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CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

How safe are asthma meds in pregnancy?

FRONTLINE MEDICAL NEWS

At the 2014 AAAAI annual meeting, Dr. Jennifer A. Namazy of the Scripps Clinic in La Jolla, Calif., summarized safety data and shared tips for keeping pregnant patients healthy and medication adherent. See the video at chestphysician.org.

Hold immunomodulators for surgery? … Maybe

BY NEIL OSTERWEIL
Frontline Medical News

SCOTTSDALE, ARIZ. – When patients on immunosuppressive therapies need surgery, the risks of disease flare and compromised postoperative recovery and rehabilitation must be weighed against the risk of increased infections and impaired wound healing.

"I'm not sure that there is necessarily a right answer, but I think most people would stop biologic [agents] beforehand," Dr. Paul Grant said at a meeting on perioperative medicine sponsored by the University of Miami.

The decision whether to suspend a disease-modifying antirheumatic drug before surgery may depend on the individual drug and on the patient, said Dr. Grant, director of perioperative and con-

See **Surgery** • *page 19*

Higher MAP target fails to improve sepsis survival

No reduction seen in organ dysfunction.

BY PATRICE WENDLING
Frontline Medical News

Use of a high mean arterial pressure during initial resuscitation in patients with septic shock did not improve mortality at 28 or 90 days in the multicenter, open-label SEPSISPAM trial.

The Surviving Sepsis Campaign guidelines recommend targeting a mean arterial pressure (MAP) of at least 65 mm Hg, but suggest a higher target may be better for patients with atherosclerosis or previous hypertension. Retrospective data also suggest a MAP of more than 75 mm Hg may be needed to maintain kidney function during early sepsis.

For the current trial, investigators at 29 centers in France evenly randomized 776 patients to vasopressor treatment adjusted to maintain a MAP of 80-85 mm Hg (high-target group) or 65-70 mm Hg (low-target group).

The study's primary endpoint of all-cause mortality at 28 days was 36.5% in the high-target group and 34% in the low-target group

See **MAP** • *page 13*

INSIDE

CRITICAL CARE COMMENTARY: Mobilize mechanically ventilated patients

BY DR. JOHN KRESS, FCCP

Survival after critical illness is common, with numerous evidence-based strategies showing impressive outcomes in recent years.[1-3] Patients requiring mechanical ventilation are at risk for developing neuromuscular weakness – a syndrome referred to as "ICU-acquired weakness" (ICU-AW). Those with sepsis seem to be at particularly high risk of developing ICU-AW.[4] Because patients supported by mechanical ventilation in the ICU may be immobile for prolonged time periods, the idea of early mobilization is attractive. Traditional management strategies during mechanical ventilation incorporated a mindset that imposed a state of passivity on patients. Such an approach

See **CC Commentary** • *page 38*

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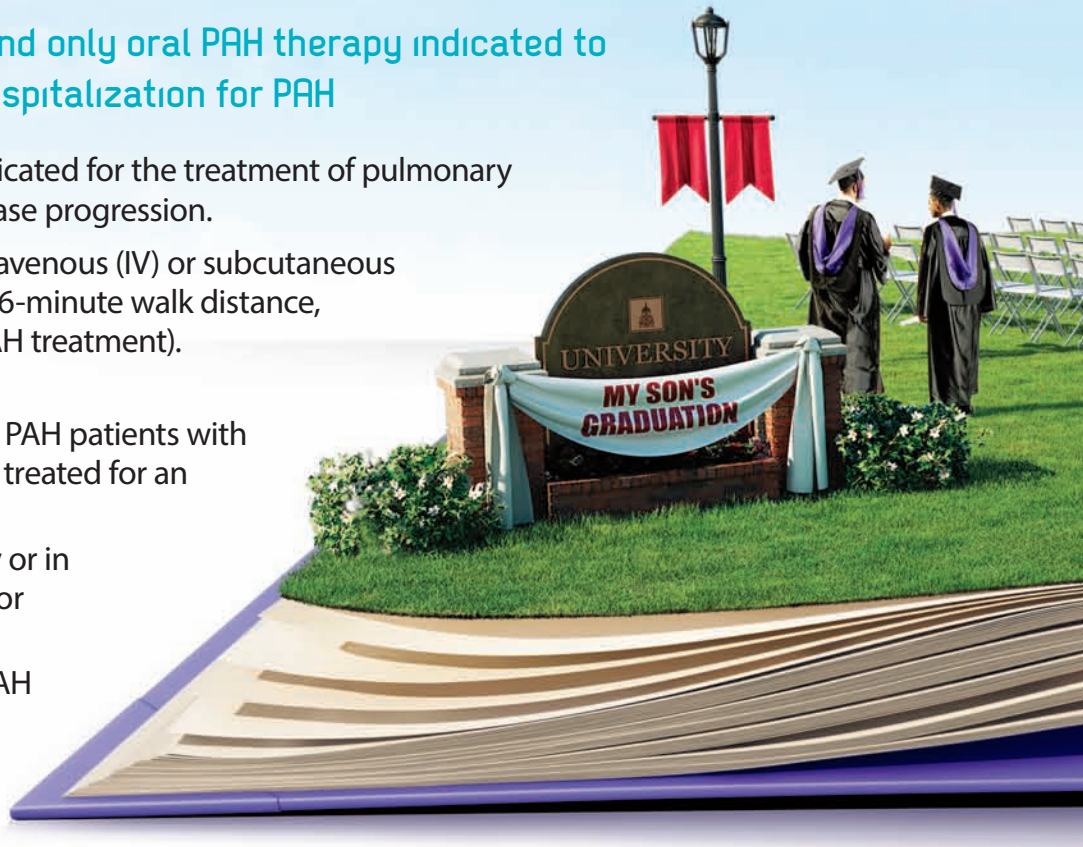
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

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

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS)**

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT

Patient dramatization

when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

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

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BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

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

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

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

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

Hepatotoxicity

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

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

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

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

Table 2: Adverse Reactions

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

DRUG INTERACTIONS

Strong CYP3A4 Inducers

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

Strong CYP3A4 Inhibitors

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

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

Animal Data

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

Nursing Mothers

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

Pediatric use

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

Geriatric use

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

Females and Males of Reproductive Potential

Females

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

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

Males

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

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

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

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

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

OPSUMIT® (macitentan)

Drug Interactions

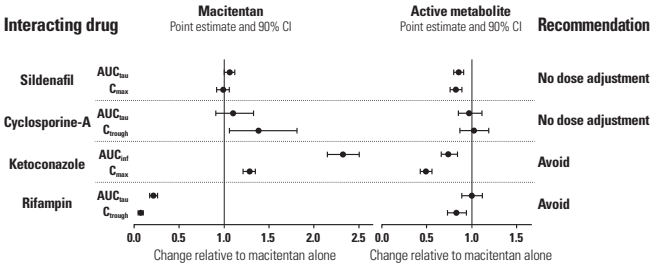
In vitro studies

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

In vivo studies

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

Figure 1



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

Effect of macitentan on other drugs

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Animal Toxicology

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

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

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South San Francisco, CA 94080, USA
ACT20131018

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

Cracking the gray ceiling with bevacizumab

For the superold, era of trial exclusion may be over.

BY PATRICE WENDLING
Frontline Medical News

MADRID – Results from a small study challenge the longstanding practice of preventing superannuated patients from participating in phase III trials.

Patients aged 75 years and older are common in everyday clinical practice and comprised almost 10% (8.6%) of 382 nonsquamous non–small cell lung cancer patients who were candidates for bevacizumab (Avastin) between 2001 and 2012, Dr. Andriani Charpidou, FCCP, said in a late-breaking session at the CHEST World Congress.

Among these 33 patients, 19 had stable cardiovascular disease, 10 had other comorbidities, and 2 had hemoptysis.

All patients were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and received a mean of 5.8 cycles (range, 1-21) of bevacizumab.

In all, 26 patients (78.8%) experienced an adverse event, but no AEs were fatal and only 5 patients (15%) discontinued therapy because of toxicities (3 hemoptysis, 1 hematoma, and 1 neutropenia), said Dr. Charpidou, a chest physician with the oncology unit, University of Athens.

Superannuated patients, however, had a higher probability for bleeding events (40%) than reported in the literature. "There were no thromboembolic events and no worsening of preexisting stable CVD [cardiovascular disease]," she said.

When the investigators compared patients younger than 80 years with those 80 years and older, there were no significant differences in AEs (19 patients vs. 7 patients; $P = .652$), AEs greater than grade 3 (7 vs. 3 patients; $P = .673$), or discontinuation due to toxicities (5 vs. 3 patients; $P = .366$).

Superannuated patients should not be excluded from the use of antiangiogenic factors based only on age.

DR. CHARPIDOU

Partial response occurred in 19% and stable disease in 42%, according to the study (Chest 2014;145[3 Suppl]:350B).

Once again, no significant differences were observed between the old and superold with regard to progression-free survival (6 months vs. 4 months; $P = .660$) or overall survival (6.8 months vs. 7.1 months; $P = .557$), Dr. Charpidou said.

"Taking in mind the limitation of a small sample size, we suggest that superannuated patients should not be excluded from the use of antiangiogenic factors based only on annual age," she said. "Nevertheless, larger cohort studies are needed."

During an interview, session moderator Dr. Mark J. Rosen, medical director of CHEST, the American College of Chest Physicians, agreed that larger studies are needed, but added,

"Every piece of evidence that says 'Let's not exclude people because they're old,' will push the ball a little further. I think it's inevitable. Trials are getting more inclusive rather than less so."

During a discussion of the results, CHEST Congress cochair Dr. Joan Soriano of Hospital Universitari Son Espases, Palma de Mallorca, Spain, said that chronic obstructive pulmonary disease trials are being enriched with superannuated patients following the 2012 validation of the Global Lung Function Initiative spirometric prediction equations in patients aged up to 95 years (Eur. Respir. J. 2012;40:1324-43).

"This has reshuffled the clinical trial inclusion criteria, and now some companies already include patients up to 95," he said in an interview. "There aren't many patients, but at least it's not an exclusion criterion.

"The populations are aging, so in theory, all these new drugs for cancer, bronchodilators, or anti-inflammatories will be used in the very elderly. So, I'm sure we will see many more superannuated patients in phase III trials."

Dr. Charpidou reported no financial disclosures.

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IN THIS ISSUE

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

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Lung transplants in HIV-positive gaining momentum

BY PATRICE WENDLING
Frontline Medical News

MADRID – Evidence is mounting that lung transplantation is feasible in highly select patients positive for human immunodeficiency virus.

A retrospective analysis of three patients revealed no long-term resurgence of HIV viremia or profound complications of overt immune suppression. CD4 counts decreased initially in one patient, but recovered after about 1 year with antiretroviral therapy (ART). All patients were adequately controlled on combination

People with in-depth knowledge of their disease and who are able to manage their HIV well are ideal candidates.

DR. SEETHAMRAJU

ART, had no HIV viremia for 2 years prior to surgery, and had no resistance to standard antiretrovirals.

"Not all HIV-positive patients would be candidates," Dr. Harish Seethamraju said during a late-breaking abstract session at the CHEST World Congress.

"You want to ensure compliance; and an ability to manage complex medication regimens would be the challenge for any person. So, people who have an in-depth knowledge about their disease and are able to manage their HIV well for a prolonged period of time would be ideal candidates."

As with other solid-organ transplants, acute rejection remains a concern and was reported in patient 1, who underwent bilateral transplant for HIV-associated pulmonary arterial hypertension. The patient experienced three episodes of rejection, including bronchiolitis obliterans syndrome and rejection with respiratory syncytial virus pneumonia requiring admission at 15 months, which tipped her course dramatically and resulted in loss of most of her lung function by post transplant 43 months, he said.

Mild acute rejection occurred in patients 2 and 3, who were transplanted for idiopathic pulmonary fibrosis, but they remain free of acute rejection and are actively employed 15 months and 41 months after transplant.

Surgeons at Houston Methodist Hospital and the University of California, San Francisco, where the transplants were performed, also learned that ART has to be initiated very early on post transplant, said Dr. Seethamraju, now medical director of the lung transplant program, University of Kentucky, Lexington.

"In patient 2, we found a resurgence of HIV viremia within 10 days, but we just stopped the medication for the first 4 days and that's all it took for the virus to come back," Dr. Seethamraju said.

The study findings should provide guidance for clinicians considering transplantation in the wake of the recently approved HIV Organ Policy

Continued on following page

Continued from previous page

Equity (HOPE) Act, which made it legal in the United States now to transplant HIV-positive organs in HIV-positive patients. HIV patients are often referred for lung transplant because of an increased incidence of pulmonary hypertension and infections, but their HIV status has traditionally been taken as a contraindication due to the potential risks of added immunosuppression, said Dr. Seethamraju.

Only one case report has been published of an HIV and hepatitis B virus coinfected patient with cystic fibrosis who underwent successful double lung transplant, he said.

Although HIV patients are often refered for lung transplantation, HIV status has traditionally been taken as a contraindication due to the potential risks of added immunosuppression.

During a discussion of the study, CHEST Congress cochair Dr. Joan Soriano, of Hospital Universitari Son Espases, Palma de Mallorca, Spain, asked whether any of the centers would consider lung transplantation in HIV-positive patients with chronic obstructive pulmonary disease (COPD).

Dr. Seethamraju replied that COPD is the second-most-common indication for transplant after idiopathic pulmonary fibrosis and interstitial lung disease, but that the United Network for Organ Sharing 2005 lung allocation scores are very low for COPD patients, and thus organs would be hard to obtain for this specific group of HIV patients.

"But it would be a great candidate for us," he added. "We would definitely do a transplant in that group of patients, irrespective of their HIV status."

Dr. Seethamraju and his coauthors reported no relevant disclosures.

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First guidelines for PH in sickle cell disease released

Hydroxyurea is top tool against high mortality risk.

BY WHITNEY MCKNIGHT
Frontline Medical News

The first treatment guidelines developed for pulmonary hypertension in sickle cell disease are now available from the American Thoracic Society.

Because more effective treatments hav e extended the lives of patients with the disease, their risk of mortality from pulmonary hypertension and elevated tricuspid regurgitant jet velocity has increased. Until now, however, there has been no standardized approach for identifying and managing these conditions.

The guidelines are published in March in the American Journal of Respiratory Critical Care Medicine (doi: 10.1164/rccm.201401-0065ST).

The multidisciplinary committee that wrote the guidelines defined mortality risk as a tricuspid regurgitant velocity (TRV) of at least 2.5 m/second; an N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level of at least 160 pg/mL; or pulmonary hypertension (PH) confirmed by a right heart catheterization (RHC).

Patients with elevated mortality risk should be treated with hydroxyurea as first-line therapy. Chronic transfusion therapy for patients who are not candidates for or responsive to hydroxyurea is noted as a "weak recommendation."

For those with RHC-confirmed pulmonary hypertension, venous thromboembolism, and no additional risk factors for hemorrhage, indefinite – not limited – anticoagulant therapy is recommended.

For patients with either an elevated TRV or an elevated NT-pro-BNP level, the guidelines strongly recommend against pulmonary hypertensive–specific therapies such as prostanoid, endothelin-receptor antagonist, and phosphodiesterase-5 inhibitor therapy.

The same guidance was given for patients who have RHC-confirmed PH.

While the guidelines recommend against targeted therapies for RHC-confirmed pulmonary hypertension, a trial of either a prostanoid or an endothelin-receptor antagonist is recommended for patients with confirmed PH and elevated pulmonary vascular resistance, normal pulmonary capillary wedge pressure, and related symptoms. These patients should not be given phosphodiesterase-5 inhibitor therapy as first-line treatment.

The lack of both large-scale clinical trials in this population and integrated standards of care limit the guidelines' effect, Dr. Elizabeth S. Klings, who chaired the guidelines committee, noted in a written statement.

"Management of [these patients] will ultimately be a collaborative effort including adult and pediatric pulmonologists, cardiologists, and hematologists," added Dr. Klings of the department of medicine at Boston University.

Dr. Klings receives support from NIH grant R21HL107993.

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VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: The guidelines are a breath of fresh air. I feel they are very well thought out. More research needs to be done on the therapies for pulmonary hypertension, but the authors of these guidelines admit that there is a paucity of data in this area.

In addition, more collaboration is needed between our pulmonary, hematology, oncology, and cardiology specialties. Pulmonologists do not perform right heart catheterizations, but when we ask cardiologists about pulmonary hypertension concerns, we regularly get shot down by the ones who feel that echocardiograms are sufficient to look for this problem. Yet when we want help managing these patients, they don't want to do that either because it is pulmonary hypertension. You need a dedicated group of people locally to workup these patients.

There are not many experienced pulmonary hypertension centers easily accessible for both adult and pediatric patient referrals. It is difficult, for example, to refer patients out of state and get it approved by insurance companies.

Minority correctly use EpiPen or metered dose inhaler

BY SHERRY BOSCHERT
Frontline Medical News

SAN DIEGO – Only 12% of 91 patients in Texas allergy/immunology clinics knew how to use an epinephrine autoinjector correctly, and only 7% of 41 patients could demonstrate correct use of their metered dose inhaler with a spacer, a small prospective study showed.

That's not good enough, Dr. Rana S. Bonds said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. Her team has begun studying interventions to improve correct use of those devices and "will be sharing that data in the near future," she said.

They asked patients to demonstrate the use of an EpiPen or a metered dose inhaler (MDI) and spacer and scored the patients' adherence to the EpiPen manufacturer's instructions or published standards for MDI/spacers.

For the EpiPen, 25% of patients missed one of the five steps for correct use, 18% missed two steps, and 19% missed three steps. "It was fairly alarming" to find that 31% got four steps wrong and 8% missed all five steps, said Dr. Bonds of the University of Texas Medical Branch, Galveston. (Percentages total more than 100% because they were rounded.)

The most common mistake with the EpiPen involved the final step. "Once they deployed the epinephrine injection, they didn't hold it down long enough. They were bouncing it off the thigh or whatever body part they thought they should inject it into," she said.

Patients' most common mistake with spacer use was failing to exhale before triggering the inhaler.

DR. BONDS

For the MDI/spacer, 16% of patients performed 1 of 11 steps for use incorrectly, 16% missed 2 steps, 21% missed 3 steps, and 18% missed 4 steps. Another 11% missed 5 steps, 5% missed 6 steps, 11% missed 7 steps, and 3% got all 11 steps wrong, Dr. Bonds and her associates reported. The most common mistake was failing to exhale before triggering the inhaler for inhalation.

The study recruited patients from the university's main allergy/immunology clinic and its satellite clinics. Trainers are available at each clinic, and patients are supposed to see them before leaving with one of the devices, but the findings raise the question of whether health care providers at the clinics consistently make sure that happens, she said.

Younger patients, males, and patients with a medical background were more likely to show that they could use the EpiPen correctly. Being African American or less educated was associated with a greater likelihood of incorrect use. Correct usage rates differed significantly between some of the clinic sites.

Factors that didn't correlate with correct or incorrect use of the EpiPen included whether a family member also used the device, being prescribed the EpiPen more or less than 1 year ago, and whether patients had ever used the EpiPen (most hadn't).

The number of patients in the MDI/spacer group was too small to permit risk factors to be analyzed, Dr. Bonds said.

Previously published studies have reported that 22% of food-allergic adolescents could demonstrate correct use of epinephrine and that rates of incorrect inhaler use ranged from 50% to 94%, she said. Other studies have shown that incorrect use reduces the treatment's clinical efficacy, and that repeated instruction increases the likelihood of correct use.

Dr. Bonds reported having no relevant financial disclosures.

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Blacks don't embrace radiotherapy for early NSCLC

BY PATRICE WENDLING
Frontline Medical News

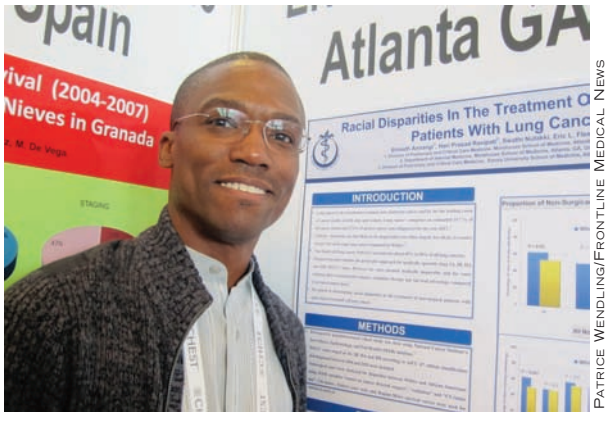
MADRID – Black patients may need additional guidance from clinicians to use radiotherapy for potentially curable lung cancer, a retrospective, population-based study suggests.

Among 6,628 patients diagnosed with early-stage nonsquamous non–small cell lung cancer (NSCLC), primary radiation therapy doubled median survival from 11 months to 22.6 months for cases not receiving surgery.

Despite the survival advantage, blacks were significantly more likely than whites were to skip radiotherapy for stage IA NSCLC (46% vs. 37.5%), Dr. Eric Flenaugh, FCCP, chief of pulmonary and critical care medicine and vice chair of the department of medicine at Morehouse School of Medicine, Atlanta, reported at the CHEST World Congress.

A subgroup analysis of nonsurgical stage IA cases in which surgery was not recommended or was contraindicated showed that 61% of whites went on to radiotherapy, compared with 47% of blacks. When surgical resection was recommended but not performed, radiotherapy use was similar between races.

"What this basically says is that if they [blacks] chose not to have surgery, then they weren't going to have anything," Dr. Flenaugh said in an interview. "We have to look at our approach to discussing with African Americans that have curable-stage cancer, particularly the IAs, that if you're not a surgical candidate or choose not to have surgery, there are other options like radiotherapy that can improve your survival."



PATRICE WENDLING/FRONTLINE MEDICAL NEWS

Dr. Eric Flenaugh: More guidance could lead to survival of more African American patients.

The data did not allow the investigators to determine patients' chemotherapy status or what factors drove the lower uptake of radiotherapy, but prior research has shown that blacks undergo surgery for lung cancer less often than whites, even after access to care has been demonstrated (J. Clin. Oncol. 2006;24:413-8).

The current analysis, led by internal medicine resident Srinadh Annangi, MBBS, used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results database for 6,628 patients diagnosed with NSCLC between 2004 and 2010, of which 4,210 did not receive surgery. NSCLC was staged as IA, IB, IIA, and IIB according to American Joint Committee on Cancer 6th edition classifications.

A little more than half of the 5,915 whites and 713 African Americans were male, with a median age of 78 years and 67.5 years.

The proportion of tumors less than 2 cm in size for stages IA and IIA and less than 5 cm for stages IB and IIB was not significantly different between races, according to the poster presentation. No significant racial disparities were seen for nonsurgical stage IB, IIA, and IIB cancers.

Among operable NSCLC cases, whites were significantly more likely to have surgery than were blacks (37% vs. 32%), whereas blacks were significantly more likely to have surgery recommended, but refused or not performed (9% vs. 6%). Importantly, the proportion of blacks undergoing their recommended surgery was lower for both stage IA (78.3% vs. 86%) and IB cancers (74.6% vs. 81.3%).

The authors note that surgical resection remains the preferred treatment approach for operable stage I and II NSCLC, but conclude that eliminating racial disparities in radiotherapy for early-stage NSCLC deemed inoperable or where surgery is refused can improve survival in the African American population.

Dr. Flenaugh and his coauthors reported no financial disclosures.

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Phytoestrogens may be helpful in asthma and allergy

BY M. ALEXANDER OTTO
Frontline Medical News

SAN DIEGO – Could increased consumption of phytoestrogens help prevent or treat asthma and allergy?

Dr. Jessica Savage, an allergist and immunologist at Brigham and Women's Hospital, Boston, and her colleagues correlated one-time urinary phytoestrogen measurements from 7,909 subjects in the National Health and Nutrition Examination Survey, 2003-2010, with histories of physician-diagnosed asthma and self-reported wheezing.

If the association holds up, it might suggest a role for phytoestrogen probiotics.

DR. SAVAGE

The investigators also considered serum total and specific IgE levels obtained from a subset of 2,218 subjects. They defined atopy as having at least one positive IgE level (0.35 kU/L or above) to an aeroallergen.

Adjusting for a wide range of potential cofounders, including age, gender, race, urinary creatinine, poverty, body mass index, smoking, and smoke exposure, they found that, for every natural log increase in urinary enterolactone, the odds of asthma decreased by 8%.

Enterolactone also was significantly inversely associated with asthma prevalence and had the strongest inverse association with wheezing.

For every natural log increase in urinary o-desmethylangolensin (ODMA), there was a 7% decrease in the odds of wheeze. The odds of atopy significantly decreased with increasing ODMA levels.

"We can't say anything about cause and effect" yet, but if the association holds up with further investigation, it might suggest a role for phytoestrogen probiotics to help treat the conditions, Dr. Savage said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Phytoestrogens are plant-derived compounds. Gut bacteria convert lignans, which are particularly plentiful in flax seeds, into enterolactone, and the isoflavone daidzein, particularly plentiful in soybeans, into ODMA.

"Increased consumption of sources of phytoestrogens or probiotics to increase precursor conversion may help prevent or treat asthma and allergic disease," Dr. Savage said. "I was really surprised that the enterolactone signal is very strong both for asthma and for wheezing."

Although soy-derived compounds have been associated with better lung function and decreased lung symptoms in the past, "there's really not a lot known about enterolactone," she said. "The idea is that somehow these metabolites are anti-inflammatory. Urinary levels are partly due to your diet and partly to having the right bacterial flora in your gut. Our findings could be explained by people just having different diets; they could also be explained by people with asthma having lower levels of the right kind of bacteria."

About half the subjects were female, and about 80% were over age 18 years; 70% of the study population was white. Enterolactone tertiles were defined as 0.2-178; 179-644; and 645-122,000 ng/mL urine. ODMA tertiles were defined as 0.1-1.4; 1.5-12.8; and 12.9-18,500 ng/mL urine.

The study was funded by the National Institutes of Health. The investigators reported having no disclosures.

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VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: It is a novel idea that phytoestrogens could prevent or treat allergy and asthma. However, this study population had few pediatric subjects, the majority of patients were white, and it was a one-time measurement. Before we recommend to our patients to increase consumption of phytoestrogens, further research to include pediatric patients, a more diverse ethnic background, and frequent monitoring of urinary levels will be helpful to document if there is a true cause and effect.

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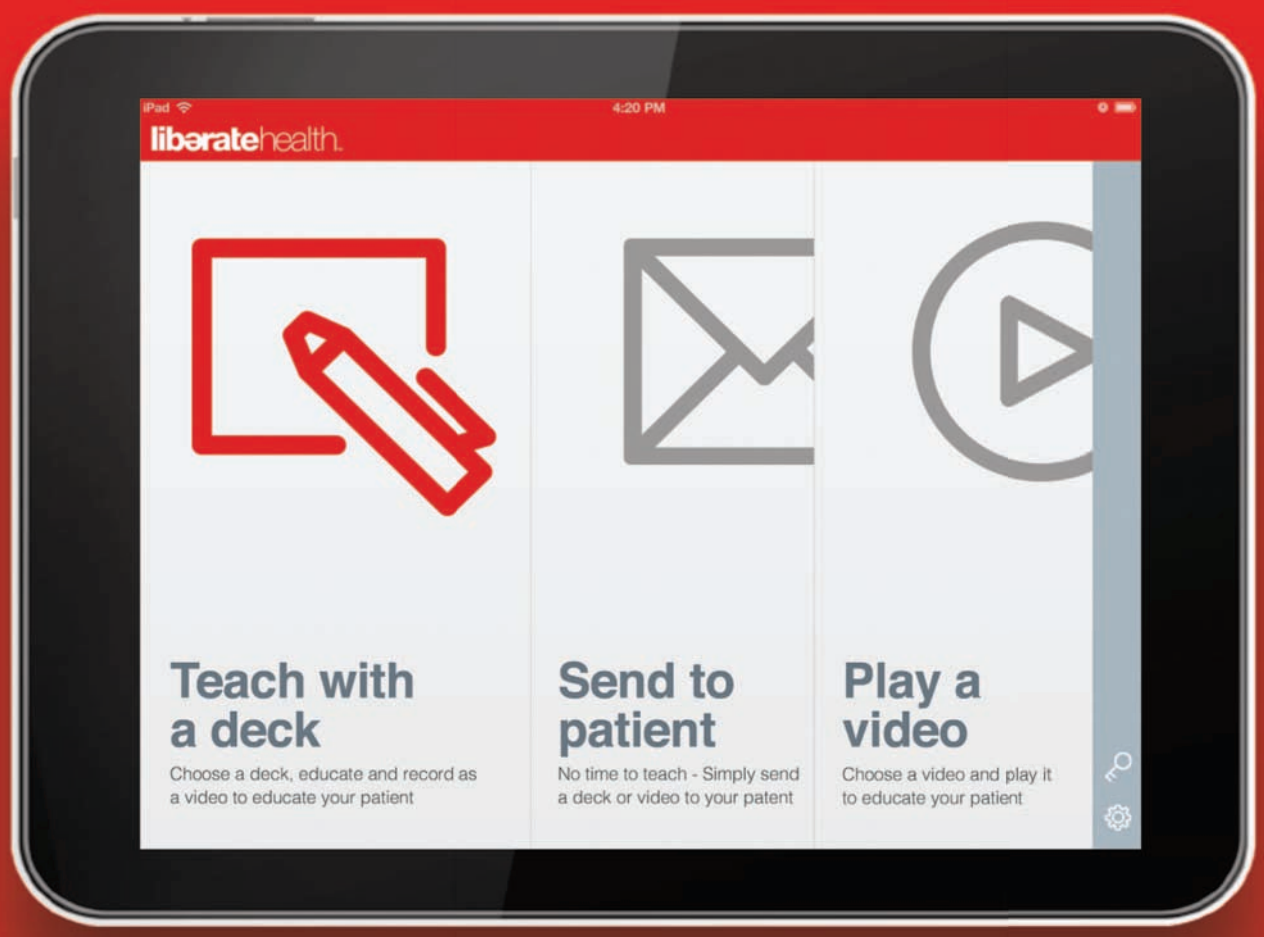

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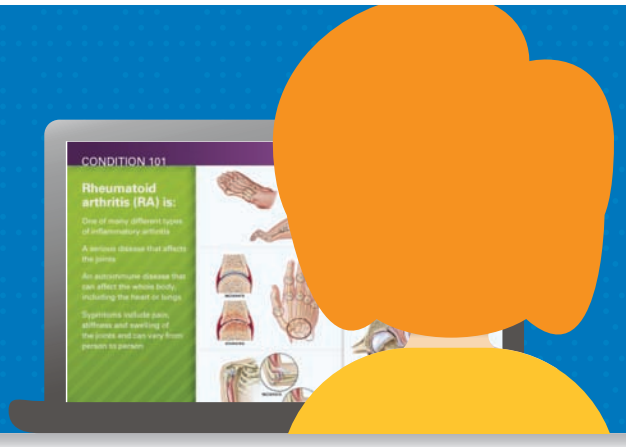

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Sepsis mortality declines in tandem with ICU mortality

BY MARY ANN MOON
Frontline Medical News

Mortality related to severe sepsis steadily and substantially declined between 2000 and 2012 across Australia and New Zealand, contrary to the pervasive sense that little progress has been made in achieving that goal, according to a report presented at the International Symposium on Intensive Care and Emergency Medicine.

The findings of this study challenge the view that little progress has been made.

DR. KAUKONEN

The report was simultaneously published in JAMA.

In a retrospective analysis of information in the Australian and New Zealand Intensive Care Society adult ICU database, which covers more than 90% of all ICU admissions in both countries, researchers examined time trends in mortality among 101,064 patients who had severe sepsis, both with and without septic shock. Even though the incidence of severe sepsis increased during the study period, sepsis-related mortality steadily declined from 35.0% in 2000 to 18.4% in 2012, said Dr. Kirsi-Maija Kaukonen of the Australian and New Zealand Intensive Care Research Centre, department of epidemiology and preventive medicine, Monash University, Melbourne, and her associates.

At the same time, the rate of discharge to home increased and that of discharge to rehabilitation facilities dropped, indicating that the decreased in-hospital mortality wasn't a statistical artifact resulting from transferring out the sickest patients who were most likely to die imminently, the investigators said.

The decreased mortality extended across all subgroups of patients and remained robust in several sensitivity analyses and after numerous adjustments of the data for factors such as illness severity, hospital size, length of stay, and patient age and comorbidities. "Similar decreases in mortality over time have been reported in other retrospective studies" in the United States and elsewhere, Dr. Kaukonen and her associates said (JAMA 2014 March 18 [doi:101001/jama.2014.2637]).

A similar decline in mortality occurred among nonseptic ICU patients during this time interval. "It is unclear whether any improvements in diagnostic procedures, earlier and broader-spectrum antibiotic treatment, or more aggressive supportive therapy" contributed to the decrease in sepsis mortality. But the observation that "an equivalent improvement occurred in nonseptic patients supports the view that overall changes in ICU practice rather than in the management of sepsis explain most of our findings," they wrote.

During the study period, many treatments to improve survival in severe sepsis, including activated protein C, low-dose hydrocortisone, antithrombin III, tifacogin, vaso agents, fludrocortisone, intensive insulin therapy, large-molecular-size hydroxyethyl starch, and eritoran, showed initial promise in animal and phase II trials but have ultimately failed to do so in real world practice. "These failures have led to a sense that little progress has been made in decreasing the mortality of severe sepsis," but the findings of this study challenge that view, Dr. Kaukonen and her associates said.

Dr. Kaukonen reported no financial conflicts; one of her associates reported receiving support from Gambro, Baxter, Philips, and Braun.

VIEW ON THE NEWS

This "compelling" study "overcomes many of the limitations of prior studies" concerning sepsis-related mortality by virtue of its careful design, according to Dr. Theodore J. Iwashyna and Dr. Derek C. Angus.

The study investigators first amassed a huge amount of data to examine from an ICU registry of more than 1 million patients seen during an extended (12-year) period. Then they diligently identified all hospitalizations for infection, even those that weren't labeled as "severe sepsis," then applied "objective definitions of acute organ dysfunction carefully abstracted at the bedside by nurse abstractors."

Dr. Kaukonen and her colleagues used a variety of analytical strategies to verify that what they found were not misleading artifacts but "true changes in the epidemiology of severe sepsis." And they performed several sensitivity analyses of the data, all of which confirmed the results of the main analysis.

These observations were taken from an editorial by Dr. Iwashyna and Dr. Angus accompanying Dr. Kaukonen's report (JAMA 2014 March 18 [doi:10.1001/jama.2014.2639]). Dr. Iwashyna is with the division of pulmonary and critical care in the department of internal medicine at the University of Michigan, Ann Arbor, and is with the Veterans Affairs Ann Arbor Health System. Dr. Angus, a contributing editor at JAMA, is in the department of critical care medicine at the University of Pittsburgh. Dr. Iwashyna reported no potential financial conflicts of interest; Dr. Angus reported ties to several pharmaceutical firms.

Higher MAP target doesn't reduce organ dysfunction in sepsis

MAP *from page 1*

(nonsignificant hazard ratio in the high-target group, 1.07), according to data presented at the International Symposium on Intensive Care and Emergency Medicine and simultaneously published online (N. Engl. J. Med. 2014 March 18 [doi:10.1056/NEJMoa1312173]).

In addition, there were no significant differences between the high- and low-target groups in the secondary outcomes of 90-day mortality (43.7% vs. 42.3%; HR, 1.04), need for mechanical ventilation, ICU length of stay, or Sequential Organ Failure Assessment score at day 7.

Atrial fibrillation, however, was significantly more common in the high-target group than in the low-target group, at 6.7%, compared with 2.8%. This could be related to the high-target group receiving significantly higher doses of vasopressor catecholamines over a significantly longer time period, although other confounding factors cannot be ruled out, lead author Dr. Pierre Asfar of University Hospital of Angers (France), reported on behalf of SEPSISPAM investigators.

Among patients with chronic arterial hypertension, who comprised more than 40% of the study population, use of the high MAP target significantly reduced both the incidence of doubling of plasma creatinine (39% vs. 52%) and the rate of renal-replacement therapy (31.7% vs. 42.2%).

The authors noted that, although investigators were asked to treat patients to a MAP of 65-70 mm Hg in the low-target group, the observed pressures were for the most part between 70 and 75 mm Hg. The high-target group was likewise off goal, at a mean of 70 mm Hg. They also acknowledged that the lower-than-expected death rate, albeit in line with more recent trials, led to an underpowered study.

The French Ministry of Health funded the trial. Dr. Asfar reported lecture fees from LFB Biomedicaments.

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VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: Since organ dysfunction in severe sepsis and septic shock is believed to be caused by inadequate perfusion, it was tempting to hypothesize that a higher MAP target could result in reduced organ dysfunction and improved survival. Unfortunately, we still are not certain that the negative result of this trial is the final word, because the average achieved MAP in both patient groups was so similar. Nevertheless, there remains, for now, no compelling reason to shoot for a higher MAP than 65 mm Hg in clinical practice.

Coding practices could bias pneumonia mortality rates

Hospital quality comparisons waver when nosocomial cases are excluded, researchers say.

BY AMY KARON
Frontline Medical News

Variability in coding of pneumonia cases skewed risk-standardized mortality rates and hospital performance rankings, investigators reported in Annals of Internal Medicine.

'Misclassification could harm individual hospitals and weaken confidence in public reporting.'

DR. ROTHBERG

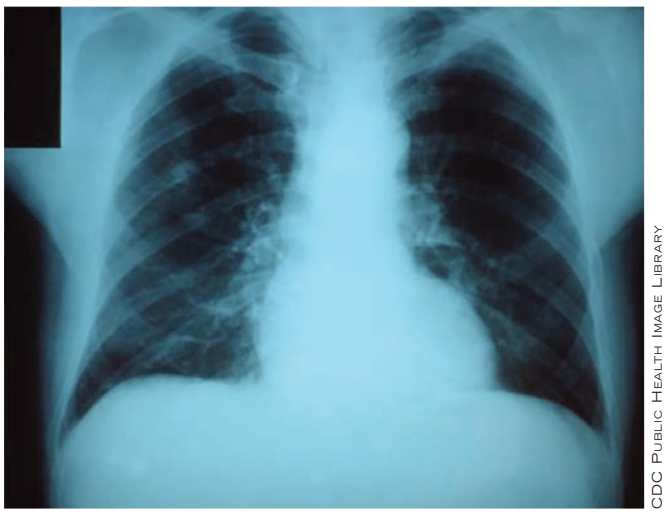
The bias could impede efforts to compare quality of care among hospitals, Dr. Michael Rothberg of the Cleveland Clinic in Ohio and his associates said (Ann. Int. Med. Mar. 17 [doi:10.7326/M13-1419]).

The Centers for Medicare & Medicaid Services partially based hospital reimbursements on 30-day risk-standardized mortality rates. To exclude nosocomial pneumonia cases, CMS included only patients with a primary diagnosis of pneumonia when estimating 30-day risk-standardized pneumonia mortality rates.

But over time, hospitals changed how they coded the sickest patients with pneumonia, Dr. Rothberg and his associates said. These patients increasingly received a principal diagnosis of sepsis or organ failure, instead of pneumonia, and thus were excluded from mortality estimates.

"These events gave the false impression that pneumonia outcomes had improved more than they had," they said, adding that "just as changes in coding over time could lead to erroneous conclusions about decreasing mortality rates, variation in coding across hospitals could lead to biased estimates of their relative mortality rates."

The investigators conducted a cross-sectional study of more than 250,000 hospitalizations of adults with a principal or secondary diagnosis of pneumonia at 329 U.S. hospitals between 2007 and 2010.



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Sepsis or organ failure, not pneumonia, is often the principal diagnosis for hospitals' sickest patients.

When the definition of pneumonia excluded patients with primary sepsis or respiratory failure, 4.3% of hospitals had mortality rates that were significantly better than the mean, and 6.4% had rates that were significantly worse. But when the expanded definition was used, 12% of hospitals had mortality rates that were better than the mean, while 23% had rates that were worse. Performance ranking changed for 28% of hospitals.

The bar for coding a patient with sepsis is low and hospitals interested in maximizing revenue while reflecting the severity of illness among their patients will work to clear that bar.

When the expanded case definition was used, outlier status worsened for 41% of the hospitals with the highest proportions of patients with primary sepsis or respiratory failure, but improved for 20% and worsened for none of the hospitals with the lowest proportions of these patients.

"Efforts to broaden the scope of hospital performance measures from the initial set of measures based on processes to those focused on patient outcomes are laudable, but caution is required," the investigators said. "Misclassification could harm individual hospitals and weaken confidence in public reporting."

Adding principal diagnoses of respiratory failure or sepsis with secondary pneumonia to the definition of pneumonia could help lessen the biases, they said.

The findings "comport with what we see in our own practice," Dr. Scott A. Flanders and Dr. Sanjay Saint said in an editorial accompanying Dr. Rothberg's report (Ann. Intern. Med. 2014;160:430-1).

"Hospitals caring for a patient with pneumonia coded with sepsis might capture a diagnostic-related group-based payment of more than $15,000 compared with only $6,000 if that patient were coded with 'just' pneumonia."

As the investigators pointed out, "the bar for coding a patient with sepsis is low and hospitals interested in appropriately maximizing revenue while accurately reflecting the severity of illness in their patient population will work to clear that bar."

Just as hospitals have changed course and modified their approach to care to better address quality concerns articulated in current measures, the Centers for Medicare & Medicaid Services and others should also learn from "end users" and researchers and adapt their approach to measurement, they said.

"Perhaps we should declare a 'time-out' on developing new performance measures until we ensure that the current ones are appropriate and serve their intended purposes."

The study was supported by the Agency for Healthcare Research and Quality.

VIEW ON THE NEWS

Dr. James A.L. Mathers Jr., FCCP, comments: This report raises the very important issue of accurate coding and documentation. With the imminent implementation of the ICD-10 system, increased scrutiny of health care services, and the imposition of significant financial penalties for outliers, attention to the new coding and documentation requirements will be crucial for all providers.

Pages 14a—14ft

E-cigarettes trigger sharp rise in poison control calls

BY MIKE BOCK
Frontline Medical News

Calls to U.S. poison control centers because of e-cigarette exposure increased from 1 per month in September 2010 to 215 per month in February 2014, according to a new study published in the Morbidity and Mortality Weekly Report.

"Calls about exposures to e-cigarettes, which were first marketed in the United States in 2007, now account for 41.7% of combined monthly e-cigarette and cigarette exposure calls to [poison control centers]," wrote the investigators, led by Dr. Kevin Chatham-Stephens of the CDC (MMWR 2014;63:291-2).

Researchers from the Centers for Disease Control and Prevention analyzed data from 2,405 e-cigarette calls to poison control centers in all 50 states, the District of Columbia, and U.S. territories from September 2010 to February 2014. Although calls regarding overexposure are much more common with conventional tobacco products (16,248 calls over the same period of time), the investigators noted that 42% of the e-cigarette exposure calls involved people aged 20 years and older, whereas 94.9% of tobacco exposure calls involve children younger than 5 years.

In addition, health care facilities were responsible for significantly more of the e-cigarette exposure calls than for cigarette exposure calls, 12.8% vs. 5.9%. And callers were significantly more likely to report adverse health effects with e-cigarette exposures (57.8% of calls) than with cigarette exposures (36% of calls).

Poisoning cases can occur either from an exposure to the device itself or to the nicotine liquid contained in a small cartridge that the user inserts into the e-cigarette. Exposure to the liquid can occur through inhalation, ingestion, or absorption and the most common adverse health effects in e-cigarette exposure calls were vomiting, nausea, and eye irritation.

Currently, e-cigarettes are not regulated by the FDA Center for Tobacco Products, but by the FDA Center for Drug Evaluation and Research.

Currently, e-cigarettes and their components that are marketed for therapeutic purposes such as smoking cessation are not regulated by the FDA Center for Tobacco Products, but are instead regulated by the FDA Center for Drug Evaluation and Research.

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CDC sounds alarm on hospital antibiotic overuse

BY PATRICE WENDLING
Frontline Medical News

A scathing new report by the Centers for Disease Control and Prevention found ample room for improvement in inpatient antibiotic prescribing.

Findings include continued overuse of antibiotics in hospitals, errors in prescribing, and the lifesaving potential of efforts to reduce antibiotic use:

- Physicians in some hospitals prescribed three times as many antibiotics as doctors in other hospitals, even though patients were being cared for in similar areas of each hospital.
- Antibiotic prescriptions contained an error in 37% of cases involving treatment for urinary tract infections or use of the common and critical drug, vancomycin (Vancocin).
- Models predicted that a 30% decrease in the use of broad-spectrum antibiotics would lead to a 26% reduction in *Clostridium difficile* infections, which kill roughly 14,000 hospitalized patients each year.

"Antibiotics are often lifesaving, and we have to protect them before our medicine chests run empty," CDC director Tom Frieden said during a press conference highlighting the report, released in the CDC's Morbidity and Mortality Weekly Report (2014 March 4;63:1-7).

Dr. Frieden announced that the CDC's fiscal 2015 budget, part of President Obama's budget initiative, contains a $30 million increase in funds to establish a robust infrastructure that will detect antibiotic threats and protect U.S. patients and communities.

The new monies would allow the CDC to extend the "detect and protect" strategy to combat antibiotic resistance outlined last year, help support state and hospital efforts to implement antibiotic stewardship programs, and improve rapid detection of antimicrobial threats and outbreaks.

"One of the things that makes us so focused on antimicrobial resistance is that not only is it a really serious problem, but [also] it's not too late," Dr. Frieden said.

If funded, he anticipates the CDC and other stakeholders will be able to reverse drug resistance and cut in half the rate of *C. difficile* and the "nightmare" carbapenem-resistant Enterobacteriaceae infections.

It was noted that robust efforts to improve the use of antibiotics associated with *C. difficile* in the United Kingdom have resulted in more than a 50% reduction in use of those targeted agents and a roughly 70% reduction in *C. difficile* infections over the past 6-7 years.

The CDC is strongly recommending that every hospital in the United States have an antibiotic stewardship program and is providing a new checklist to help facilities with the task. The checklist contains seven core elements of an effective program: leadership commitment; accountability for outcomes under a single leader; drug expertise under a single pharmacist leader; taking action on at least one prescribing improvement practice; tracking antibiotic prescribing and resistance patterns; reporting regularly to staff about these patterns; and educating staff on antibiotic resistance and improving prescribing practices.

Specific advice was also given to clinicians to order recommended cultures before antibiotics are given and to start drugs promptly; make sure the indication, dose, and expected duration are specified in the patient record; and reassess patients within 48 hours and adjust treatment, if necessary, or stop treatment, if indicated.

The new CDC report is based on a review of data from all 323 hospitals in the MarketScan Hospital Drug Database and from hospitals in the CDC's Emerging Infections Program.

Dr. Frieden and Dr. Combes reported having no financial disclosures.

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VIEW ON THE NEWS

Dr. Daniel Oulette, FCCP, comments: In 1942, a young woman dying from streptococcal sepsis became the first person to be treated with penicillin. Her treatment and subsequent recovery heralded the dawn of an era of effective antibiotic treatment for many illnesses due to infection. Seven decades later, we know that there is another side to this story.

The dose of penicillin needed in 2014 to treat a similar illness is more than 100-fold higher than that used in 1942. Emerging bacterial resistance requires us not only to treat patients with innovative dosing stratagems, but to rush to develop an increasingly large menu of antibiotic choices to beat the race against resistant organisms.

The scientific insights of the 20th century led to the development of new wonder drugs; the scientific insights and methodology of the 21st century will be required to maintain their effectiveness. The watchwords of the next age may not be antibiotic identification and chemical synthesis but antibiotic rotation, reduction of variance in practice, assessment of risk-benefit ratios, and outcomes research. The Centers for Disease Control and Prevention in the United States has taken up the banner of antibiotic stewardship by earmarking an additional $30 million in the proposed 2015 budget targeting antibiotic use. In addition, the CDC has provided a seven-point checklist to help institutions develop and manage stewardship programs. Significantly, the first three of the seven points refer to leadership. The combination of funding and leadership may allow physicians to continue to treat patients with infections successfully into the future.

Aspirin sensitivity is signal for asthma severity

BY PATRICE WENDLING
Frontline Medical News

MADRID – Aspirin sensitivity was strongly associated with asthma severity and the presence of chronic rhinosinusitis with nasal polyps in a prospective, multicenter study.

"Aspirin sensitivity may be considered a clinical marker for severe asthma and for the presence of chronic rhinosinusitis with nasal polyps, and a potential marker for united airway disease," Dr. José Antonio Castillo reported at the CHEST World Congress.

Patients with aspirin-intolerant asthma showed significantly higher Lund & McKay CT scores than aspirin-tolerant asthmatic patients.

Aspirin-exacerbated respiratory disease is commonly associated with chronic rhinosinusitis (CRS) with nasal polyps, but little information is available on the correlation between aspirin sensitivity and severe asthma.

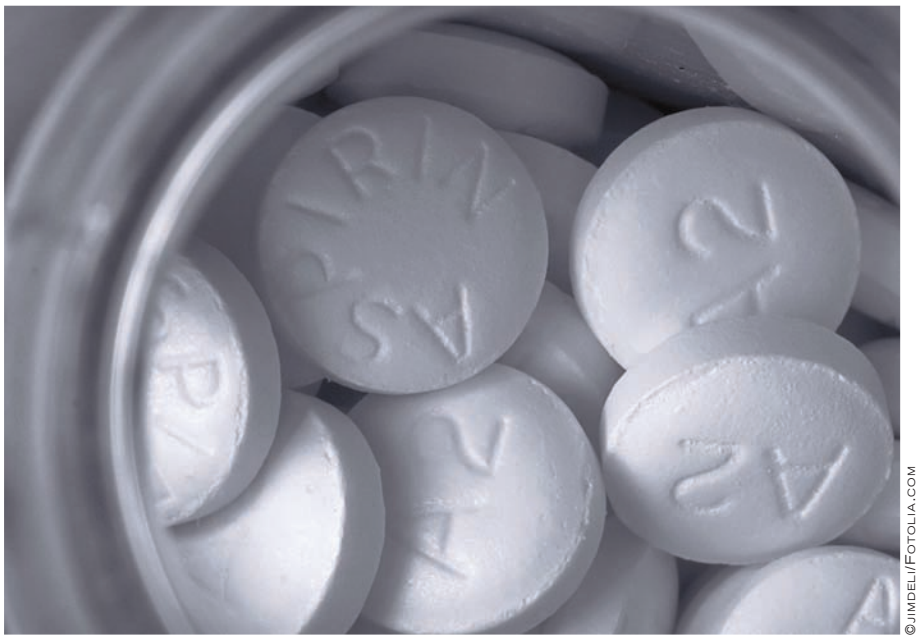
To evaluate the presence of aspirin sensitivity and CRS with nasal polyps in a cohort of asthmatic patients, pulmonologists and ENT specialists at 23 hospitals in Spain and Latin America recruited 492 patients, aged 18-70 years, attending outpatient clinics with the diagnosis of asthma for at least 1 year. Aspirin sensitivity was assessed by clinical history and/or aspirin challenge, and CRS with nasal polyps was assessed by nasal symptoms, nasal endoscopy, and sinus computed tomography (CT) scan.

Among 473 evaluable patients, 72 (15%) were aspirin sensitive, 14.6% had no nasosinal disease, 12.6% nonallergic rhinitis, 36.8% allergic rhinitis, 16.6% CRS without nasal polyps, and 19.4% CRS with nasal polyps.

Aspirin-intolerant asthma was strongly related to asthma severity. In all, 3 of the 72 (4.2%) aspirin-intolerant patients were classified as having intermittent asthma (odds ratio, 1); 17 (23.6%) as mild persistent (OR, 4.3); 21 (29.2%) as moderate persistent (OR, 4.3); and 31 (43%) were classified as having severe persistent asthma, which was statistically significant (OR, 7.8; *P* less than .05), reported Dr. Castillo, with the pneumology service at Chiron Dexeus University Hospital, Barcelona.

The presence of chronic rhinosinusitis with nasal polyps was also associated (38.9%; 28/72 patients) with aspirin sensitivity (OR, 9.05; *P* less than .001).

Aspirin sensitivity was present in 4.5% of patients with no nasosinal disease, 18.6% of those with nonallergic rhinitis, 9.2% with allergic rhinitis, 17.5% with CRS with no nasal polyps, and 29.8% with CRS and nasal polyps.



In the multicenter study, 43% of aspirin-intolerant patients were classified as having severe persistent asthma.

Further, patients with aspirin-intolerant asthma showed significantly higher Lund & McKay CT scores than aspirin-tolerant asthmatic patients, according to the poster presentation.

The current results perhaps could be validated by matching aspirin sensitivity with a biomarker of severe asthma, that is, periostin, but are such that they already use aspirin sensitivity as a clinical marker of severe asthma, Dr. Castillo said in an interview with this newspaper.

Patients in the study had a mean age of 45 years and a mean body mass index of 26.9 kg/m^2 (range, 16.8-49.8 kg/m^2); 70.5% were female, and 9.6% were smokers.

Asthma was intermittent in 85 patients, mild persistent in 122, moderate persistent in 154, and severe persistent in 131, according to Global Initiative for Asthma (GINA) severity criteria.

Dr. Castillo and his coauthors reported no financial disclosures.

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Abdominal pain during desensitization? Think pancreatitis

BY BRUCE JANCIN
Frontline Medical News

KEYSTONE, COLO. – Pancreatitis may be a rare complication of aspirin desensitization therapy – and perhaps actually not so rare – in patients with aspirin-exacerbated respiratory disease.

"Be aware: If you're doing desensitization and a patient reports severe abdominal pain, please check the pancreatic enzyme levels," Dr. Rohit K. Katial urged at a meeting on allergy and respiratory diseases sponsored by National Jewish Health.

He and his coworkers were the first to describe this novel complication in a report detailing three cases. Two occurred during the 2-day aspirin desensitization procedure, with pancreatic lipase levels of 425 and 789 U/L, respectively, with normal defined as 13-63 U/L. The third involved a subacute presentation beginning 4 days after finishing desensitization, with a lipase level of 207 U/L while the patient was on standard postdensensitization high-dose aspirin therapy at 650 mg b.i.d. (J. Allergy Clin. Immunol. 2012;129:1684-6).

Gallbladder disease, alcohol, drugs, and other secondary causes of pancreatitis were ruled out in all three cases, noted Dr. Katial, professor of medicine at the University of Colorado, Denver, and director of allergy and immunology clinical services at National Jewish Health.

This link between pancreatitis and aspirin desensitization may actually not be all that uncommon.

DR. KATIAL

This previously unreported close temporal association between pancreatitis and aspirin desensitization is of particular interest because it may actually not be all that uncommon. Indeed, other investigators, in a study of 172 aspirin-desensitized patients, reported that 27% of them discontinued high-dose maintenance aspirin therapy during the first year. The most common reason for doing so was the emergence of epigastric pain, accounting for 14 discontinuations. Another two patients discontinued therapy because of GI bleeding (J. Allergy Clin. Immunol. 2003;111:180-6).

These gastrointestinal reactions weren't extensively investigated, since it's well known that high-dose aspirin is associated with gastritis and peptic ulcer disease. So it's quite possible that some of these cases of what was classified clinically as gastritis were actually pancreatitis, according to Dr. Katial.

The mechanism involved in pancreatitis in the setting of aspirin desensitization is unknown. Animal studies suggest the marked increase in leukotriene levels occurring during aspirin desensitization may play a role. Even though all three patients were on prophylactic montelukast (Singulair) at the time of aspirin challenge, the leukotriene receptor antagonist may not provide complete protection in a subset of vulnerable patients.

Dr. Katial reported serving as an advisor to and on the speakers bureau for Teva Pharmaceuticals.

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Asthma may increase risk of cardiovascular events

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Having asthma appears to significantly increase a patient's risk for cardiovascular events, while having allergic rhinitis appears to lower a patient's risk of some such events, results from a large cohort study demonstrated.

Studies of mouse models have suggested that Th1 inflammation "is associated with atherosclerosis and plaque development, while the Th2 or general allergic response seems to be protective against atherosclerosis," Dr. Angelina Crans Yoon said during a press briefing at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. At the same time, results from human studies regarding the association between allergic rhinitis and cardiovascular

Patients with allergic rhinitis had a significantly lower risk of myocardial infarction.

DR. CRANS YOON

events are mixed, said Dr. Crans Yoon, a first-year allergy fellow at Kaiser Permanente Los Angeles Medical Center.

In an effort to assess the relationship between cardiovascular disease and allergic rhinitis, she and her associates used the Kaiser Permanente Southern California regional database and ICD-9 codes to compare the incidence of cardiovascular and cerebrovascular events and all-cause mortality in a cohort of 109,229 allergic rhinitis patients and 92,775 asthma patients who were seen between Jan. 1, 1995, and Dec. 31, 2012. The cohorts were matched by age, sex, and ethnicity to reference cohorts and followed for a median of 8 years.

Patients with allergic rhinitis had a significantly lower risk of myocardial infarction (hazard ratio, 0.75), cerebrovascular disease (HR, 0.81), and all-cause mortality (HR, 0.51), yet their risk of all cardiovascular events was equal to that of the control cohort (HR, 0.97). At the same time, patients with asthma had a significantly higher risk of all cardiovascular disease (HR, 1.36), yet no significantly higher risk of cerebrovascular disease (HR, 1.03) or all-cause mortality (HR, 1.00).

The findings "led us to think of more questions," Dr. Crans Yoon said. "Why is there this decreased risk of events in patients with allergic rhinitis? What explains the risk of cardiovascular events in patients with asthma? Is atopy related to these differences? We started some secondary analyses looking at medication use. It looks like if you use any medications for allergic rhinitis or asthma, you have a decreased risk of some of these events, except for long-acting beta-agonists, which is consistent with previous reports." It also looks like positive IgE testing may be associated with a decreased risk of these events, she said.

Dr. Crans Yoon reported she had no relevant financial conflicts.

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Hold the ACE inhibitors during surgery?

BY NEIL OSTERWEIL
Frontline Medical News

SCOTTSDALE, ARIZ. – When it comes to holding or continuing with ACE inhibitors before surgery, all bets are off, a perioperative medicine consultant suggested.

Patients on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) have about a 50% risk of developing hypotension during surgery, and a significant proportion of those episodes could be severe, said Dr. Paul Grant, of the University of Michigan Health System in Ann Arbor.

"I recommend having some sort of standard approach [to perioperative ACE inhibitor use] at your institution if that's at all possible, either for a certain surgery type or across the board," he said at a meeting on perioperative medicine sponsored by the University of Miami.

Evidence from a small number of randomized trials and observational studies suggests that continuing ACE inhibitors during cardiac surgery may result in less cardiac enzyme release, less kidney injury, and a lower incidence of atrial fibrillation. In vascular surgery, evidence suggests that patients on ACE inhibitors who are undergoing surgery have less of a drop in cardiac output and may have improved creatinine clearance.

On the other hand, patients who remain on ACE inhibitors during surgery can experience a "profound" drop in blood pressure requiring immediate intervention, he said.

Data to support the continue vs. hold debate are sparse, but include a trial of 51 patients randomized to continue ACE inhibitors on the day of surgery or to have the drugs held for 12-24 hours before surgery. In all, 33 of the patients were on captopril (Capoten), and 18 were on enalapril (Vasotec).

Patients who remain on ACE inhibitors during surgery can experience a 'profound' drop in blood pressure.

DR. GRANT

The investigators found that among patients randomized to continue ACE inhibitor therapy, 7 of 7 on captopril and 9 of 14 on enalapril developed hypotension, defined as a systolic blood pressure (SBP) less than 90 mm Hg. In contrast, among patients assigned to the ACE-inhibitor hold protocol, only 2 of 11 on captopril and 4 of 19 on enalapril developed hypotension during surgery.

In a second randomized trial, investigators looked at 37 patients on an ARB who were randomly assigned to either discontinue ARB on the day before surgery (18 patients), or to receive their ARB 1 hour before anesthesia induction (19 patients).

The authors defined hypotension for their study as an SBP less than 80 mm Hg for more than 1 minute. They found that all 19 patients who continued on ARB had hypotension during surgery, compared with 12 of 18 who discontinued their ARB the day before. Patients who received their ARB on the day of surgery used significantly more vasoactive drugs. Despite the discontinuation of the ARB, there were no differences in hypertension between the groups in the recovery period. Postoperative cardiac complications occurred in one patient in each group.

In the final randomized study that Dr. Grant cited, 40 patients on an ACE inhibitor with good left-ventricular function were scheduled to undergo coronary artery bypass graft (CABG). They were randomly assigned to hold or continue on ACE inhibitors on the day of surgery.

Patients in whom the ACE inhibitors were held before CABG had higher mean blood pressures than patients who continued on the drugs, and they used less vasopressor during the surgery. In contrast, patients who continued on ACE inhibitors needed more vasodilators after CABG and in the recovery period. The authors of this trial did not study other clinical endpoints, Dr. Grant noted.

Evidence from two observational studies was more equivocal, however.

In a retrospective observational study, investigators studied the relationship between the timing of discontinuing ACE inhibitors and angiotensin II receptor subtype 1 antagonists (ARA) and the onset of hypotension in 267

Continued on following page

When to hold immunomodulators preoperatively

Surgery *from page 1*

sultative medicine at the University of Michigan Health System in Ann Arbor.

For example, it appears to be safe for patients on methotrexate to continue on therapy during elective orthopedic surgery. Evidence for this comes from a randomized clinical trial in which patients with rheumatoid arthritis (RA) were assigned to either continue on methotrexate (MTX) or suspend taking it for 2 weeks before and 2 weeks after surgery. The study also contained a control of patients with RA who were not on MTX (Ann. Rheum. Dis. 2001;60:214-7).

The investigators found that there were no significant differences in early complication rates or in complications up to 1 year of follow-up between patients who suspended or remained on MTX. Patients who stayed on the drug had significantly lower rates of RA flare.

Two systematic reviews also looked at the question. One review of eight studies echoes the findings of the aforementioned randomized trial (Clin. Exp. Rheumatol. 2009; 27:856-62), while the other review of four studies concluded that "continued MTX therapy appears to be safe perioperatively and seems also to be associated with a reduced risk of flares" (Clin. Rheumatol. 2008; 27:1217-20). None of the examined papers addressed the issue of safety in connection with comorbidities, age, or high doses of methotrexate.

"The bottom line here is that methotrexate should be continued for most surgeries. I think it might be reasonable to hold it in certain situations, for example if the patient has pretty bad kidney or liver disease, or if it's surgery to treat a major infection," Dr. Grant said.

TNF-alpha antagonists

In contrast, the data on tumor necrosis factor–alpha (TNF-alpha) antagonists are fuzzier, with limited and conflicting information on perioperative use of these agents (etanercept, infliximab, adalimumab, certolizumab, golimumab).

"The major concern with these drugs is infection," Dr. Grant said. He pointed to a meta-analysis published in JAMA in 2006, which showed that taking the drugs doubled the risk of serious infections in general. The study did not specifically look at perioperative use of TNF-alpha antagonists (JAMA 2006;295:2275-85).

A retrospective cohort study of 127 patients with RA who were undergoing various orthopedic procedures found that there were no differences in surgical site infections but more cases of wound dehiscence in patients who continued on the drugs, compared with those who interrupted their use perioperatively (Clin. Exp. Rheumatol. 2007;25:430-6).

A second, prospective study in 31 patients with RA undergoing foot/ankle surgery found that there were no significant differences in infection or healing between patients who interrupted therapy and those who did not (Foot Ankle Clin. 2007;12:509-24).

Other studies and systematic reviews in patients with RA or Crohn's disease generally found no significant differences in serious infection rates, but they did detect a higher incidence of skin and soft-tissue infections among patients on anti-TNF-alpha agents vs. other disease-modifying antirheumatic drugs.

The bottom line: Methotrexate should be continued for most surgeries, unless the patient 'has pretty bad kidney or liver disease, or if it's surgery to treat a major infection.'

The risk of infections tends to be highest at the start of therapy with a TNF-alpha antagonist, and stopping therapy is more likely to result in RA flares among patients with established disease, compared with those in the early stages of RA. Therefore, TNF-blocker therapy should be restarted as soon as possible after surgery to prevent flare, Dr. Grant said.

The American College of Rheumatology and British Society of Rheumatology recommend holding TNF-alpha antagonists for one dosing cycle before major surgery. For etanercept (Enbrel), that translates to a 1-week before surgery hold, for infliximab (Remicade) 6-8 weeks, and for adalimumab (Humira) 2 weeks. These agents should also be held for 10-14 days after surgery or until wound healing is satisfactory.

"It's probably safe to continue these medications for minor surgeries," Dr. Grant said.

Other agents

The anti-CD20 agent rituximab (Rituxan) – currently used to treat RA, vasculitis, hematologic malignancies, and other conditions – has a lower risk for bacterial infections than do TNF-alpha antagonists and has been shown to be safe in patients with a history of recurrent bacterial infections.

"Hydroxychloroquine (or Plaquenil) is felt to be safe during the preoperative period. It is recommended to continue this medication without stopping," Dr. Grant said.

There is conflicting information on infection risk with the use leflunomide (Arava), but it may be wise to stop therapy 2-4 weeks before nonurgent surgery in higher-risk patients.

There is consensus that sulfasalazine (Azulfidine) and azathioprine (Imuran) can be safely continued perioperatively, he said, although some advise holding sulfasalazine on the day of surgery.

Regarding perioperative steroids, Dr. Grant recommended determining the patient's steroid exposure over the past year.

"Stress dose steroids are not routinely needed as long as the patients continue their normal dose.

"That's really the important piece: If someone's taking prednisone every day, make sure they take at least that dose on the day of surgery," he said.

Continued from previous page

patients scheduled for general surgery.

They found that patients exposed to an ACE inhibitor or ARA within 10 hours of anesthesia had an adjusted odds ratio of 1.74 for moderate hypotension (SBP 85 mm Hg or less; $P = .04$), but there was no difference in severe hypotension between these patients and those who discontinued the drugs more than 10 hours before surgery. There were no differences in either vasopressor use or postoperative complications, including unplanned intensive care unit stay, myocardial infarction, stroke, renal impairment, or death.

A second, smaller study compared 12 vascular surgery patients on ARB the day of surgery with matched cohorts of patients taking beta-blockers and/or calcium channel blockers the day of surgery, or ACE inhibitors held on the day of surgery.

Hypotension (SBP less than 90 mm Hg in this study) occurred in all of the patients on ARB but in only 60% (27 of 45) patients on the beta-blocker/calcium channel blockers, and in 67% (18 of 27) in the ACE-inhibitor hold cohort. The ARB patients were also less responsive to ephedrine and phenylephrine than other patients, and in some cases responded only to a vasopressin system agonist, Dr. Grant noted.

Finally, the authors of a random-effects meta-analysis of five studies with a total of 434 patients reported that patients receiving an immediate preoperative ACE inhibitor or ARA dose had a relative risk of 1.50 for developing hypotension requiring vasopressors at or shortly after induction of anesthesia, compared with patients who did not receive the drugs.

Dr. Grant noted that the American College of Physicians' Smart Medicine guidelines on perioperative management of hypertensive patients recommend continuing ACE inhibitors "with caution," and they advise clinicians to avoid hypovolemia in patients maintained on ACE inhibitors during surgery. He said that in certain cases it may be appropriate to continue surgical patients on ACE inhibitors or ARB, as in patients with hypertension that is difficult to control with multiple medications, or in those with severe heart disease who have adequate blood pressure.

Dr. Grant reported having no financial disclosures.

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: The findings of the studies presented by Dr. Grant have important implications for understanding the significant issue of hypotension that the postoperative patient may face. However, the studies are relatively small, and in some cases the results are conflicting. A larger randomized, controlled trial would help shed light on how we can better identify the patients who can benefit from these therapeutic choices.

For your patients with chronic obstructive pulmonary disease (COPD) who require maintenance bronchodilator treatment

Help Your Patients Breathe Better With ANORO ELLIPTA

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.

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.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

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

Once-daily ANORO ELLIPTA

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

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

WARNING: ASTHMA-RELATED DEATH

Long-acting $beta_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting $beta_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting $Beta_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

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

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

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

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ANORO ELLIPTA.

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

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

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

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

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

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance.

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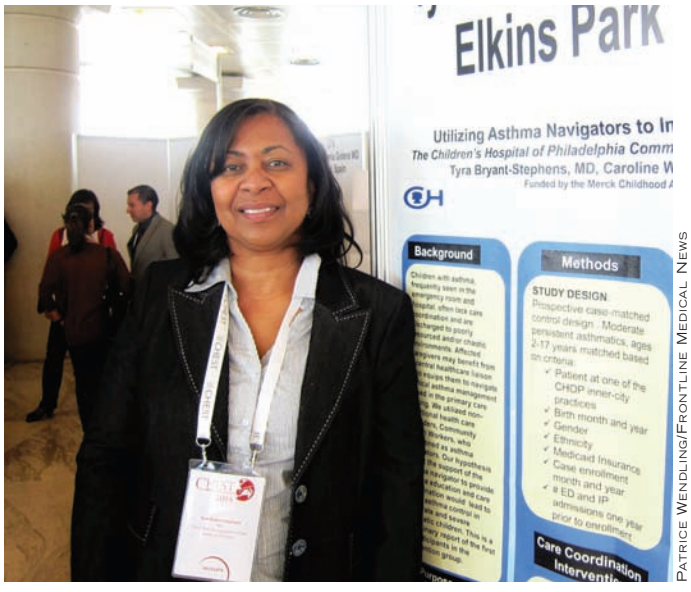
Practice-based asthma navigators trim symptoms

BY PATRICE WENDLING
Frontline Medical News

MADRID – Use of practice-based asthma navigators significantly reduced symptoms and emergency department and inpatient visits among inner-city children with moderate to severe asthma in a prospective, case-matched study.

"We've seen with our home-visit studies that we're able to reduce asthma morbidity, but what we hear from the parents all the time is that they feel their communication with providers is lacking, and that they really needed someone to help them navigate the clinical system," Dr. Tyra Bryant-Stephens, founder and director of the Community Asthma Prevention Program at Children's Hospital of Philadelphia (CHOP), said in an interview.



PATRICE WENDLING/FRONTLINE MEDICAL NEWS

Dr. Tyra Bryant-Stephens stated that navigators have been effective in bringing patients back to the office and lowering overall health care use.

To overcome this hurdle, CHOP began integrating community health workers as asthma navigators into the clinical team at its inner-city asthma clinics. Key tasks are to teach caregivers about the Asthma Care Plan, and proper use of controller medications, facilitate appointment scheduling and set up reminders, contact and share asthma care plans with school nurses, work with social workers to identify appropriate resources for families, and set care coordination goals.

The study enrolled 256 children, aged 2-17 years, on at least two asthma control medications. The participants had been hospitalized or had at least two emergency department (ED) visits in the past year. Their average age was 4.6 years.

After 12 months in the navigator program, preliminary data on 99 children revealed a clear 2- to 3-day reduction over the past 14 days in days using rescue asthma medications (5.28 vs. 3.07), days with symptoms (6.93 to 3.8), and nights with symptoms (6.11 to 3.34), Dr. Bryant-Stephens reported at the CHEST Word Congress. All of the findings were statistiscally significant.

Compared with baseline, the number of days not taking asthma medications at 12 months was not significantly different (1.48 vs. 1.22) nor was the number of days during which activities had to be slowed (4.41 vs. 3.73).

Enrollment in the navigator program, however, lowered the number of school days missed (16 vs. 2), workdays missed (9.11 vs. 1.13), unscheduled visits to the doctor (2.5 vs. 0.5), ED visits (3.65 vs. 1.31), and hospitalizations (1.73 vs. 0.4).

Although the final analysis comparing participants with matched controls receiving usual care is not yet complete, the data so far show a definite reduction in health care utilization by participants, despite controls being less sick at baseline, Dr. Bryant-Stephens said.

This is particularly encouraging because earlier studies at CHOP showed that roughly 50% of asthmatic children never made it back to their primary care physician for follow-up between ED visits.

Making appointments for and keeping follow-up visits were listed by 146 of 157 (93%) caregivers as one of the most important care coordination goals, and were achieved by 80% at 12 months with the assistance of phone calls from the asthma navigator, transportation tokens, and insurance cotransportation, according to the poster presentation.

Success among the other top five caregiver goals was 92% for learning how to properly use asthma medications (126/136 caregivers), 98% for reducing asthma triggers (154/157), 54% for stopping smoking in the house and car (23/42), and 94% for the surprising goal of losing weight in hopes it would reduce asthma symptoms (34/36).

There is no "magic bullet," or single component of the navigator program responsible for the results, but "I think what the navigators have been most effective at is bringing them back to the office. It's unbelievable compared with the control group," Dr. Bryant-Stephens said at the meeting.

Ultimately, the goal is to make the program self-sufficient, with a pilot program currently underway that partners CHOP with Pennsylvania's largest Medicaid provider, Keystone First, to assign an asthma navigator to members with the highest rate of hospitalizations and ED visits in order to improve adherence to their Asthma Action Plan.

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VITALS

Major finding: After 12 months in the asthma navigator program, children had fewer unscheduled visits to the doctor (2.5 vs. 0.5; *P* less than .05), emergency department visits (3.65 vs. 1.31; *P* less than .01), and hospitalizations (1.73 vs. 0.4; *P* less than .01).

Data source: A prospective case-matched study in 256 children with moderate to severe asthma.

Disclosures: Dr. Bryant-Stephens reported funding from the Merck Childhood Asthma Network.

Hello, this is your child's inhaler calling ...

M. ALEXANDER OTTO/FRONTLINE MEDICAL NEWS

Video: Software can call parents when their kids' inhaled corticosteroid prescription should be running low, explains Bruce Bender, Ph.D., of National Jewish Health.

BY M. ALEXANDER OTTO
Frontline Medical News

SAN DIEGO – A newly developed computer program mines electronic medical records to find pediatric asthma patients who are about to run out of their inhaled corticosteroids, then calls their parents to help them order new ones.

It's not a robocall. Parents don't push buttons to signal their response. Instead, they speak to the computer, and it understands what they say, just like the automated speech-recognition telephone systems used by credit card companies, airlines, and other industries. The software was developed by team from National Jewish Health and Kaiser Permanente Colorado, both in Denver.

At 24 months, adherence – measured by medication possession ratio – was 44.5% among 452 children randomized to the calls and 35.5% among 447 who were not, a statistically significant 25% difference.

"It takes a fair amount of work to get a system like this going, but then the computer does the rest. Most adherence interventions expect busy health care providers to do something; this doesn't add any burden to their day. Think of it as the electronic health record picking up the phone and talking with patients," said project leader Bruce Bender, Ph.D., head

Continued on following page

Continued from previous page

of pediatric behavioral health at National Jewish Health in Denver.

The system calls parents 10 days before the child is due to run out of the inhaler. "It pulls information out of the EHR, so when it talks to the parent, it references the prescribing physician, the name of the child, and the last time the inhaled corticosteroid prescription was filled."

When the computer program talks to the parent, it references the prescribing physician, the child's name, and the last time the inhaler prescription was filled.

It then gives parents options to refill the prescription or talk with an asthma nurse or pharmacist, among other things, he said.

The 25% adherence improvement was consistent throughout the investigation and in subgroups stratified by age, gender, race, body mass index, or disease-related characteristics.

ED visits and admissions did not differ between the call and control groups. "We were a little bit surprised by that, because this is a bigger bump in adherence than you typically see in adherence interventions." Maybe it was because "care is already pretty good in [our system]; we keep people out of the ED pretty effectively." In both groups, there were 0.09 ED visits per person in the year before enrollment, Dr. Bender said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

"It could also be that in asthma, you really need to change the [adherence] curve more dramatically to see a change in outcomes," he said.

Children in the study were aged 3-12 years. About 10% of parents contacted declined to participate in the program; about 90% of those who did said in subsequent surveys that they liked the calls and found them helpful. Dr. Bender and his colleagues said they hope to scale up the system for cardiovascular and adult asthma patients.

If parents did not pick up the phone, the system would leave a message and try a few more times, but "we capped it at three [callbacks]. We didn't want people to feel harassed," he said.

Eliza Corp. developed the program's software. The efforts were funded by the National Heart, Lung, and Blood institute. Dr. Bender said he has no relevant disclosures.

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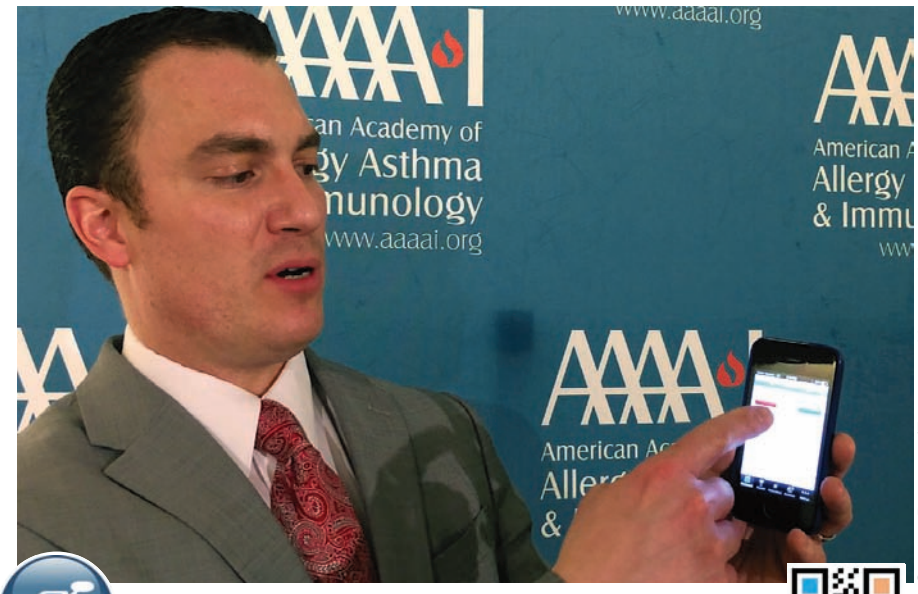
Asthma management app for teens shows promise



SHERRY BOSCHERT/FRONTLINE MEDICAL NEWS

Dr. David Stukus presented a 30-day pilot study indicating how a smartphone app designed for youth with asthma improved medication adherence.

BY SHERRY BOSCHERT
Frontline Media News

SAN DIEGO— A smartphone app designed for children and teenagers with asthma improved medication adherence in a 30-day pilot study of 21 patients.

Dr. David Stukus talked with us at the annual meeting of the American Academy of Allergy, Asthma, and Immunology about the app's design and use of evidence-based medicine, how well it worked with adolescents, and a larger prospective trial that's in the works.

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Texting reminders improved pediatric asthma control

BY SHERRY BOSCHERT
Frontline Medical News

A small study presented at the American Academy of Allergy, Asthma, and Immunology meeting in San Diego adds to a growing body of evidence that texting patients reminders to take their medication may improve asthma control.

Dr. Humaa M. Bhatti's ongoing study is one of the few so far to look not just at medication adherence but at health outcomes. But, like similar studies before it, the trial's small size and short duration so far preclude any definitive pronouncements about the effectiveness of using text messages (also known as short message service) via mobile phones to influence patient behavior. A couple of recent reviews of the literature, however, show mostly positive results.

Starting in April 2013, Dr. Bhatti and her associates recruited 37 patients up to 18 years of age with asthma to receive twice-daily texts from a research assistant reminding them to take medication. Texts went to the parents of children and/or directly to the adolescents. Patients or parents also could reply to communicate with the research assistant.

For the 29 patients who received 3-9 months of texting at the time of preliminary analysis of results (8 patients dropped out), records showed that 21 patients had two or more steroid bursts in the 12 months prior to the start of texting (72%), 28 had at least one urgent visit (96%) in that year, and 28 had been hospitalized for asthma at least once (96%).

The number of asthma exacerbations requiring prednisone decreased from a mean of 3.4/patient before the trial to 1.6/patient with texted reminders. Hospitalizations decreased from a mean of 1.6/patient before the trial to 0.8/patient. Urgent or emergency visits decreased from a mean of 3/patient before the trial to 1.4/patient. Those differences were statistically significant, reported Dr. Bhatti, an allergy and immunology fellow at the Children's Hospital of Michigan, Detroit.

Since the texting started, 16 of the 29 patients (55%) had no steroid bursts, emergency department visits, or hospitalizations. Similar results were seen for 25 patients who were added to the study since November 2013, a preliminary analysis found.

The study soon will open to all patients with asthma at the hospital to see if results remain positive and are sustained over longer periods. With more patients to text, the investigators are considering using an automated text-sending program that would not allow the recipients to reply, and patients may be randomized to receive texts from either the research assistant or the text program to see if there is a difference in outcomes.

A separate systematic review of the literature found five randomized controlled trials and one "pragmatic" randomized controlled trial reporting evidence that daily technology-based reminders improved asthma medication adherence. None of these trials documented improved clinical outcomes or changes in asthma-related quality of life. The reminder systems studied included text messages, automated phone calls, or audiovisual reminder devices. The median follow-up time was 16 weeks (J. Asthma 2014 Feb. 13 [doi: 10.3109/02770903.2014.888572]).

Texting also looked good in another literature review that found 13 controlled clinical trials of interventions using text messages, audiovisual reminders from electronic reminder devices, or pagers for patients on chronic medication. Of the four studies using texting, medication adherence improved in the one study of asthma and in two studies of HIV, but made no difference in one study of women on oral contraceptives (J. Am. Med. Inform. Assoc. 2012 [doi: 10.1136/amiajnl-2011-00748]). The one study on patients with asthma in that review was, again, a small, short study of 26 adults. Adherence to treatment improved after 12 weeks by an absolute rate of 18% in the texting group compared with controls (Respir. Med. 2010;104:166-71).

Dr. Bhatti had no financial disclosures.

HFOV leads to 'modestly' better lung function later

BY MARY ANN MOON
Frontline Medical News

School-aged children who had received high-frequency oscillatory ventilation when they were born extremely prematurely showed modestly better lung function compared with those who had received conventional ventilation at birth, according to researchers.

Neurodevelopmental outcomes were comparable between the two groups. The report was published online in the New England Journal of Medicine.

In high-frequency oscillatory ventilation (HFOV), "a constant pressure is applied to improve lung volume and oxygenation, while ventilation is achieved with the use of very low tidal volumes." This strategy was compared against conventional ventilation in a randomized trial of 1-year outcomes at 25 medical centers in the United Kingdom, Singapore, and Australia in the early 2000s; the authors now report long-term outcomes in 319 of the participants who are now 11-14 years of age.

The primary long-term outcome – small-airway function as assessed by forced expiratory flow at 75% of the expired vital capacity (FEF-75) – was "significantly, albeit modestly" better after HFOV than after conventional ventilation. Results also were slightly better for other FEF measures, forced expiratory volume in 1 second, forced vital capacity, peak expiratory flow, and diffusing capacity, said Dr. Sanja Zivanovic of the Medical Research Council Centre for Allergic Mechanisms in Asthma at King's College, London, and her associates.

The differences in lung-function measures were small, with an average of approximately 0.3 standard deviations. However, in a further analysis, 47% of the conventional-ventilation group fell below the 10th percentile for FEF-75, compared with only 37% of the HFOV group. This represents "a difference that is likely, in our opinion, to be of clinical importance," the investigators said (N. Engl. J. Med. 2014;370:1121-30 [doi:10.1056/NEJMoa1309220]).

"The poorer lung function in the conventional-ventilation group than in the HFOV group may have consequences over time – for example, by causing greater vulnerability to lung-function insults such a smoking," they noted.

"We were concerned that any respiratory benefit associated with the use of HFOV might have been associated with adverse neurodevelopmental outcomes, because in some trials HFOV has been associated with an increased risk of neonatal brain injury." However, no differences were found between the two study groups in health-related quality of life or behavior, and teachers rated the HFOV group as significantly better at art and design, information technology, and design and technology, "suggesting the possibility that visuospatial skills were better in that group than in the conventional-ventilation group," Dr. Zivanovic and her associates said.

This study was supported by various U.K. agencies. Dr. Zivanovic reported no financial conflicts of interest; some of her associates reported industry ties.

VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: Overall survival continues to improve for premature infants. However, bronchopulmonary dysplasia remains an important complication of birth prior to lung maturity. HFOV has been studied as a possible means to reduce this complication, with mixed results. The United Kingdom Oscillation Study (UKOS) was a multicenter, randomized trial comparing HFOV to conventional ventilation in a group of 797 infants during the early 2000s. Mortality and lung function at 1 year of corrected age were not significantly different. In a follow-up investigation of lung function in a subset of this group at 11-14 years of age, the authors report significantly higher measures of small airway function (FEF-75), FEV_1, FVC, PEF, and DLCO in the children ventilated with HFOV. However, these differences were relatively small and their clinical relevance uncertain. Follow-up of this cohort into adulthood may provide additional important information.

Asthma more common in EoE than previously thought

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – A recent analysis presented during a late-breaker abstract session at annual meeting of the American Academy of Allergy, Asthma, and Immunology found that up to 70% of children with eosinophilic esophagitis may suffer from asthma.

"Clinicians treating children with eosinophilic esophagitis [EOE] should consider asking additional history questions related to asthma symptoms

Clinicians should consider pulmonary function testing or referral to a specialist for children with EoE.

DR. KRUPP

and may also want to consider pulmonary function testing or referral to an asthma specialist for evaluation," lead author Dr. Nadia L. Krupp said in an interview prior to the meeting.

Dr. Krupp, director of the Riley Asthma Care Center in the section of pulmonology, allergy, and critical care medicine at Riley Hospital Children, Indianapolis, and her associates conducted a cross-sectional study of 33 children aged 6-18 years with EoE and 37 healthy controls. Methacholine challenge was performed (airway hyperresponsiveness defined as provocative concentration of methacholine less than 8mg/mL) and exhaled nitric oxide was assessed. Peripheral blood was analyzed for total IgE, eosinophil count, eotaxin, and serum cytokines.

Baseline spirometry did not significantly differ between EoE subjects and controls. However, airway hyperresponsiveness was present in 33% of children with EoE, compared with only 10.8% of controls ($P = .04$). In addition, 20% of the 15 EoE subjects with asthma had airway hyperresponsiveness, compared with 44% of the 18 EoE subjects without asthma. Overall, 69.7% of EoE subjects had either asthma or airway hyperresponsiveness.

The researchers found that airway hyperresponsiveness correlated strongly with serum IgE (P less than .0001) and exhaled nitric oxide ($P = .0002$), while epidermal growth factor (EGF) and fibroblastic growth factor–2 (FGF-2) were elevated in subjects with EoE and asthma, compared to healthy controls and those with EoE but no asthma (P less than .05). In addition, subjects with EoE and asthma who were on asthma controller medications had similar levels of EGF and FGF-2 as controls, while Th2 cytokines and eotaxin did not differ significantly among groups.

She acknowledged certain limitations of the study, including its cross-sectional design and "the fact EoE subjects may have had significant variability in the current activity of their esophageal disease at the time of enrollment."

The study was partially funded by Aerocrine. Dr. Krupp said that she had no relevant financial conflicts.

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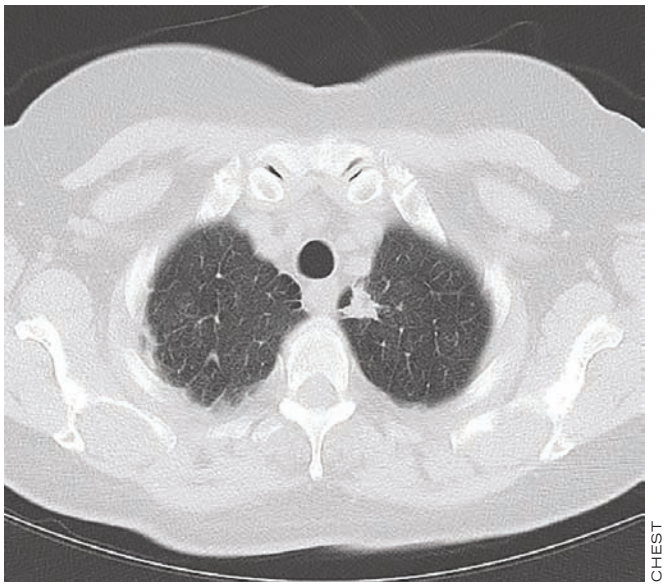
PULMONARY PERSPECTIVES: Biomarkers for early lung cancer detection

BY DR. CHRISTOPHER DECOTIIS; DR. JUN-CHIEH J. TSA; DR. ALISSA K. GREENBERG; AND DR. WILLIAM N. ROM, FCCP

Biomarkers for the early diagnosis of lung cancer have the potential to drastically reduce mortality. Lung cancer is the leading cause of cancer mortality worldwide largely due to advanced stage at time of diagnosis. The National Lung Cancer Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality with annual CT scanning compared with chest radiography (National Lung Screening Trial Research Team et al. *N Engl J Med.* 2011;365[5]:395). The US Preventive Services Task Force (USPSTF) released a draft statement recommending annual low-dose CT scanning for high-risk patients. However, the NLST also showed a 24% false-positive rate with CT screening, which leads to patient anxiety, additional radiation exposure, and increased cost and added risks, as nodules that are ultimately found to be benign are monitored with serial CT scans, biopsied, or even surgically resected. Biomarkers for lung cancer may be used to further characterize high-risk populations to enhance screening efficacy, and more importantly, may determine the risk for malignancy in the 7- to 30-mm size nodule.



CHEST

Significant challenges in resolving the quandary of the indeterminate nodule weaken the role of serial CT as a stand-alone screening test.

Finding the biomarker

The challenges are to find a biomarker with organ and cell type specificity and to develop an assay for accurate, efficient, and cost-effective measurement. A major challenge is in tumor heterogeneity. A single biomarker may only detect a small percentage of cancers. To address this issue, several biomarkers may be tested together as a panel to achieve increased sensitvity and specificity. When multiple biomarkers are to be tested, a high-throughput technology is desirable to increase the speed of both the discovery and validation steps in biomarker development. Thus, the relatively new high-throughput technologies, such as micoarray platforms, have led to important advances in biomarker research.

The ideal biomarker is noninvasive, expeditiously processed in various clinical settings, cost-effective, accurate, and reproducible. In addition, a biomarker must be able to perform well despite confounders, such as advanced age, smoking history, COPD status, tumor type, and concomitant disease. To be effective in early detection, a biomaker must have strong sensitivity and specificity at early tumor stages in which therapeutic intervention is likely to have the most impact. The testing of biomarkers for lung cancer has proven to be challenging, and validation in independent cohorts is essential. Pepe and colleagues have developed a paradigm for biomarker discovery and validation that requires progression from case-control studies for discovery, followed by validation studies using high-risk cohorts in which cancers may be detected prospectively (Pepe et al. *J Natl Cancer Inst*. 2008;100[20]:1432). This technique has become the research paradigm for biomaker discovery and validation.

Independent validation studies require large numbers of patients with cancer and appropriately matched control subjects. The National Cancer Institute's Early Detection Research Network (EDRN) has organized large cohorts of case and high-risk control patients who serve as a substrate for these studies. EDRN has funded biomarker discovery laboratories and integrated these with clinical validation centers and reference laboratories to develop and test candidate biomarkers. The EDRN categorizes by organ site and collaborates with numerous industry partners and affiliate members. Their collaborative approach, which includes focusing on high-risk cohort development and dozens of scientific meetings and publications, has led to the development of many promising lung cancer biomarkers and the imminent commercialization of some of these markers.

DNA aptamers

An encouraging development in the field of lung cancer biomarkers is the collobaration with biotechnology companies. New advances in technology resulting in large sample analysis have further streamlined discovery endeavors and reduced the cost-to-potential-benefit ratio. One such company, a Colorado-based biomarker discovery company, developed an aptamer-based technology to identify potential lung cancer biomarkers. DNA aptamers contain modified nucleotides that act as highly specific protein-binding reagents. A multiplexed assay with these aptamers was able to quantify the levels of 813 human proteins. Ostroff and colleagues performed this assay on 1,325 patient sera from non-small cell lung cancer cases and control subjects from four different institutions. The authors identified a 12-protein panel that discriminated NSCLC cases from control subjects with 89% sensitivity and 83% specificity. As expected, these proteins are involved in cell adhesion, cell movement, inflammation, and immune monitoring. Additional analysis indicated that potential population characteristics, such as COPD status, age, and smoking history, did not affect the accuracy of the biomarker. Potential clinical applications for this biomarker include early detection of lung cancer in high-risk populations and further risk stratification of suspicious lung nodules. Another company plans to develop a panel of biomarkers identified in 2014 (Ostroff et al. *PloS One.* 2010;5[12]:e15003).

Gene profile in bronchial epithelial cells

Gene expression profiling techniques are also being used to develop lung cancer biomarkers. Spira and colleagues performed gene expression micoarrays on bronchial airway epithelial cells from brushings in 60 patients with lung cancer and 69 high-risk control subjects. An 80-gene expression signature was identified and perfomed with 83% sensitivity and 76% specificity in a small independent validation set. When combined with conventional cytology, the diagnostic sensitivity increased to 95%. Tumor location, cancer stage, and cumulative smoking history did not alter the accuracy of the biomarker assay. A Massachussets-based pulmonary genomics company has built on this research to develop a 30-gene RT-PCR assay. Preliminary data presented at the CHEST 2012 meeting of the American College of Chest Physicians demonstrated an 87% negative predictive value when this test was combined with standard bronchoscopy. This test has been confirmed to be highly reproducible and is awaiting testing in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. In addition, a multicenter study to validate the test is currently underway.

Autoantibodies

Panels of circulating antibodies to tumor-associated antigens may also have a role as lung cancer biomarkers. Boyle and colleagues used enzyme-linked immunosorbent assay (ELISA) to identify auto-antibodies to seven different cancer-associated proteins. The combination of these antibodies resulted in a sensitivity and specificity of 36% and 91%, respectively, for the detection of lung cancer. Subgroup analysis demonstrated no significant difference in the accuracy in regard to smoking status, tumor type, or stage. These data led to the EarlyCDT-Lung test, which is the first commercially available lung cancer biomarker. A follow-up study of over 500 patients with lung cancer worldwide has confirmed the accuracy of EarlyCDT-Lung (Boyle et al. *Ann Oncol.* 2011;22[2]:383; Lam et al. *Cancer Prev Res.* 2011;4[7]:1126-1134).

Proteomic classifer

Researchers from a Seattle-based molecular diagnostics company are using highly sensitive mass spectrometry to measure protein concentration for the development new lung cancer biomarkers. Li and colleagues used this technology to discover a 13-plasma protein classifier for lung cancer diagnosis (Li et al. *Sci Transl Med.* 2013; 5[207]:207). An independent validation set of greater than 100 patients demonstrated a 90% negative predictive value for lung cancer vs matched control subjects. Age, smok-

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This Month in *CHEST*: Editor's Picks

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

Rapid Lung Function Decline in Smokers Is a Risk Factor for COPD and Is Attenuated by Angiotensin-Converting Enzyme Inhibitor Use. *By Dr. H. Petersen et al.*

Predicting Survival Across Chronic Interstitial Lung Disease: The ILD-GAP Model. *By Dr. C. J. Ryerson et al.*

Differences in Disease Expression Between Primary Ciliary Dyskinesia and Cystic Fibrosis With and Without Pancreatic Insufficiency. *By Dr. M. Cohen-Cymberknoh et al.*

Continued from previous page

ing history, and nodule size did not affect the accuracy of the classifier. Large prospective validation studies are underway to determine the utility of this test in determining risk of malignancy in the 7- to 30-mm pulmonary nodule.

Many other types of biomarkers are being investigated. The concept of field of cancerization, in which the presence of lung cancer is associated with molecular alterations in adjacent tissues (or even more distal portions of the respiratory tract), supports the use of nasal or buccal brushings, exhaled breath analysis, and sputum analysis as viable candidates for biomarker studies. Furthermore, research in blood gene expression profiles, microRNA patterns, and DNA methylation patterns has made great strides toward developing clinically applicable methods of early detection.

The early detection of lung cancer is critical to improve patient outcomes. Serial CT scanning has earned a place in the diagnostic algorithm, yet significant challenges in resolving the quandary of the indeterminate nodule weaken its role as a standalone screening test. Minimally invasive biomarkers are an adjunctive tool to increase screening efficacy. Advancing technologies and more high-risk cohorts fuel novel research in the field of lung cancer detection.

The authors are from the Division of Pulmonary, Critical Care, and Sleep Medicine, NYU School of Medicine, New York, New York.

A new look for *CHEST*

In late March, the CHEST Publications website debuted its new look reflecting the new brand launched by the American College of Chest Physicians at CHEST 2013. You can view the new website at: publications.chestnet.org. The *CHEST* website can be seen at journal.publications.chestnet.org and CHEST books at books.publications.chestnet.org.

With the July 2014 issue, this new look will be incorporated into the print journal from the cover to the interior pages. We are very excited about the change that raises *CHEST* to a new level in visual quality.

NETWORKS: Deadly air, patient SME, ethics rounds, sleep e-talk

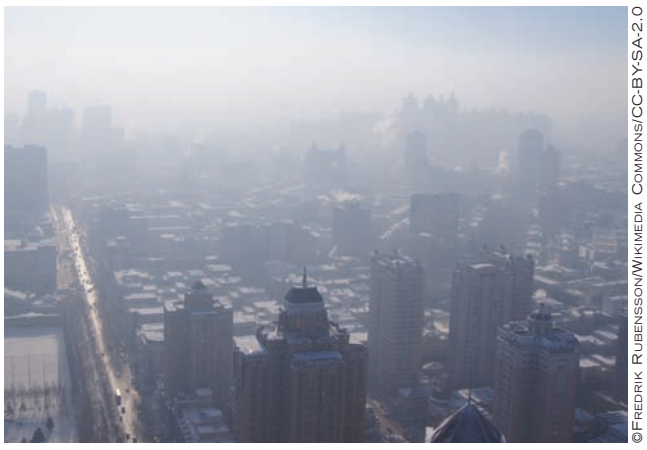
Occupational and Environmental Health

From dust to dust: Deadly air goes global

Over a million premature deaths and 31 million disability-adjusted life years (DALYs) are attributable to solid cooking fuel household air pollution in India. More alarming are the 627,000 premature deaths and nearly 17.8 million DALYs attributed to fine particulate matter less than or equal to 2.5 micrometer (PM2.5). This is 3% of the national disease burden (Balakrishnan K et al. *Environ Health Perspect*. 2014;122(1):A6). Air quality in cities and rural areas leaves much room for improvement. Recent news reports have highlighted the high level of air pollution in India's capital New Delhi and, alarmingly perhaps, higher than Beijing at some time points. There is inadequate research in this area, but there are efforts by national bodies to document and initiate steps to tackle ambient air pollution.

CHEST has the opportunity to review air pollution effects on cardiorespiratory health and issue guidelines for members to become advocates of healthy air in their communities around the world. Our NetWork has initiated a discussion on the e-community to get ideas on this topic. Readers are encouraged to log in and contribute. While there are online ways to measure and assess the level of air pollution at various locations, it does not simplify the reality that many patients have no choice but to live and work in densely polluted regions. Travelers to China and India will see a variety of mask equivalents and sometimes colorful and inventive face coverings. It is unclear if these actually serve the purpose, and it would be useful for an objective analysis to be conducted.

Dr. Sai Praveen Haranath, FCCP
Steering Committee Member



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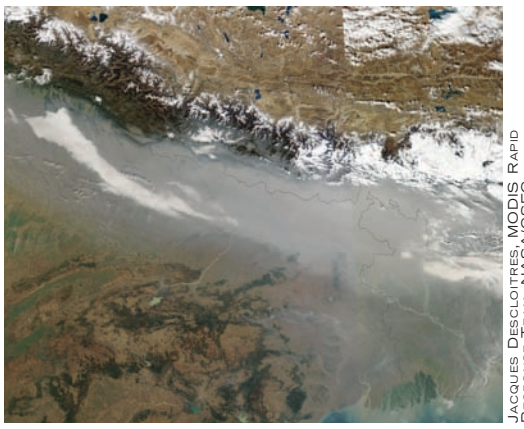
Advocacy needed: Heavy smog has replaced healthy air in Harbin and other cities in China.



Jacques Descloitres, MODIS Rapid Response Team, NASA/GSFC

Air pollution is a persistent problem in both cities and mountainous areas in India.

Respiratory Care

Pulmonary patient self-management education (SME) and training services: "The Medicare Respiratory Therapist Access Act of 2013"

On July 8, 2013, HR Bill 2619 was introduced in Congress to amend title XVIII of the Social Security Act to provide for Medicare coverage for pulmonary patient self-management education and training services furnished by a qualified respiratory therapist in a physician practice for patients with COPD, asthma, pulmonary hypertension, pulmonary fibrosis, and cystic fibrosis. This issue generated discussions in the respiratory care and the pulmonary communities, resulting in a spirited debate published in the February 2014 issue of *CHEST*. Here is a summary of the debate.

On the pro side, Dr. Thomas M. Fuhrman, FCCP, and Dr. Robert Aranson, MD, FCCP (*Chest* 2014;145(2):210) noted that respiratory care practitioners (RCPs) are expected to become educated with a minimum of a bachelor's degree and trained specifically in advanced practices. The RCP would maximize care of pulmonary patients by using their training in evidence-based medicine, medical literature assessment, research, managerial skills, quality improvement, electronic medical records, and more. The RCP of the future would perform clinical evaluations, periodic testing, patient education, and alert the physician about a rescuing intervention. Such a team approach between RCP and physician could avert an ED visit or hospital admission. In essence, the RCP would care for the pulmonologist's patients as a true physician extender, not as a physician alternative. RCP licensure and scope of practice would be determined on a state-by-state basis. In summary, the authors conclude that an appropriately educated, properly credentialed, independent RCP could follow a thoughtfully delineated scope of practice based upon evidence-based medicine and the needs of the physicians and their patients.

On the con side, Dr. Katherine Courtright and Dr. Scott Manaker, FCCP (*Chest* 2014;145(2):213) noted that only a small body of international literature supports the efficacy of COPD self-management education (SME). One trial, in which RCPs were the majority of the educators, was stopped early for a significant increase in mortality in the intervention group. This certainly does not imply causation but simply highlights the need for stronger supportive evidence for the efficacy and cost-effectiveness of RCPs providing COPD SME before initiating independent practice and billing for these services. COPD is costly, both in human lives and health-care resources. In this era of high-value care initiatives, direct implementation without evidence of effectiveness and cost-effectiveness is inadvisable and contravenes our national, overarching health-care priorities. In summary, these authors conclude that projected potential cost savings from COPD SME, whether by decreased ED visits or hospital readmissions, would need to be evaluated in the context of sufficient evidence and increased billing for these services.

HR 2619 was assigned to the congressional House Ways and Means Committee, which will consider it before possibly sending it on to the House or Senate as a whole. Unfortunately, this bill has a small chance of getting past committee status.

Do you have an opinion pro or con on this issue? You can use the ACCP e-community website to voice your view.

Dr. Herbert Partrick, FCCP
Chair

Palliative and End-of-Life Care

New practice: clinical ethics length of stay rounds in the ICU

Healthcare costs in the United States are the highest among the developed world. According to the Organization for Economic Co-operation and Development (OECD) report from 2012, the United States spends 17.6% of the GDP on health. Costs associated with hospital stays were the third highest. Medicare spent $554 billion on health care in 2011 and, of that, 28% or $170 billion was spent on patients' during the last 6 months of life, according to Kaiser Health News.

The current standard for determining dying is based on the "surprise question (Weissman. *J Palliat Med*. 2011;14[9]:1065)." The "surprise question" asks would the physician be surprised that the patient died within 6 months. Decreasing the use of expensive, nonbeneficial, life-sustaining technologies and increasing appropriate end-of-life care interventions will significantly decrease the amount of money spent by Medicare.

Our ethics ICU length of stay rounds are designed to assist clinicians with early ethics involvement to improve end-of-life care planning and decrease reactionary consults. Clinical ethicists round daily in the ICUs on all patients with greater than 5 days LOS to address ethical issues that can become barriers. Retrospective work has already suggested a need for earlier ethics consultation during a patient's hospital course. (Johnson et al. *The American Surgeon*. 2012; 78[7]:735). Our current pilot data reveal more than 10 consults initiated during week 1 that could have developed into barriers if they were left unaddressed and suggest that improved patient care and decreased of extensive length of stay are achievable through this intervention.

Nneka Mokwunye, PhD
Steering Committee Member
and Dr. Laura Johnson

Sleep Medicine

Sleep Medicine e-Community update

The CHEST e-community has become a resource for providers to share their experiences, gauge the pulse of their colleagues, and ask opinions about breaking news in the literature. The last year was an incredibly successful one for our NetWork online; despite having just over half as many members as the two largest NetWorks, we have had more active discussions than either of them! As new e-community moderators for the Sleep NetWork, we are looking to continue this success by developing resources to improve the value of the forum for our members. In an effort to develop a more engaging environment, we plan to regularly add interesting or challenging images to the discussion forum. The images

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will vary from sleep epochs to hypnograms, CPAP downloads, and radio graphic and physical exam findings. We look forward to commentary and critique from our colleagues about this endeavor as it develops.

This visual upgrade is a harbinger to further planned changes in the sleep e-community. Members will be able to upload challenging cases with supporting data, while others will have the opportunity to address the case and offer opinions or advice. Other plans include the development of multiple-choice challenge questions, opinion polls, and contests. We will also occasionally feature a "what's trending" sleep article, based upon a search of recent relevant literature, and occasional journal clubs as were published online over the last year. Particularly popular e-Community posts will hopefully be shared on social media such as CHEST's Facebook, Twitter, and YouTube accounts.

With all these opportunities, now is a better time than ever to let your voice be heard as we try to increase the exposure of all CHEST members to our exciting field of medicine. So, what can we do to get you online?

Dr. Wajahat H. Khan
and Dr. Thalia N. Casimire
Sleep Medicine e-Community Moderators

CHEST 2014: Recharge while you learn in Austin

When you think of Texas, you may envision cowboy boots and hot summer days. While you're attending CHEST 2014 from October 25 to 30 in Austin, Texas, we encourage you to trade those cowboy boots for hiking boots or athletic shoes, and get outside during your free time.

With temperatures averaging in the mid to upper 70s in October, Austin visitors will enjoy the sunshine and moderate climate. You may be surprised to find many opportunities for outdoor exploration within this urban metropolis.

Located 20 minutes away from the Austin Convention Center by bus or 10 minutes away by car, Zilker Metropolitan Park is Austin's largest and most popular park. The park offers hiking and biking trails, sand volleyball courts, picnic tables, and much more. If you love the water, you'll enjoy Barton Springs Pool, a spring fed swimming hole that is always 68 degrees, and you can also paddle a canoe on Town Lake. Plus, Zilker Zephyr miniature train offers a leisurely ride and provides you with views of the park and river.

Other local, scenic spots include McKinney Falls State Park and Mount Bonnell. Located south of Austin, McKinney State Park is home to 635 acres of trails, campgrounds, picnic areas, and waterfalls. It's a great place to camp, fish, and hike. Northwest of Austin, Mount Bonnell is one of Austin's oldest tourist destinations. Be sure to have water and comfortable shoes because you'll climb a long staircase to arrive at one of the highest points in Austin. The exercise will pay off when you reach beautiful views of Lake Austin and the city.

Note that both of these destinations are best accessed by car. While buses will take you to these locations from the Convention Center, you will need to allot over an hour for commuting if you plan to take the bus. By car, McKinney Falls State Park is only 15 minutes away from the convention center, and Mount Bonnell is a short 11-minute ride.

While Austin refreshes you with outdoor beauty and sunshine, CHEST 2014 will energize and recharge you with the latest information in chest medicine. You'll connect with an international community of the best minds in pulmonary, critical care, and sleep medicine. Find everything you need to know to make the best clinical decisions and inspire your patient care.

Learn more at chestmeeting.chestnet.org.

The CHEST Foundation welcomes grant applications

Each year, The CHEST Foundation offers grant opportunities for clinical and translational research, leadership, and volunteer community service. In 2014, grants are offered in thrombosis, lung cancer, pulmonary arterial hypertension, COPD and alpha-1 antitrypsin deficiency, end-of-life care, women's lung health, pulmonary fibrosis, and community service. Among these opportunities is the CHEST Diversity Committee Young Investigator Grant, designed to support underrepresented young researchers.

The application deadline for all grants is May 31, 2014.

GlaxoSmithKline Distinguished Scholar in Thrombosis
The Distinguished Scholar in Thrombosis grant supports a clinical educational project designed to improve patient care and is intended for the investigation of issues that are not easily supported through traditional sources. Funding is $150,000 over the course of 3 years. Applicants must be Fellows of the American College of CHEST Physicians (FCCP).

The CHEST Foundation Clinical Research Grant in Lung Cancer
This 2-year, $100,000 grant ($50,000 annually) supports a clinical/translational research project that could lead to improved treatment and/or cure of lung cancer. Applicants must be CHEST members who have completed at least 1 year of a pulmonary or critical care fellowship or a thoracic surgery residency and are within 7 years of completing training. This grant is supported by Genentech.

The CHEST Foundation Clinical Research Grant in Pulmonary Arterial Hypertension
This 1-year, $50,000 grant supports a clinical/translational research project that contributes to the understanding of the pathophysiology or treatment of pulmonary arterial hypertension (PAH). Applicants must be CHEST members who have completed at least 1 year of a pulmonary or critical care fellowship and be within 7 years of completing training. This grant is supported by Actelion Pharmaceuticals, US, Inc.

The CHEST Foundation and the Pulmonary Fibrosis Foundation Clinical Research Grant in Pulmonary Fibrosis
This 1-year, $30,000 grant supports a clinical/translational research project that could contribute to effective treatments or a cure for pulmonary fibrosis. Applicants must be CHEST members who have completed at least 1 year of a pulmonary or critical care fellowship and are within 7 years of completing training.

The CHEST Foundation and the Alpha-1 Foundation Clinical Research Grant in COPD and Alpha-1 Antitrypsin (AAT) Deficiency
This 1-year, $25,000 grant supports research focused on COPD and AAT deficiency. While research projects primarily in usual COPD (not associated with AAT deficiency) are allowed, those with a focus on AAT deficiency are encouraged. Applicants must be in an ACGME fellowship program and within 5 years of completion.

CHEST Diversity Committee Young Investigator in Pulmonary, Cardiovascular, Critical Care, or Sleep Research Grant
This 1-year, $25,000 grant is designed to encourage outstanding underrepresented young investigators in their careers in pulmonary, cardiovascular, critical care, or sleep research. The grant supports clinical/translational research in pulmonary, cardiovascular, critical care, or sleep medicine. Applicants must be underrepresented minority investigators and CHEST members who have completed at least 1 year of a pulmonary or critical care fellowship and are within 7 years of completing training.

The CHEST Foundation and the Respiratory Health Association Clinical Research Grant in Women's Lung Health
This 1-year, $10,000 grant supports clinical research related to women's lung health. Topics may include research on gender differences in lung diseases, such as COPD and lung cancer. Applicants must be ACCP members.

Community Service Grants Honoring D. Robert McCaffree, MD, Master FCCP
The Foundation offers community service grants, from $5,000 to $15,000, to support the volunteer efforts of those CHEST members who donate time and medical service to improve the health of people in communities throughout the world. Funds are granted to the nonprofit or nongovernmental organizations for which CHEST members give pro bono service.

For more information about The CHEST Foundation's 2014 grants program, or to apply, visit chestnet.org/grants.

BRONCH Express™ arrives for EBUS-TBNA simulation training

The American College of Chest Physicians (CHEST) is excited to lead the way in delivering medical simulation education by introducing BRONCH Express. This new device promotes bronchoscopy education by providing portable and cost-effective simulation for EBUS-TBNA training. BRONCH Express was developed as a collaborative venture between CHEST and Simbionix, a world leader in medical simulation.

BRONCH Express was unveiled at the 2014 CHEST World Congress in Madrid, and it will be available to participants at various CHEST bronchoscopy and interventional pulmonology courses.

Mounted inside a carry-on case, this desktop simulator is easy to set up and repack. Virtual patient cases offer a realistic anatomical environment based on actual patient data. The BRONCH Express provides a meaningful yet affordable hands-on training solution for medical students, new pulmonary and critical-care fellows, and attending physicians to train on EBUS-TBNA.

CHEST Senior Vice President, Business Development, Megan Schagrin, CAE, CFRE, said that it is exciting to expand the role of simulation education by offering portable and cost-effective medical simulation training.

"We look forward to seeing how BRONCH Express transforms medical simulation training. This suitcase-sized product, which is available for a considerably lower cost than other simulation equipment, can now be used by medical schools, hospital systems, and even large group practices. CHEST will receive a royalty on each sale."

CHEST President Dr. Michael H. Baumann, FCCP, added that there is great value in partnering with Simbionix to develop innovative training tools like BRONCH Express.

"Our commitment to helping chest medicine professionals to develop new skills and knowledge to improve patient care around the globe make partnerships such as this a logical step for our organization," Dr. Baumann said. "The partnership with Simbionix allows expansion of important clinical training in an affordable and accessible manner."

CHEST

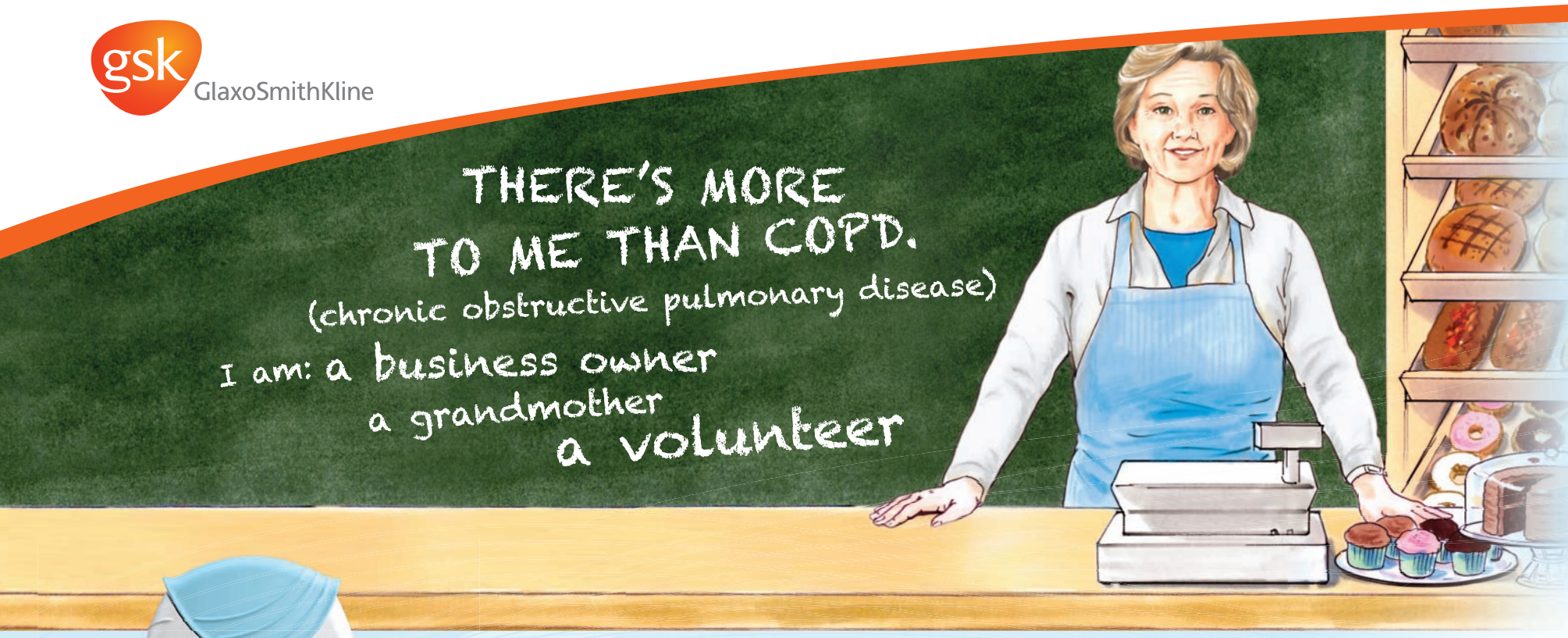
The portable device offers virtual patient cases and a realistic anatomical environment.

Many of CHEST's upcoming live-learning courses will feature BRONCH Express; these courses will be held at our new Innovation, Simulation, and Training Center located in Glenview, Illinois:

- Essentials of Bronchoscopy
  June 5-6 and Sept 24-25
- Endobronchial Ultrasound
  June 7-8 and Sept 26-27
- Comprehensive Pleural Procedures
  June 20-21
- Peripheral Bronchoscopy
  June 22
- Therapeutic Bronchoscopy in Asthma and Persistent Air Leaks
  June 23

Learn more about CHEST's live-learning courses by going to chestnet.org/live-learning. Bronch Express is also available for purchase exclusively through Simbionix global sales network. Learn more at simbionix.com.

GlaxoSmithKline



BREO ELLIPTA

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

Indications

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

Important Safety Information for BREO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

BREO ELLIPTA. One inhalation. Once daily.

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

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

Important Safety Information for BREO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

BREO ELLIPTA was developed in collaboration with Theravance

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

BREO™ ELLIPTA™
(fluticasone furoate and vilanterol inhalation powder)
FOR ORAL INHALATION USE

The following is a brief summary only; see full prescribing information for complete product information

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA. A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO ELLIPTA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO ELLIPTA has been conducted. The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD. The initiation of BREO ELLIPTA in this setting is not appropriate. BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of BREO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but at times therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia An increase in the incidence of pneumonia has been observed in subjects with COPD receiving the fluticasone furoate/vilanterol combination, including BREO ELLIPTA 100 mcg/25 mcg, in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 6% [48 of 820 subjects]; 100 mcg/25 mcg: 6% [51 of 806 subjects]; or 200 mcg/25 mcg: 7% [55 of 811 subjects]) than in subjects receiving vilanterol 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving fluticasone furoate/vilanterol 100 mcg/25 mcg and in 7 subjects receiving fluticasone furoate/vilanterol 200 mcg/25 mcg (less than 1% for each treatment group).

5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO ELLIPTA may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amount of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe COPD exacerbation. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV$_1$]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO ELLIPTA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, and depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic dose of BREO ELLIPTA. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD symptoms should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

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

5.11 Hypersensitivity Reactions Hypersensitivity reactions may occur after administration of BREO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not take BREO ELLIPTA *[see Contraindications (4)]*.

5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher systemic exposure than seen in patients with COPD) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPTA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered. In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2% [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 818 subjects]).

5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those receiving vilanterol 25 mcg alone (1% [9 of 818 subjects]).

5.15 Coexisting Conditions BREO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In 4 clinical trials of 6- and 12-month duration evaluating BREO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warnings and Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Increased risk for decrease in bone mineral density *[see Warnings and Precautions (5.13)]*.

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical program for BREO ELLIPTA included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects have received at least 1 dose of BREO ELLIPTA 100 mcg/25 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6-month and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with BREO ELLIPTA in Table 1 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 1,224 and n = 1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were Caucasian. They had a mean age of 62 years and an average smoking history of 44 pack

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

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

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

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

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

7 DRUG INTERACTIONS

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

10 OVERDOSAGE

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

17.4 Risks Associated With Corticosteroid Therapy

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

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

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The right move: early mobilization of mechanically ventilated patients

CC Commentary *from page 1*

seems largely driven by the notion that the ventilator should "take over" breathing and that any patient interaction would be detrimental to this goal. Deep sedation and suspension of physical and mental activity is typically the end result. It is remarkable that harm from complete bed rest was described generations ago,[5] but complete bed rest in patients supported by mechanical ventilation in the ICU remains the norm. It appears that the improved survival of patients with critical illness, which leads to more survivors with persistent physical and mental impairments, has heightened awareness of the problem among clinicians. This has been the springboard from which the notion of mobilization during critical illness has emerged.

DR. KRESS

Persistent physical weakness and functional impairment is one of the greatest burdens on ICU survivors.[6-9] Margaret Herridge and colleagues[6] published a sentinel paper describing the 1-year outcomes in patients recovering from ARDS. One hundred percent noted loss of muscle bulk, proximal muscle weakness, and fatigue; half of this relatively young group of patients was unemployed 1 year after their ICU experience. At the 5-year mark after discharge, the remaining survivors continued to have physical dysfunction. Their scores on the physical portion of the SF-36 score were markedly lower than the normal population. The 6-minute walk distances were significantly reduced.[7]

ICU-acquired weakness

Critical illness polyneuropathy, first described by Charles Bolton and colleagues in the 1980s,[10] is characterized by a primary axonal degeneration, typically affecting motor nerves more than sensory nerves. These investigators noted severe motor and sensory polyneuropathy at the peak of critical illness, along with difficulty liberating patients from mechanical ventilation. Critical illness polyneuropathy is often seen in those with sepsis or systemic inflammatory response syndrome (SIRS) and is a common finding in those with ICU-AW.[11] Because electrophysiologic nerve studies are necessary to diagnose critical illness polyneuropathy (and such tests are rarely done), its true incidence is not known.

A separate entity known as critical illness myopathy (CIM) is another important contributor to ICU-AW. Patients with this syndrome have generalized muscle weakness but preserved sensory function.[12] The myopathy is thought to be driven by muscle injury from systemic inflammation[13,14] and skeletal muscle proteolysis from the catabolic state of critical illness. Prolonged physical immobility with resulting deconditioning is another important contributor.[15] When electrophysiologic and histopathologic analyses are performed, many patients with ICU-AW manifest both neuropathic and myopathic physiologic findings. However, since few patients receive such testing, it is not clear if this observation applies to the general population of patients with ICU-AW.

The extent to which ICU-AW is the result of immobility is not known, since all studies describing this problem have been performed in a population of patients who are immobile. Since this state is a constant, it remains speculative whether early mobility can attenuate or eliminate the specific pathologic and pathophysiologic conditions of peripheral nerves and skeletal muscle that are described in the literature. Indeed, altering the natural history of ICU-AW is a major objective of early mobilization. Even if the neural and muscular pathologic condition cannot be fully eliminated, the ability to have improved mental awareness during critical illness (ie, reduced delirium) can lend itself to a chance for better outcomes. For example, if a patient with some degree of ICU-AW can understand the nature of his/her handicap and adapt to this limitation, functional outcomes may improve. Such early activity allows therapists to teach patients strategies that will work optimally in spite of physical limitations. Such an approach offers the opportunity for patients to accommodate to their physical weaknesses and maintain independence.

Early mobility in the ICU

In 2007, the first report of early mobilization in mechanically ventilated ICU patients was reported by Bailey et al.[16] This descriptive study took place in the respiratory ICU at LDS Hospital in Salt Lake City, Utah. Patients were supported by mechanical ventilation for more than 4 days in this ICU and were transferred there after being cared for in another ICU in the hospital for an average of 10 days. Targeted activities included sitting on the edge of the bed, sitting in a chair after bed transfer, and ambulation. Ventilator settings required were $FIO_2 < 0.6$ and PEEP < 10 cm H_2O. Patients could not have orthostatic hypotension and were required to be off catecholamine infusions. More than half of the activity events were ambulation – with nearly half of these occurring in intubated patients! The median ambulation distance was 200 feet and over 80% of patients survived to hospital discharge. There were very few adverse events and no unplanned extubations. The same group reported a follow-up study to determine the change in mobilization frequency when patients were transferred from other ICUs to their respiratory ICU where a culture of early ambulation had been well established.[17] In this ICU where mobilization was an expected part of care, patients were more than two times as likely to receive mobility therapy (OR 2.47; 95% CI 1.9-3.4, $P < .0001$). Avoidance of sedation also increased the chances of mobilization (OR 1.90; 95% CI 1.2-3.2, $P < .009$).

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Early mobilization patients demonstrated better maximal walking distances while in the hospital (33.4 vs 0 meters) and more ventilator-free days (23.5 vs 21.1).

Morris and colleagues[18] published the first prospective trial of mobilization in mechanically ventilated ICU patients. Enrollment was in a nonrandomized block allocation manner, done within 48 hours of intubation; all subjects were treated with evidence-based ICU care strategies (ie, protocolized treatment for sepsis resuscitation, glycemic control, sedation, and ventilator liberation). A team of care providers used a progressive strategy of mobility. This started with passive range of motion exercises, sitting up in the bed, turning and dangling legs, standing, and, ultimately, ambulating. There was nearly a doubling of physical therapy sessions (80% vs 47%), and the mobilization group got out of bed sooner (8.5 days vs 13.7 days; $P < .001$) with reduced hospital days (14.9 vs 17.2; $P=0.05$).

In 2009, Burtin et al.[19] reported on a randomized controlled trial of early exercise using a bedside bicycle ergometer. There was a considerable delay in the time from ICU admission to enrollment in this trial (14 days post-ICU in the intervention group vs 10 days post-ICU in the control group). The majority of the patients were intubated and mechanically ventilated. Those subjected to cycling had better SF-36 physical function scores and scored higher on 6-minute walk tests and quadriceps force at hospital discharge. The intervention was well tolerated with no serious adverse events.

Schweickert et al[20] reported findings from the first prospective randomized trial of very early physical and occupational therapy in patients intubated for respiratory failure. The mobilization intervention in this trial was much earlier than in previously published work – an average of 1.5 days after endotracheal intubation. MICU patients undergoing mechanical ventilation who were functionally independent prior to ICU admission were enrolled. The therapy algorithm focused on mobilization and achievement of ADLs. The control group did not receive physical or occupational therapy until after they were extubated.[16-18,21-23] All received evidence-based ICU therapy, including daily sedative interruption,[24] daily spontaneous breathing trials,[25] early enteral

Continued on following page

Continued from previous page

nutrition, and tight glucose control. After sedative interruption when patients were awake, a physical and occupational therapist worked with patients in a progressive, step-wise manner. The protocol started with sitting at the edge of the bed, engaging in simulated activities of daily living, transfer training, standing, and ambulation. Therapists blinded to patient randomization assignment (ie, different than the therapists who performed the early mobility intervention) evaluated functional outcomes. The primary endpoint of the trial was the return to "functional independence" at hospital discharge – defined as the ability to perform ADLs and walk independently.

Patients were able to accomplish remarkable milestones while intubated and mechanically ventilated. Bed mobility was accomplished in 76%, a median of 1.7 days after intubation; standing in 33% (median 3.2 days after intubation); chair sitting in 33% (median 3.1 days after intubation); and ambulation in 15% (median 3.8 days after intubation; median ambulation distance 15 feet).[26] Early mobilization patients demonstrated better maximal walking distances while in the hospital (33.4 vs 0 meters, $P = .004$) and more ventilator-free days (23.5 vs 21.1; $P = .05$). The early mobilization strategy improved functional independence dramatically (59% vs 35%; $P = .02$), and patients were more likely to go home rather than going on to institutional care or death (43% vs 24%; $P = .06$). ICU delirium days were reduced by 50% (2.0 vs 4.0 days, $P = .03$) in spite of no differences in sedatives administered.

Needham et al[27] reported a quality improvement project targeting reduced sedation and delirium in order to permit mobilization in ICU patients and improve functional mobility. The format for this evaluation was a baseline and follow-up model. The group reported a reduction in sedative and opiate use, with a concomitant reduction in ICU delirium. Length of ICU stay decreased by 2.1 days (95% CI, 0.4-3.8); hospital length of stay decreased by 3.1 days (95% CI, 0.3-5.9). Patients in the follow-up mobilization group received more rehabilitation treatments and accomplished a higher level of functional mobility. This before-after study format could not separate the effects of early mobilization from the effects of sedative reduction, since both changes occurred simultaneously in the follow-up group.

Conclusions

Patients requiring mechanical ventilation may suffer from prolonged physical dysfunction after ICU discharge. Published literature suggests that physical and occupational therapy for mechanically ventilated patients can improve functional status in these survivors. We do not know if the benefits of mobilization in the ICU are sustained for the long term. We also do not know which patients are most likely to benefit from early mobility; accordingly, how best to allocate limited resources (ie, therapists) is not clear. It is clear that deep sedation will lead to prolonged immobility. A patient care strategy based upon current evidence[28] is necessary to optimize outcomes in these high-risk patients.

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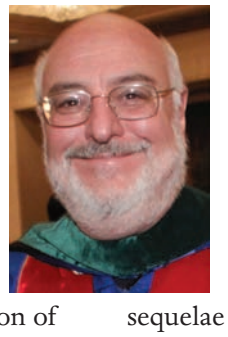
EDITOR'S COMMENT

In this very important and well thought out commentary, Dr. Kress addresses some of the most important issues in critical care, after mortality, what happens after you survive, and how can we affect it proactively.



Deconditioning and weakness occur frequently in survivors of critical illness who required mechanical ventilation. The benefits of early mobilization of mechanically ventilated patients in the ICU are well described and reviewed here; this approach to care is beginning to replace the traditional strategy of prolonged bed rest. Minimizing sedation during mechanical ventilation is an important step toward early mobilization. Mobilization is safe and can be carried out even in patients with high illness acuity.

Critical illness is a devastating, multisystem disease with long-term sequelae that we are trying to optimize and address.

Dr. Peter Spiro, FCCP
Section Editor

Med-reconciliation toolkit makes positive first marks

BY MARY ELLEN SCHNEIDER
Frontline Medical News

LAS VEGAS – Tired of getting a patient medication list that isn't reliable? A 3-year study on medication reconciliation could offer a roadmap for improving that list and reducing potentially harmful errors.

Preliminary results from MARQUIS (the Multi-Center Medication Reconciliation Quality Improvement Study) Toolkit indicate that hospitals are able to reduce unintentional medication discrepancies by implementing a menu of interventions ranging from training providers to take a better medication history to stationing a designated provider in the emergency department (ED) to reconcile the patient's information with pharmacies and primary care offices. But outside forces, such as problems with an electronic health record (EHR) system, can offset those effects.

The 3-year study, which will wrap up in the next few months, is sponsored by the Society of Hospital Medicine, with $1.5 million in funding from the Agency for Healthcare Research and Quality.

In the first phase of the study, researchers identified evidence-based techniques for taking the best possible medication history from hospitalized patients and synthesized them into a toolkit for clinicians. The free toolkit includes how-to videos and pocket cards. The second phase of the study is the mentored implementation of the techniques at five sites: two academic medical centers, two community hospitals, and one Veterans Affairs medical center.

'Somebody needs to be spending that 18 minutes' interviewing patients and verifying their medication lists.

DR. STEIN

While one community hospital site was able to lower medication discrepancies significantly, a second community hospital site had a spike in discrepancies as it underwent a problematic implementation of a new EHR system.

At the first site, a Medication Reconciliation Assistant (MRA) program was used. The MRA is stationed in the ED and interviews patients about their medications and then verifies that list with the pharmacy, the primary care physician, or the skilled nursing facility. That new medication list is then handed off to the admitting physician. The process usually takes 18-20 minutes. They MRA program is staffed by four full-time employees, all pharmacy technicians with experience in retail pharmacies, who work 8-hour shifts.

"It doesn't have to be a pharmacy technician," Dr. Jason Stein, a MARQUIS coinvestigator and professor of medicine at Emory University, Atlanta, said at the annual meeting of the Society of Hospital Medicine. "But somebody needs to be spending that 18 minutes doing something that roughly looks like this."

At that first site, unintentional medication discrepancies from either history or reconciliation errors dropped from 4.5 per patient in the preintervention period to 3.4 per patient. Potentially harmful discrepancies fell from 0.25 to 0.09 per patient.

At the second site, a smaller community hospital, the quality improvement team provided training to front-line providers on medication history taking and counseling at discharge and created a new hospital policy that clarified expectations about who would perform medication reconciliation and when they would do it. And recently, they began stationing a provider in the ED 5 days a week to work on medication reconciliation.

But shortly after the second hospital began implementing the MARQUIS interventions, the hospital launched a new EHR system that created problems for medication reconciliation. The result was that, after some initial success, unintentional medication discrepancies spiked, rising from 2.0 per patient to nearly 5 discrepancies per patient after the rollout of the new EHR system. They have since fallen back down to 3.8 per patient. Similarly, potentially harmful discrepancies rose from 0.20 to 1.11 per patient.

The free MARQUIS toolkit is available at hospitalmedicine.org/marquis.

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On Twitter @maryellenny

Physicians may not get paid if patients don't pay ACA premiums

BY ALICIA AULT
Frontline Medical News

Will you get paid for the care you provide to patients who have gained insurance coverage through the Affordable Care Act's health insurance claims? You'll soon find out.

Under the health reform law, patients must pay their first month's premium to be considered enrolled; they then have 90 days to pay the next premium.

If the patient doesn't pay his or her premiums for the second month, the insurer can hold or "pend" all claims. By the third month, if the patient still has not paid, the insurer can terminate his or her policy. The physician is left to collect whatever is owed for all outstanding claims from the patient.

The Centers for Medicare & Medicaid clarified the grace period policy in a letter to insurers last year.

The first ripples could come in April. Patients who started and paid for coverage in January, but who did not pay in February or March, might get dropped from coverage. That could leave physicians scrambling to cover the unreimbursed care.

Physicians' organizations including the American Medical Association, the American College of Physicians, and the American Academy of Family Physicians have been working to reverse this provision of the Affordable Care Act, to no avail so far.

In a March 5 letter to the CMS, dozens of organizations and state medical societies urged the agency to require insurers to tell physicians whether patients had up-to-date coverage during the verification of eligibility. As the law and current regulations are written, insurers can notify physicians on their own timeline whether a patient's coverage has lapsed.

The organizations also asked the CMS to "require issuers to assume full financial responsibility if an issuer provides inaccurate eligibility information during the last 60 days of the grace period."

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FRONTLINE MEDICAL COMMUNICATIONS

Kansas City, Missouri

Children's Mercy Hospitals & Clinics is seeking Pediatric Pulmonology physicians to join the current faculty. The Division was built upon a foundation emphasizing multidisciplinary team models for children who have a wide variety of acute and chronic respiratory and sleep disorders. It currently includes General Pulmonary Medicine, a comprehensive Pediatric Sleep Disorders Center and an active Cystic Fibrosis Care Center. We seek to expand existing programs and develop new programs in Pulmonary Hypertension, Chronic Lung Disease of Infancy, Home Ventilation, Neuromuscular Diseases, Rare and Interstitial Lung Diseases, Aerodigestive Disorders, and Sickle Cell Related Pulmonary Disease.

Candidates should be board certified/ eligible in Pediatric Pulmonology and have established clinical skills, interest in scholarly activity, and willingness to participate in educational activities. Academic appointment is with the University of Missouri-Kansas City School of Medicine. Qualified candidates should submit their CV to **physicianjobs@cmh.edu** EOE/AAP

For more information visit **http://www.childrensmercy.org/Clinics_and_Services/Clinics_and_Departments/Pulmonary_and_Sleep_Medicine/** or contact:
Christopher M Oermann, MD
Division Director of Pulmonary and Sleep Medicine Children's Mercy Hospitals and Clinics Kansas City, MO 866-264-4652

Michigan

Bronson Healthcare Midwest in Kalamazoo, Michigan, is seeking a Board Certified Pulmonologist to provide locums work a week or weekend per month for their established pulmonary group.

The group provides inpatient consults and maintains an outpatient pulmonary practice, which is located on the campus of Bronson Methodist Hospital.

Evening coverage is provided by the Bronson Adult Critical Care service.

This would be an employed contracted position covering travel, meals and malpractice insurance.

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269-341-8631
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BRONSON

Pulmonologist

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Bronson Healthcare Midwest is a subsidiary of Bronson Healthcare Group in Kalamazoo, Michigan. The practice operates within Bronson Methodist Hospital which is an award winning, tertiary healthcare system serving 10 counties in southwest Michigan. With a workforce of more than 7,000, Bronson is one of the area's largest employers. We offer a full range of services from primary care to advanced critical care and have multiple service locations in Kalamazoo, Calhoun and Van Buren counties.

Kalamazoo, located midway between Detroit and Chicago, is a diverse university town with highly rated public schools and affordable real estate. Offering art, symphony, theater, museums and year round festivals, there are many activities for the whole family including numerous parks, lakes, fine dining and Lake Michigan is less than an hour's drive away.

For more information about Bronson or Kalamazoo visit **www.bronsonhealth.com** or **www.kalamazoomi.com**
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Ideal agent for insomnia not always clear cu

BY DOUG BRUNK
Frontline Medical News

LAS VEGAS – Many patients with insomnia reach for certain dietary supplements and herbal preparations for relief, but their efficacies have not been established in well-controlled studies.

"Dietary supplements and herbal preparations not regulated by the FDA [Food and Drug Administration]," Dr. Karl Doghramji said at the annual psychopharmacology update held by the Nevada Psychiatric Association. "There is some question about the purity of these agents, and also about the active ingredient. There are many ingredients in these so-called nutraceutical compounds. Which is the active ingredient? We're not quite sure."

If clinicians recommend agents whose effectiveness is not well established, "are we delaying treatment for insomnia and other conditions, which may have a negative impact in daytime performance and may impair mood?" asked Dr. Doghramji, professor of psychiatry, neurology, and medicine at Thomas Jefferson University, Philadelphia. "That's a concern."

One of the more commonly used natural supplements for insomnia is valerian in a dose of 400-450 mg/day. This herb is believed to have some anxiolytic, muscle relaxant, and sleep-promoting properties, "yet data regarding efficacy are mixed," said Dr. Doghramji, who also directs the university's Sleep Disorders Center. "Safety data are scant, yet side effects appear to be rare and mild, primarily GI irritation and headache. There are case reports of hepatotoxicity in persons taking herbal products containing valerian."

He described melatonin as the most commonly used natural supplement for insomnia. A review of 139 published studies commissioned by the Agency for Healthcare Research and Quality suggests that melatonin has no effectiveness in the treatment of everyday regular insomnia (AHRQ Publication No. 05-E002-2;2004). "But, some evidence suggests that it is effective in treating delayed sleep-phase syndrome with short-term use," Dr. Doghramji noted. "On the other hand, evidence suggests that melatonin is not effective in treating most secondary sleep disorders with short-term use, and no evidence suggests that melatonin is effective in alleviating the sleep disturbance aspect of jet lag and shift-work disorder."

Though valerian is believed to have anxiolytic, muscle relaxant, and sleep-promoting properties, the efficacy data are mixed.

Melatonin had no effectiveness for the treatment of everyday regular insomnia in an AHRQ review.

DR. DOGHRAMJI

Certain prescription agents might benefit patients with insomnia, he continued. FDA-nonapproved agents for insomnia include sedating antidepressants, antipsychotics, and anticonvulsants. FDA-approved hypnotics include benzodiazepine-receptor agonists, melatonin-receptor agonists, and H_1-receptor antagonists.

"At appropriate doses, sedating antidepressants are effective for mood and anxiety disorders; there is a low abuse risk, low cost, and there is a large dose range," Dr. Doghramji said.

"One of the disadvantages is that they tend to be long acting and have anticholinergic and antihistaminic side effects." A 42-day controlled study of doxepin 25-50 mg found that the agent did not produce any change in terms of sleep latency (J. Clin. Psychiatry 2001;62:453-63). However, "it did increase their total sleep time, suggesting that they didn't necessarily fall asleep more quickly, but they had fewer awakenings after they did fall asleep," he said. "So, if doxepin is to be used for insomnia, it seems to be best

Continued on following page

VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: This is a well written and concise review of the common medications and other agents used in the treatment of insomnia to guide clinicians, pointing out the caution that the non-prescription items have limited scientific evidence to support their regular use. Some of the prescription medications are reviewed as well.

Continued from previous page

suited for the insomnia characterized by middle of the night awakening and late morning insomnia."

A 2-week study that compared trazodone with zolpidem in primary insomnia demonstrated that trazodone did seem to help people fall asleep more quickly in the first week or so (Hum. Psychopharmacol. 1998;13:191-8). "It also helped them feel as though they had slept longer," said Dr. Doghramji, who was not involved with the study. "The problem was, tolerance occurred within 2 weeks. The issue there is, should you increase the dosage or keep the same dosage for a while? We don't have a lot of data on this."

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Sedating antidepressants have the disadvantages of being long acting and having anticholinergic side effects.

From a pharmacokinetic standpoint, trazodone has a long half-life (5-12 hours) and features a complex set of pharmacodynamics. "It not only has some serotonergic potential, it has some histaminic potential, making it an agent that can have multiple side effects, so be careful with it," he said.

Clinicians likely use benzodiazepine-receptor agonists more than any other agent for insomnia. These include the benzodiazepines, such as estazolam, flurazepam, quazepam, temazepam, and triazolam; and the nonbenzodiazepines (also known as selective benzodiazepine-receptor agonists) such as zaleplon, zolpidem and its various preparations (oral, sublingual, and oral spray); and eszopiclone. Adverse effects may include daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life), rebound insomnia, and respiratory depression in vulnerable populations. All of these are classified as schedule IV controlled substance by the Drug Enforcement Administration. New drugs, which do not have a DEA schedule classification, include ramelteon, a melatonin-receptor agonist, and low-dose doxepin.

Choosing which antidepressant agent to use for a patient with depression and comorbid insomnia poses a certain clinical dilemma, Dr. Doghramji concluded. "Do you start with a sedating agent when your patient is both depressed and cannot sleep? Or do you put them on any old agent, regardless of whether it's sedating or not? Unfortunately, at this point, there are not a lot of data guiding us on this."

Dr. Doghramji disclosed that he is a consultant for UCB, Teva Pharmaceuticals, Vanda Pharmaceuticals, and Jazz Pharmaceuticals, and that he holds stock in Merck.

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