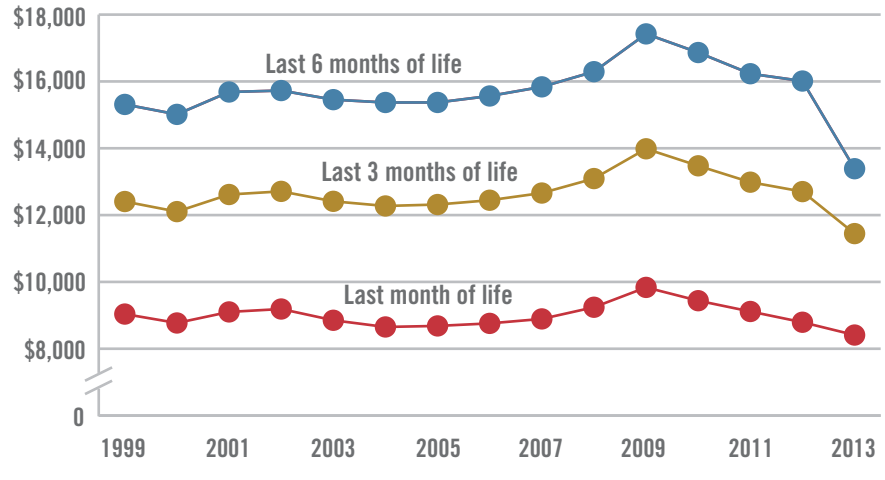
The investigators noted that "approximately 60% of spending in the last 6 months of beneficiaries' lives occurred during their final month."

The analysis included 60,056,069 individuals who were aged 65 years or older who were enrolled in a Medicare fee-for-service plan for at least 1 month between 1999 and 2013.

Dr. Krumholz is supported by a grant from the National Heart, Lung, and Blood Institute.

rfranki@frontlinemedcom.com

Adjusted Medicare inpatient spending per death, 1999-2013



Notes: Based on data for 60,056,069 beneficiaries aged 65 years or older who were enrolled in the Medicare fee-for-service program for at least 1 month. Adjusted for inflation to 2013.

Source: JAMA. 2015;314(4):355-365

What constitutes proper practice in telemedicine?

BY ALICIA GALLEGOS
Frontline Medical News

For the last few months, family physician R. Russell Thomas Jr. has split his time between visiting patients at his practice in Eagle Lake, Tex., and treating children who reside more than 300 miles away in Sheffield, Tex., via telemedicine. His virtual tool belt includes an electronic stethoscope that enables Dr. Thomas to hear a patient's heartbeat in real time and a high-definition camera to view and diagnose skin lesions.

The telehealth services are part of a new initiative at Rice Medical Center, a 25-bed, critical access hospital in rural Eagle Lake – population 3,700. Dr. Thomas has thus far used the technology to treat patients at an at-risk children's academy and a local primary school. Soon, he and other physicians will also use telemedicine to consult with cardiologists and internists who practice 70 miles away in Houston.

"I look at telemedicine not so much as a practice like cardiology or orthopedics, but more [as] a tool like a percussion hammer or an otoscope," Dr. Thomas said in an interview. "It's a tool to practice whatever it is that you do."

Dr. Thomas is far from alone. Analysts predict vast growth in the telemedicine industry in the coming years. The number of health providers offering telemedicine is expected to rise from 22% in 2014 to 37% in 2015, according to research by Towers Watson. Another report, by BCC Research, shows the global telehospital/clinic and telehome market is expected to reach about $43 billion in 2019, up from $19 billion in 2014.

The explosion of telemedicine is driven by two primary factors, said Dr. Joseph P. McMenamin, a Richmond, Va., attorney who specializes in medical malpractice defense and telemedicine.

"As a society, we are increasingly reliant upon and enamored of electronic methods of communications," Dr. McMenamin said in an interview. "In one sense, it's just part of a larger trend. The other, more specific reason, perhaps, is the widespread dissatisfaction with the way our health care system operates today. We are blessed in the United States to have some of the finest physicians in the world. … and then we have this terribly complex, burdensome system for getting people to where they need to be to get care. Telemedicine, by comparison is quick, convenient, and relatively inexpensive."

But for doctors, the practice of telemedicine is strewn with challenges. Barriers include reimbursement, licensing, malpractice, and regulation. Topping the barriers is a lack of uniform standards about practices. A key question: What constitutes the responsible use of telemedicine?

States have differing ideas. Some require a physical examination by a physician prior to telemedicine. Some allow that encounter to be conducted via telemedicine, while others mandate the visit is in-person. Alabama, Georgia, and Texas require an in-person follow-up visit after a telemedicine encounter, according to 2015 data from the American Telemedicine Association (ATA). Sixteen states and Washington, D.C., have informed consent requirements for telemedicine patients. Still other states have no defined rules for the practice of telemedicine.

COURTESY DR. RUSSELL THOMAS

"I look at telemedicine ... more [as] a tool like a percussion hammer or an otoscope," explained Dr. Russell Thomas Jr. of Eagle Lake, Tex.

To promote consistency and better usage, the Federation of State Medical Boards in 2014 issued a model policy to state medical boards about the recommended practice of telemedicine. The policy maintains that the same standard of care applied to face-to-face encounters be applied to telemedicine encounters, said Lisa A. Robin, chief advocacy officer for the Federation of State Medical Boards (FSMB). At least 29 state boards have telemedicine rules that are consistent with the model policy, Ms. Robin said in an interview.

"As telemedicine continues to evolve, we believe there must be a very strong focus on ensuring patient safety through sound policy making and regulatory practices," she said.

From practice debate to court dispute

Medical specialty societies are beginning to weigh in on acceptable telehealth practices for doctors.

In July, the American Academy of Pediatrics issued guidance advocating that use of telemedicine for episodic care should be done within the context of the medical home and that fragmented telemedicine services should be avoided. Guidance issued by the American Medical Association makes it clears that physicians who prescribe using telemedicine need to first establish a patient-physician relationship. In September, the American College of Physicians (ACP) also issued policy in support of expanded telemedicine use, but cautioned the practice should be between a physician and patient who have an established relationship. The FSMB guidance also states that doctors should establish a relationship with patients before practicing telemedicine.

But how that relationship is created is up for debate. In Texas, disagreement over what creates a physician-patient relationship has led to litigation between national telemedicine company Teladoc and the Texas Medical Board.

The case centers on a medical board rule that requires physicians to have a face-to-face visit with patients before treating them through telemedicine. The relationship can be created through telemedicine at an established medical site, but it may not be established through an online questionnaire, email, text, chat, or telephonic evaluation or consultation.

Teladoc sued the medical board in April claiming the rule violates federal antitrust laws. Teladoc provides access to medical care via phone or interactive video and treats patients for nonemergency conditions. A judge halted the rule's enforcement in May. The company sued to ensure patients have access to the same high-quality telehealth care they've received for decades, said Teladoc CEO Jason Gorevic.

"We have employers, health plans, and hospital systems who are coming to us because telehealth is a solution to access-to-care challenges as well as a mechanism to control the cost of care," Mr. Gorevic said in an interview. "It was our responsibility and quite frankly, our obligation, to take action where they were regulations being adopted that were counter to the interests of patients, payers, and physicians in the state."

In an April statement, Dr. Michael Arambula, president of the Texas Medical Board (TMB), said the rule represents the best balance of convenience and safety by ensuring quality health care for patients.

"The board recognizes that as technology evolves, so too must regulations governing telemedicine," Dr. Arambula said in the statement. "However, a telephone medicine scenario that allows a physician to treat an unknown patient without any objective diagnostic data and no ability to follow up with the patient sacrifices the patient's safety for convenience."

The Texas Medical Association (TMA) supported the TMB rule. Dr. Thomas, a former TMB member who is active with the TMA, said the rule's logic is simple.

'Telehealth is a solution to access-to-care challenges [and] a mechanism to control the cost of care.'

MR. GOREVIC

Without a face-to-face visit, "the doctor has no knowledge of the patient, except for what they tell you in that one encounter," he said in an interview. "There are no follow-up opportunities, no mechanism for further assessment. It's episodic care at its worst."

However, Dr. Reed V. Tuckson, president of the American Telemedicine Association, stresses rules such as the Texas Medical Board's are unnecessarily intrusive to doctors and diminish the range of possibilities for telemedicine care.

"We do not believe the restrictive covenants that are being applied by far too many state medical boards are appropriate," Dr. Tuckson said in an interview. "We do not believe they should dictating to physicians the tools that they should be able to use in partnership with their patients to meet [patients'] individual needs."

agallegos@frontlinemedcom.com

President's Report: American College of Chest Physicians in 2015: Bigger Tent and Bigger Team

BY DR. CURTIS N. SESSLER, FCCP

Created in 1935, the American College of Chest Physicians (CHEST) has existed for 80 years and continues to excel at meeting the professional society needs of chest physicians in North America. However, my experience this past year as President of CHEST has reinforced my appreciation that our organization is much more to many individuals involved in the care of patients with diseases of the chest and related conditions. We have truly become a global professional society that focuses on serving all care providers and the entire health-care team. The Vision of CHEST speaks to these priorities clearly, "The American College of Chest Physicians is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care." We've become a professional home for many and, accordingly, the tent has grown in size and diversity.

The Global Tent

While CHEST has had a presence well beyond North America for many years, we have developed a renewed emphasis on serving the needs of physicians around the globe. About 20% of our 18,700 members hail from countries other than the United States and Canada. Leaders from numerous countries provide important representation to the organizational structure of CHEST as Global Governors. The Chair and Vice-Chair of the Global Governors serve as important members of the Board of Regents, helping to shape the direction and strategic plan of the organization. At the member level, more and more exchange of information occurs on an electronic level, figuratively shrinking the world. The new CHEST membership model offers more options to suit the international member, who, for example, may prioritize receiving the *CHEST* journal only electronically at a reduced rate.

Speaking of our flagship journal, *CHEST* has a robust global presence, with approximately 50% of published manuscripts being submitted by international investigators and authors. While receiving an English language version of *CHEST* electronically may be the approach taken by many, an exciting international connection is publication of international editions of *CHEST* in China, India, Italy, Mexico, the Middle East, and Spain.

The American College of Chest Physicians has long been a leader in providing face-to-face continuing medical education and scientific sessions. CHEST continues to partner with other international and regional professional societies in contributing to excellent medical meetings. In the past year, CHEST has endorsed and participated by providing speakers at meetings in Greece, Italy, Turkey, and Argentina, to name but a few. Even our annual scientific meeting in October has enjoyed locations outside of the United States, reflecting the prominent role our Canadian colleagues play in the organization, with CHEST 2015 in Montréal right around the corner. Continuing this approach, our annual meeting will be held in Toronto and Vancouver in the next half-dozen years.

DR. SESSLER

Several decades after the last formal global CHEST-sponsored meeting was held, we relaunched the concept of CHEST World Congress (CWC) with a highly successful meeting in Madrid, Spain, in the spring of 2014. Next April, CHEST breaks new barriers by having CHEST World Congress 2016 in Shanghai, China. This comprehensive scientific and continuing education meeting will include a mix of didactic, live-learning/simulations, and research presentations. In the same year as CWC-Shanghai, the inaugural class of the first formal Pulmonary and Critical Care Medicine (PCCM) fellowship training programs in China will graduate. In a unique partnership, North American experts in graduate medical education from CHEST have partnered with leaders from the Chinese Thoracic Society (CTS) and from Chinese major medical centers to develop a robust formal fellowship curriculum and materials – a first for medical subspecialties in China. There are now PCCM fellowship programs in a dozen major teaching hospitals in China with more planned.

In other international efforts, CHEST continues to play a prominent role in efforts to improve lung health globally through membership in the Forum of International Respiratory Societies (FIRS). Recently, FIRS has become increasingly active and more visible as a prominent voice for lung health. FIRS has published a highly regarded roadmap to global lung health, provided experts to the World Health Organization (WHO) and the United Nations, published statements on electronic cigarettes and other issues, and helped to raise awareness about lung cancer and other respiratory conditions.

Finally, there is a rich tradition of support for care providers and patients in need, domestically and worldwide, through the philanthropic arm of CHEST – the CHEST Foundation. For example, over the years, the foundation has provided millions of dollars in grants and awards to individuals and organizations in support of their local efforts to improve health-care delivery and education in challenging circumstances worldwide.

So, it is easy to see the rapidly expanding global footprint of CHEST, as we provide a professional societal home for many clinicians and scientists around the world and work diligently to improve lung health worldwide.

A Bigger Tent for a Bigger Team

The majority of CHEST members describe themselves as physicians who specialize in pulmonary disease or pulmonary and critical care medicine. The three pillars of CHEST medicine are pulmonary disease, critical care medicine, and sleep medicine. Much of the work of CHEST is related to clinical practice, clinical research, and medical education in these areas. Without a doubt, the American College of Chest Physicians is, and will continue to strive to be, the professional society home for these core groups of physicians working in these areas. Also, physicians in closely related disciplines, including intensivists, pediatric pulmonologists, thoracic surgeons, and cardiologists who manage diseases of the chest and critical care play important roles in CHEST. They have been, and continue to be, important members of the CHEST family, and their needs are consistently addressed.

Much of the emphasis of CHEST efforts has been on meeting the needs of the practicing clinician – whether in academic medicine or community practice. Also, central aspects of the mission of CHEST include the important roles of knowledge development and translation through support for clinical research, publication of original investigations and reviews, and development and dissemination of clinical practice guidelines. We have had a consistently strong emphasis on training the next generation of chest specialists with innovative programs directed toward fellowship-level trainees. A great example is the unique CHEST Challenge, pitting teams of fellows from various training programs in a series of exciting head-to-head knowledge-based competitions. Impressively, CHEST Challenge has been expanded to India, where an estimated 90% of PCCM fellows participate. I'm excited about the latest expansion of our membership model to extend beyond subspecialty fellows to include residents, students, and other trainees. I have met many students and residents who have attended our annual meeting and report having a tremendous experience. This expansion of our membership model represents an important investment in the future of the organization.

Recent trends in the practice of medicine emphasize the growing roles of a diverse group of care providers and the importance of the team in optimal care delivery. These concepts are enthusiastically embraced by CHEST. Nurse practitioners and physician assistants make up an increasingly important group of care providers referred to as advanced practice providers (APPs). These individuals are working hand in hand with physician colleagues and participate in continuing medical education that includes attending the annual CHEST meeting, attending board review courses, and joining in other live-learning events. CHEST is developing more opportunities for APP education and training, including a specially designed concentrated mix of didactic and simulation sessions focusing on the APP. Also, APPs are included in a new category of clinicians with advanced degrees who may quality for FCCP status – an honor previously available only to physicians and PhDs.

Physician and APP providers are important members of the health-care team that also includes respiratory therapists (RT), nurses, clinical pharmacists, and other therapists and technicians. RTs have played prominent roles in CHEST for years and continue to be key contributors to advancing lung health. We are proud to offer the ability of RTs with advanced degrees and other qualifications to apply for FCCP status, reflecting our recognition of their

Continued on following page

CHEST Around the Globe

BY DR. MARK J. ROSEN, MASTER FCCP
Medical Director, CHEST

CHEST Collaborates With Chinese Physicians to Advance Pulmonary and Critical Care Medicine

With the goal of advancing our educational mission and our profession, CHEST continues to expand its collaboration with Chinese leaders in pulmonary, critical care, and sleep medicine in a variety of venues.

In July 2015, faculty representing CHEST and the Chinese Thoracic Society worked together to conduct the First Sino-American Respiratory Forum, a 2-day program in Beijing that focused on clinical features and management of COPD, sharing knowledge and experience among Chinese and CHEST faculty. We plan for this to be an annual event with a different general topic each year.

Our work to introduce pulmonary and critical care medicine (PCCM) as a new subspecialty in China is moving ahead; the first step is to establish fellowship training programs that use a common curriculum across 12 academic sites in China. In collaboration with our Chinese colleagues, eight programs based in Beijing, Shanghai, Changsha, Chengdu, and Guangzhou have been activated, with four more joining in the coming year. Each of the eight active sites were visited over the last year by members of the CHEST PCCM Steering Committee, chaired by Darcy D. Marciniuk, MD, FCCP, a Past President of CHEST. These visits are intended to observe the programs in action, to monitor progress with implementation, and to offer feedback on how to continue to improve the quality of training. We anticipate visiting the sites annually as part of a continuing evaluation process, offering interim assessments with audit of adherence to program requirements and fellows' knowledge. We look forward to the first "graduating class" in the fall of 2017.

Finally, plans are proceeding rapidly for CHEST World Congress 2016, April 15-17, in Shanghai. With the support of the Chinese Thoracic Society, this will be another outstanding CHEST educational experience for the global professional community. Co-chaired by Dr. Marciniuk and Dr. Chen Wang, FCCP, President of the Chinese Thoracic Society, the program has been developed by an international committee, designed to fulfill the goal of delivering practical clinical education in formats that include plenary sessions by global experts, panel discussions, interactive case-based sessions, and hands-on simulation activities.

We look forward to keeping you informed of our progress, and hope you will join us in Shanghai in April 2016.

CHEST

L-R: Dr. Chen Wang, FCCP, and Dr. Darcy D. Marciniuk, FCCP; Co-Chairs of the PCCM Steering Committee and CHEST World Congress 2016.

Trainee Resource Hub

As a new feature, the Trainee Resource Hub provides trainee members with access to personal and professional resources tailored to each early career level.

These resources provide tools needed to become clinicians, scholars, and teachers, to foster active participation and progress in the CHEST community.

There are three distinct resource areas for fellows, medical students and residents, and those transitioning out of fellowship. We hope trainee members find this tool useful throughout their journey in the chest medicine industry.

Learn more at chestnet.org/traineehub.

Continued from previous page

contributions to team-based care.

It is clear that it takes an army to provide optimal comprehensive care to sick patients. CHEST strongly endorses the importance of the health-care team and is expanding membership opportunities, as well as opening the opportunity for individuals to qualify for FCCP status. Our philosophy is that team quality and, thus, delivery of effective patient care, is optimized by enhancing the clinical skills of each member of the team. In addition to our traditional educational offerings, we are advancing the health-care team by collaborating with other professional societies, such as the American Association of Critical-Care Nurses (AACN) and by developing new educational opportunities geared to individual members, as well as the team as a whole.

Finally, while not directly involved in patient care, professional representatives from the pharmaceutical and device industries benefit from increased knowledge about medical conditions that their products are intended to help evaluate or treat. Through CHEST Enterprises (the for-profit CHEST subsidiary launched in 2013), education is provided to our industry partners through the Professional Representative Education Program (PREP), contributing to improving patient outcomes.

In summary, the American College of Chest Physicians is rapidly advancing patient outcomes by expertly delivering medical education and leading knowledge development and dissemination to many individuals in the health-care industry worldwide. From the perspective of enhancing these goals, 2015 has been an exciting year of continued global expansion and strengthening the health-care team. We look forward to ongoing strengthening of the relationships of the many people under the big CHEST tent.

And speaking of big tents and great relationships, I will be wrapping up my year as President of CHEST in October and have many wonderful people to thank. It has been a unique and rewarding experience for me, and our CHEST team has done some great work this year! It really is all about the people! This team includes superb colleagues in CHEST leadership, tremendous CHEST staff, my "day job" colleagues at Virginia Commonwealth University, and my wife Pam and family. Thank you all!

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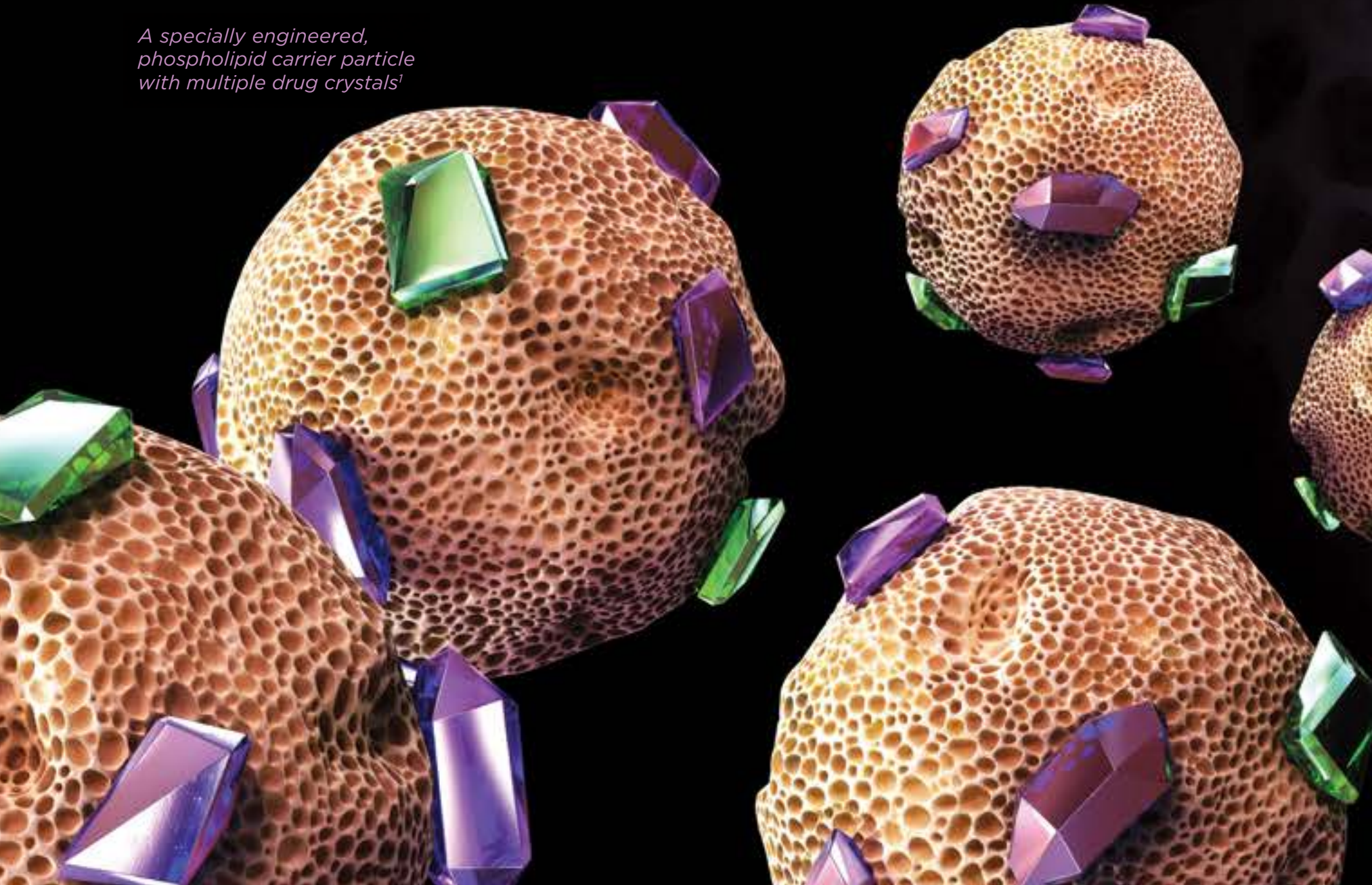

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AstraZeneca

NETWORKS: EBUS-TBNA mutation analysis. Pediatric ARDS.

Interventional Chest/Diagnostic Procedures

Brief update on molecular analysis from EBUS-TBNA specimens

With the breakthroughs in molecular targeted therapies for non–small cell lung cancer (NSCLC), EBUS-TBNA remains well-suited to obtain material for mutation analysis (*Am J Respir Crit Care Med*. 2012;185[2]:1316). Techniques for maximizing material for mutation analysis via EBUS-TBNA have been described (*J Thorac Oncol*. 2011;6[1]:203) and are continually being refined. With a combination of EBUS and rapid on-site evaluation (ROSE), a minimum of four needle passes should be considered to provide adequate specimen for mutation analysis (*Ann Am Thor Soc*. 2013;10:636). This use of EBUS and ROSE may prevent a repeat invasive diagnostic procedure aimed at molecular profiling in at least 1 out of 10 patients with advanced lung cancer and reduces the risk of retrieving inadequate samples for mutation analysis (*Chest*. 2015;doi: 10.1378/Epub ahead of print).

DR. PASTIS

Targetable mutations such as EGFR, ALK, and ROS1 have FDA-approved treatments, while others are being studied to determine their clinical significance, particularly as it relates to the development of tyrosine kinase inhibitor (TKI) resistance. For example, some mutations have alternative mechanisms of signaling activation downstream of EGFR. The *EGFR* T790M mutation (the most common mechanism of drug resistance to TKIs) was recently shown to respond well to AZD9291 in patients with lung cancer who previously had disease progression during prior therapy with TKIs (*N Engl J Med*. 2015;372[18]:1689). MET gene encodes a transmembrane tyrosine kinase receptor, and aberrant MET activation in NSCLC has also been linked with acquired resistance to EGFR TKIs. Several MET inhibitors are being developed and tested as potential therapies for NSCLC (*PLOS ONE*. 2015;doi:10.1371).

An emerging role for EBUS is identifying programmed death-ligand 1 (PD-L1) expression on tumor cells in mediastinal lymph nodes. Although it is not a definitive predictive marker of response to PD-1 inhibitors like nivolumab (a human anti-PD-1 monoclonal antibody that works as an immune checkpoint blocker), this biomarker is the single factor most closely correlated with response to anti–PD-1 blockade (*Clin Cancer Res*. 2014;20[19]:5064).

To apply an individualized treatment paradigm in advanced NSCLC, mutation analysis is now mandatory, and EBUS-TBNA is a cornerstone of this strategy. Perfecting techniques to maximize material obtained by EBUS-TBNA is becoming critically important as the role of this procedure expands to include evaluation of new clinically relevant biomarkers.

Dr. Nicholas Pastis, FCCP
Steering Committee Member

An emerging role for EBUS is identifying programmed death-ligand 1 expression on tumor cells in mediastinal lymph nodes. This biomarker is the single most closely correlated with response to anti–PD-1 blockade.

Pediatric Chest Medicine

Is ARDS consistent across ages? Contemplating the new Pediatric Acute Lung Injury Consensus Conference (PALICC) guidelines

A unique challenge of caring for children is the wide range of developmental and physiologic stages that influence the response to lung injury and infection. As they grow, children experience tremendous alveolar proliferation, changes in airway size and resistance, alterations in chest wall compliance, and development of collateral ventilation channels. Immune system development over time will also significantly affect children's response to lung injury. When considering the complex pathophysiology of acute respiratory distress syndrome (ARDS), we must be cognizant that children are not merely "little adults." In response, 27 international pediatric lung injury experts utilized current evidence and expert opinion to develop consensus guidelines for pediatric ARDS (PARDS) (*Pediatr Crit Care Med*. 2015;16[5]:428). The full guidelines contain 132 recommendations with 'strong agreement' and 19 with "weak agreement."

Compared with the Berlin criteria for adult ARDS (*JAMA*. 2012;307[23]:2526), notable differences for PARDS diagnosis include unilateral, as well as bilateral, infiltrates on chest radiograph, PARDS criteria for patients on full face-mask noninvasive ventilation, and preference for oxygenation index (OI) rather than P/F ratio for disease severity stratification. The guidelines also include an "at risk" definition for patients not yet meeting PARDS criteria. For therapy, the guidelines recognize the importance of ongoing investigation for tidal volume targets and specific therapies such as prone positioning that may affect ARDS outcomes differently in children than adults.

DR. REHDER

The wide heterogeneity and relatively small numbers of PARDS patients dictate that we still have much to learn; however, these new guidelines help add consistency to PARDS management across centers and provide groundwork for future studies.

Dr. Kyle J. Rehder, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Sighing dyspnea: The pulmonologists' fibromyalgia?

Evaluating unexplained dyspnea represents a challenge for the pulmonologist. However, there is a common syndrome that should be considered in certain circumstances given its consistent historical findings and a lack of physical and objective abnormalities.

Sighing dyspnea as a clinical syndrome was first thoroughly described by Dr. Charles Maytum in 1938 (J Allergy. 1938;10[1]:50). Several years earlier, Dr. Doris Baker recorded her experience with "a disorder incorrectly described by patients as breathlessness" (*Lancet*. 1934;228:174). These historical reviews both describe "attacks of sighing breathing."

Like fibromyalgia, the cause of sighing dyspnea is unknown. Management revolves around exploring psychological stressors (anxiety and depression) and an adequate explanation of the condition and its benign course.

In almost all cases, the patients use stereotypical phrases to describe their breathlessness. Characteristic descriptions include "an inability to obtain a satisfying breath" or "trouble getting in enough air." Sighing respirations are noted during the clinic visit. Fatigue and exhaustion are common. Sighing dyspnea does not wake the patient once sleeping. Frequently, a patient will bring his hand to his midsternum and tap the chest at the point where air gets stuck. A sensation of chest tightness is often described, confusing the condition with asthma. Invariably, the most distressing symptoms occur at rest and improve with exertion. The poor correlation of symptoms with the degree of exertion distinguishes sighing dyspnea from other organic causes.

Like fibromyalgia, the cause of sighing dyspnea is unknown. Management revolves around exploring psychological stressors (anxiety and depression) and an adequate explanation of the condition and its benign course. In the future, pulmonary rehabilitation emphasizing breathing techniques may prove most helpful.

Dr. Timothy Scialla
Steering Committee Member

Pulmonary Vascular Disease

Duel Drug Therapy for PAH

Treatment options for pulmonary arterial hypertension (PAH) have increased, but the efficacy of combin-

Continued on following page

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ing PAH treatments remains unclear. The recently published AMBITION trial found that treatment-naive PAH patients with functional class II or III symptoms randomized to up-front treatment with ambrisentan and tadalafil had half the rate of clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory clinical response) than patients treated with either drug alone. This study is notable for its event-driven study design (mean duration of exposure to study treatments was 517 days) and because it is the first large-scale study to examine up-front combination therapy vs monotherapy in treatment-naive PAH patients. Differences in secondary endpoints, including 6-minute walk distance, BNP [brain natriuretic peptide], and the number of patients with a favorable response, were also better with combination therapy than monotherapy at the 24-week time point in which they were measured.

Although these results clearly favor up-front dual-drug therapy, a number of questions remain. First, it is unknown whether the agents used have synergistic or additive effects or if the probability of having a clinical failure event was lessened simply because two drugs increased the chance of having a response to one of them. Second, the lower rate of events in the combination group was driven primarily by hospitalization for PAH that has not been validated as a surrogate. Finally, it is unknown if the benefits observed are limited to the drugs used or if other PAH drug combinations are superior to monotherapy. While these questions require further study, it seems reasonable to consider this combination therapy as initial treatment in PAH with functional class II or III symptoms.

While these questions require further study, it seems reasonable to consider this combination therapy as initial treatment in PAH with functional class II or III symptoms.

Dr. Corey E. Ventetuolo
Steering Committee Member
Dr. James R. Klinger, FCCP
Ex Officio

Reference

Galiè N, Barberà JA, Frost AE, and the AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373(9):834.

Thoracic Oncology

Generalizing the findings of the National Lung Screening Trial


DR. TANNER

In 2011, the landmark results of the National Lung Screening Trial (NLST) were published (*N Engl J Med*. 2011;365[5]:395). For individuals at high risk for lung cancer based on age and smoking history, screening with low-dose computed tomography (LDCT) was shown to reduce mortality by 20%. Since then, lung cancer screening programs have begun screening across the country especially since March of this year when CMS approved coverage for this service. However, there are some concerns as to the generalizability of the NLST because the participants in that study were younger, more educated, less ethnically diverse, and healthier than the average American who would qualify for lung cancer screening. (*J Natl Cancer Inst*. 2010;102[23]:1771).

Through a grant from the CHEST Foundation, Dr. Nichole Tanner sought to examine these subsets of patients within the NLST. She presented her findings at CHEST 2014. Further analysis of the NLST data revealed that screening with LDCT reduced lung cancer mortality in all racial groups. However, this benefit was more pronounced in blacks (hazard ratio, 0.61 vs 0.86). When stratified by race, black smokers were twice as likely to die of lung cancer as were white smokers (HR, 4.10 vs 2.25).

While blacks benefited more from screening with LDCT, the demographics associated with an improvement in lung cancer survival were less commonly found in this population. The authors conclude that in order to realize reductions in mortality from lung cancer screening, tailored dissemination efforts are needed to meet the needs of this community (*Am J Respir Crit Care Med*. 2015;192[2]:200).

Dr. Nichole T. Tanner, FCCP
Steering Committee Member

Common ICD-10 Codes that will keep you up at night

This month, we present a couple of code categories that will become familiar to ICU doctors. This includes some of the codes for respiratory failure and for sepsis.

While you can find additional codes in the ICD-10-CM Official Guidelines for Coding and Reporting available at http://www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html that are pertinent to critical care medicine, these codes also serve to reiterate a couple of points.

First, in the J96 codes for respiratory failure, you see a number of "Excludes1" codes. Remember that this means that a J96 category code **MAY NOT** be used if you have also chosen one of the excludes1 codes.

A type 1 Excludes note is a pure excludes note. It means "NOT CODED HERE!" An Excludes1 note indicates that the code excluded should never be used at the same time as the code above the Excludes1 note. An Excludes1 is used when two conditions cannot occur together, such as a congenital form vs. an acquired form of the same condition.

In the R65 category with the SIRS/Sepsis codes, you will notice the "code first" direction. This instructs the coder to use another code describing the cause of the SIRS/Sepsis prior to using a R65 category code.

In addition, there is a "code also" direction, which instructs the coder to add a code for any associated organ dysfunction. These instructions enhance the specificity of the coding process.

J96 Respiratory failure, not elsewhere classified		
Excludes 1:	acute respiratory distress syndrome (J80) cardiorespiratory failure (R09.2) newborn respiratory distress syndrome (P22.0) postprocedural respiratory failure (J95.82-) respiratory arrest (R09.2) respiratory arrest of newborn (P28.81) respiratory failure of newborn (P28.5)	
J96.0	**Acute Respiratory failure**	
	J96.00	**Acute respiratory failure, unspecified whether hypoxia or hypercapnia**
	J96.01	**Acute respiratory failure with hypoxia**
	J96.02	**Acute respiratory failure with hypercapnia**
J96.1	**Chronic respiratory failure**	
	J96.10	**Chronic respiratory failure, unspecified whether hypoxia or hypercapnia**
	J96.11	**Chronic respiratory failure with hypoxia**
	J96.12	**Chronic respiratory failure with hypercapnia**
J96.2	**Acute and chronic respiratory failure** Acute on chronic respiratory failure	
	J96.20	**Acute and chronic respiratory failure, unspecified whether hypoxia or hypercapnia**
	J96.21	**Acute and chronic respiratory failure with hypoxemia**
	J96.22	**Acute and chronic respiratory failure with hypercapnia**
J96.9	**Respiratory failure, unspecified**	
	J96.90	**Respiratory failure, unspecified whether hypoxia or hypercapnia**
	J96.91	**Respiratory failure, unspecified with hypoxia**
	J96.92	**Respiratory failure, unspecified with hypercapnia**

R65 Symptoms and signs specifically associated with systemic inflammation and infection		
R65.1	**Systemic inflammatory response syndrome (SIRS) of non-infectious origin**	
	Code first underlying condition, such as: heatstroke (T67.0) injury and trauma (S00-T88) **Excludes 1:** sepsis- code to infection severe sepsis (R65.2)	
	R65.10	**Systemic inflammatory response syndrome (SIRS) of non-infectious origin without acute organ dysfunction** Systemic inflammatory response syndrome (SIRS) NOS
	R65.11	**Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction** **Use additional** code to identify specific acute organ dysfunction, such as: acute kidney failure (N17.-) acute respiratory failure (J96.0-) critical illness myopathy (G72.81) critical illness polyneuropathy (G62.81) disseminated intravascular coagulopathy [DIC] (D65) encephalopathy (metabolic) (septic) (G93.41) hepatic failure (K72.0-)
R65.2	**Severe Sepsis** Infection with associated acute organ dysfunction Sepsis with acute organ dysfunction Sepsis with multiple organ dysfunction Systemic inflammatory response syndrome due to infectious process with acute organ dysfunction **Code first** underlying infection, such as: infection following a procedure (T81.4) infections following infusion, transfusion and therapeutic injection (T80.2-) puerperal sepsis (O85) sepsis following complete or unspecified spontaneous abortion (O03.87) sepsis following ectopic and molar pregnancy (O08.82) sepsis following incomplete spontaneous abortion (O03.37) sepsis following (induced) termination of pregnancy (O04.87) sepsis NOS (A41.9) **Use additional** code to identify specific organ dysfunction, such as: acute kidney failure (N17.-) acute respiratory failure (J96.0-) critical illness myopathy (G72.81) critical illness polyneuropathy (G62.81) disseminated intravascular coagulopathy [DIC] (D65) encephalopathy (metabolic) (septic) (G93.41) hepatic failure (K72.0-)	
	R65.20	**Severe sepsis without septic shock** Severe sepsis NOS
	R65.21	**Severe sepsis with septic shock**

This Month in *CHEST:* Editor's Picks

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

EDITORIAL

A Paradigm Shift in the Treatment of Central Sleep Apnea in Heart Failure. *By Drs. R. Mehra and D. J. Gottlieb.*

POINT AND COUNTERPOINT

Should Childhood Vaccination Against Measles Be a Mandatory Requirement for Attending School?
Yes – *Drs. R. D. Silverman and K. S. Hendrix*
No – *Drs. P Schroder-Back and K. Martakis*

ORIGINAL RESEARCH

Dedicated Severe Asthma Services Improve Health-Care Use and Quality of Life. *By Dr. D. Gibeon, et al.*

Will Nonasthmatic Eosinophilic Bronchitis Develop Into Chronic Airway Obstruction? A Prospective, Observational Study. *By Dr. K. Lai, et al.*

The Impact of Visceral Pleural Invasion in Node-Negative Non–small Cell Lung Cancer: A Systematic Review and Meta-analysis. *By Dr. L. Jiang, et al.*

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Memorial Healthcare System

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Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org . Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

Catching Up With Our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new.

Susan K. Pingleton, MD, Master FCCP
President: 1999-2000

My induction as President in Chicago coincided with the College's 65th birthday anniversary, so it was quite a celebratory event. Memories of my year as President include interesting travels to the Philippines, India, Germany, Italy, and Canada to meet our international colleagues and friends. Challenges included the College's first attempts to clarify any conflict of interest in our consultants and committee members resulting in the current conflict of interest disclosure requirements.

Since that time, I have been fortunate to have a continually evolving, demanding but very interesting professional life. After Division Director, I had the great honor to serve as Chair of Internal Medicine at the University of Kansas. That job provided quite a professional challenge, as well as education for me. Afterwards, on sabbatical leave, I spent a year in Washington, DC, at the Association of American Medical Colleges as the Petersdorf Fellow, learning much about health-care policy, as well as the health-care organization in DC that guides that policy. That education was capped off by a year at the University HealthCare Consortium in Chicago as the Chief Learning Officer.

Returning home to KU, I have been working in Continuing Education and Professional Development as the Associate Dean, to implement the many changes of education to our practicing physicians and health-care teams. I've also been involved in mentoring, both junior physicians in the Department of Internal Medicine, as well as junior female faculty in our Women in Medicine and Science. I've concluded a term as the McCann Professor in Women in Medicine and Science where I conducted a year-long oral history study of female professors here at KU.

Dr. Susan K. Pingleton served as the McCann Professor in Women in Medicine and Science, conducting a year-long oral history study of KU female professors.

As I reflect back on my working with the College for many years, cumulating in the Presidency, the American College of Chest Physicians provided me with essential leadership tools that I have used extensively ever since. The College has provided great value, as well as great lifetime friendships for me, for which I am most grateful.

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Quit smoking after MI: Less angina, good mental health

BY KARI OAKES
Frontline Medical News

Patients who stopped smoking after their heart attack had less chest pain and experienced better mental health than did those who continued to smoke at 1 year after their acute myocardial infarction (AMI).

Moreover, the post-MI quitters had levels of angina and mental health similar to those who had never smoked, and scores improved with the passage of time after smoking cessation, according to a prospective, multicenter study.

Smoking cessation after a heart attack reduces mortality and the risk of recurrent MI by up to 50%, according to Donna Buchanan, Ph.D., and her coinvestigators.

However, few high-quality studies to date have examined the effect of smoking cessation on overall health-related quality of life (HRQOL), she said.

For this study, Dr. Buchanan and her colleagues used data from two large multicenter AMI registries to address how smoking status after AMI is related to mental and physical health status. Using the Seattle Angina Questionnaire and the Medical Outcomes Study Short Form 12-item questionnaire, investigators tracked changes in chest pain and mental and physical health status at 1, 6, and 12 months post AMI according to smoking status.

The final cohort included 4,003 patients who were then grouped by smoking status.

Patients were grouped into never smokers (1,145), former smokers (1,374), and current smokers. A total of 1,484 patients were smokers at baseline; of those, 801 were still smoking at 1 year post MI. The remaining 683 patients quit within the year after their AMI and were classified as recent quitters. In unadjusted analysis, never smokers had the highest health status scores and current smokers the worst, with a gradation across the four categories of smoking status that was statistically significant for all domains, said Dr. Buchanan of the University of Missouri–Kansas City.

Further statistical exploration with multivariable analysis showed that former smokers and never smokers looked similar in all HRQOL, while there was more variability across HRQOL domains for recent quitters. Recent quitters were significantly more likely to report good mental health status than current smokers, even when levels of depression and social support were taken into consideration (Circ Cardiovasc Qual Outcomes. 2015 Aug 25; doi: 10.1161/circoutcomes.114.001545).

An examination of physical symptoms revealed that recent quitters had levels of angina similar to those who had never smoked, while persistent smokers had more angina post AMI than any other group. Dr. Buchanan and her colleagues noted that the oxidative stress, endothelial damage, and proinflammatory state that are caused by smoking all may contribute to ongoing angina. Smokers also experience increased adrenergic tone, and may have more coronary vasospasm.

The study was funded by CV Therapeutics and the National Institutes of Health. A coinvestigator owns the copyright to the Seattle Angina Questionnaire, used to assess angina in the study.

koakes@frontlinemedcom.com
On Twitter @karioakes

SPRINT shows lives saved with lower systolic BP

BY KARI OAKES
Frontline Medical News

Deaths were reduced by nearly one-quarter when systolic blood pressure was treated to a target of 120 rather than 140 mm Hg, according to a large National Institutes of Health-sponsored study comparing standard blood pressure treatment with more-intensive lowering of systolic blood pressure. The lower blood pressure group also saw a 30% reduction in the composite primary endpoint of cardiovascular events, stroke, and cardiovascular death.

The magnitude of the effect of the lower blood pressure target prompted the study's data safety monitoring board to end the study early, said officials from several NIH agencies at a telebriefing. The study was unblinded in August 2015, and a full report of the primary outcome measures will come in a paper due out by the end of the year, they said.

The Systolic Blood Pressure Intervention Trial, or SPRINT, is a 100-site trial that enrolled more than 9,300 people in the United States and Puerto Rico aged at least 50 years with high blood pressure and at risk for cardiovascular disease; those with diabetes were excluded. Patients were randomized to a standard treatment target of 140 mm Hg or less, or to a more intensive 120 mm Hg.

SPRINT participants received evidence-based treatment with a variety of antihypertensives, with the intervention arm requiring an average of almost three medications, compared with just under two for the less-intensive treatment arm.

Against a backdrop of uncertainty in the literature about what the target systolic blood pressure should be for those with hypertension and at risk for cardiovascular events or kidney disease, the study provides compelling evidence that more-aggressive blood pressure lowering is important. "More-intensive management of blood pressure can save lives," said Dr. Gary Gibbons, director of the National Heart, Lung, and Blood Institute. This is good news, he said, since about one in three Americans has high blood pressure, and only about half of those 70 million currently have their blood pressure under control.

'This is a time of enlightenment.'

DR. OPARIL

Dr. Jackson T. Wright Jr., SPRINT study lead and director of the clinical hypertension program at Case Western Reserve University in Cleveland, also emphasized that intensive blood pressure management can prevent the cardiovascular complications of hypertension. Though subgroup analysis is ongoing, the effect seems robust and consistent across age groups, sex, and ethnicity, he said. SPRINT, he said, also "offers an excellent opportunity to examine the tolerability and safety of the lower target." The first look at the safety data shows that the more-intensive treatment is well tolerated, though data analysis is ongoing, he said.

Dr. Suzanne Oparil, director of the vascular biology and hypertension program at the University of Alabama–Birmingham, said, "This is a time of enlightenment." The previous absence of compelling data played a part in the debate surrounding blood pressure levels that should be used in guidance documents, and Dr. Gibbons and Dr. Wright both emphasized that they would expect the forthcoming primary outcomes paper to have an impact on guideline-writing bodies. Dr. Wright said, however, "We are not providing guidance for providers or patients right now. The study was just unblinded a little less than 3 weeks ago."

In 2014, the group of experts who had constituted the JNC 8 panel, a team assembled in 2008 by NHLBI to update official U.S. hypertension management guidelines, set the target blood pressure for the general population aged 60 years or older to less than 150/90 mm Hg, a major break from long-standing practice to treat such patients to a target systolic pressure of less than 140 mm Hg (JAMA. 2014;311[5]:507-20). These guidelines, released after SPRINT began, remain controversial.

The SPRINT MIND trial, tracking the relationship between systolic blood pressure and cognitive impairment or dementia, is ongoing. The study is also still collecting data about kidney function in study participants.

The study was funded by the National Institutes of Health. Two drug companies, Takeda and Arbor, provided some medication for the trial.

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INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Considering treatment options for your pulmonary arterial hypertension (PAH) patients?

REVATIO® (sildenafil)— is now available as an oral suspension treatment for PAH

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

Please see brief summary of Full Prescribing Information on following pages.

Revatio® sildenafil
20 mg tablets

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