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CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Emily Goodman

Simple strategy: Advising seniors to keep medications in the bathroom increased adherence, Dr. Alex Federman found.

Daily routine boosted asthma med adherence

BY MICHELE G. SULLIVAN
Frontline Medical News

Two simple recommendations for older patients with asthma – keeping medication in the bathroom and integrating its use into a daily routine – can significantly improve adherence to inhaled corticosteroids.

When patients consistently did either of those, adherence rose threefold, compared with patients who didn't, Dr. Alex Federman and his associates wrote in the August issue of the Journal of Internal Medicine.

The findings suggest that clinicians might help improve adherence by suggesting that their patients store the medication in their bathroom cabinet, and take it, for example, when they brush their teeth every day.

"Because adherence strategies are modifiable, the findings in this study may provide clinicians and care coaches with straightforward and useful messages to help older patients improve their medication adherence," wrote Dr. Federman of Icahn School of Medicine at Mount

See **Seniors** • *page 18*

Mass critical care update takes lessons from recent crises

Surge response, ICU evacuations detailed.

BY SHERRY BOSCHERT
Frontline Medical News

Care of critically ill or injured patients during Hurricane Sandy, the 2010 earthquake in Haiti, and the H1N1 influenza pandemic in Mexico City played a role in shaping new recommendations from CHEST.

The 14-part consensus statement (Chest 2014 [doi:10.1378/chest.14-0732]) from the College's Task Force for Mass Critical Care updates and expands on the task force's previous recommendations from 2008, which did not address pediatrics, trauma, subspecialty critical care, or critical care during disasters in the developing world, among other topics.

Although there is some overlap with the 2008 recommendations, "by and large the specific suggestions are all new or have been updated since the 2008 guidelines, based upon lessons learned from pandemics and disasters that have occurred in the interval," Dr. Jeffrey R. Dichter said in an interview.

If history is any guide, clinicians will want to incorporate the 2014 recommendations as a matter of routine instead of placing them on a shelf to be re-

See **CHEST** • *page 7*

INSIDE

SLEEP STRATEGIES

OSA and insomnia often share a bed

BY DR. MICHELLE ZEIDLER AND DR. JENNIFER L. MARTIN

As health-care professionals, we are attuned to the stereotypical presentations of both obstructive sleep apnea (OSA) and insomnia. An overweight middle-aged man walks into the office, led by his spouse who is complaining of his snoring and is concerned about his witnessed apneas and daytime fatigue. Our next patient might be a thin, anxious, and hyper-aroused insomnia patient who reports an inability to wind down and shut off the mind at night. However, the situation becomes markedly more complicated when OSA and insomnia coex-

See **Strategies** • *page 38*

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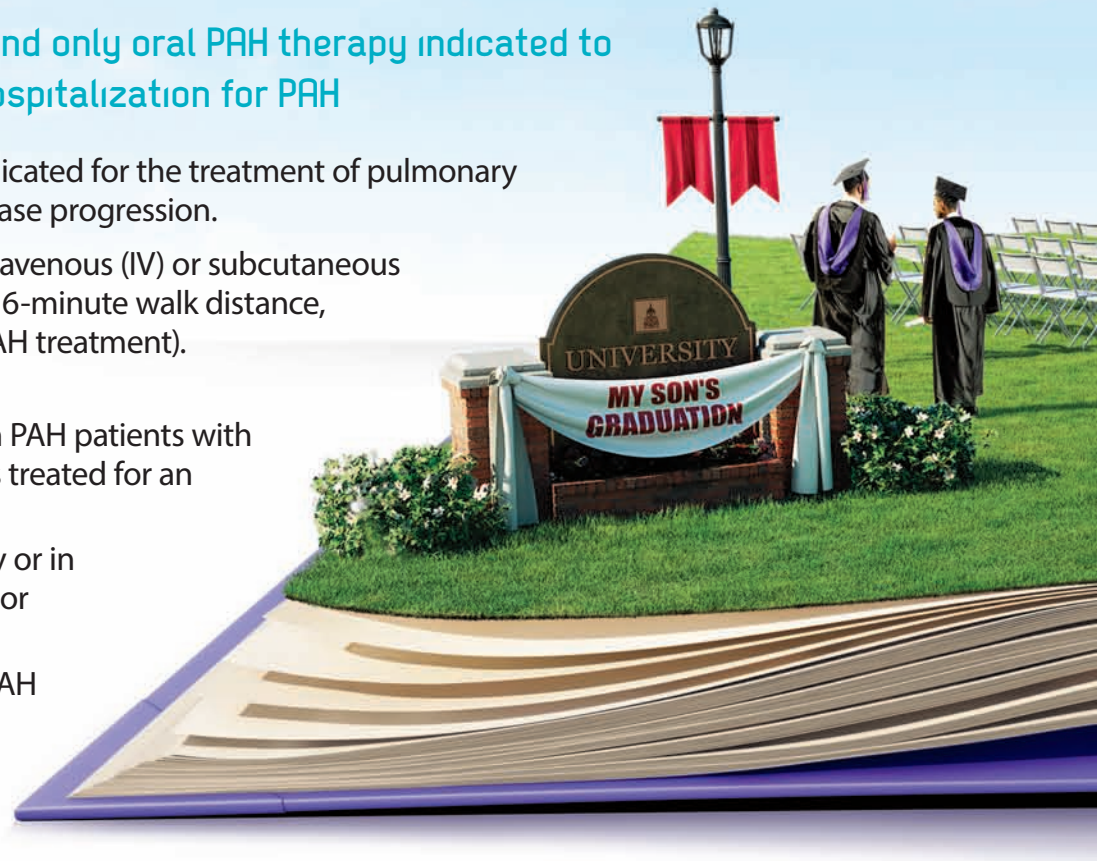
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

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

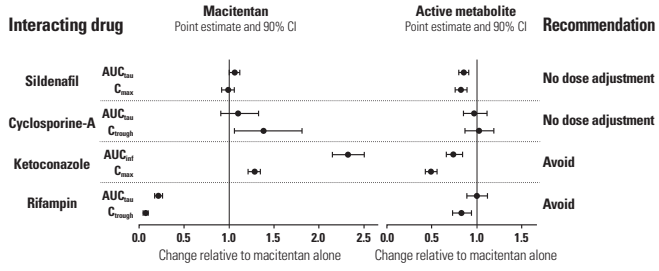
In vitro studies

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

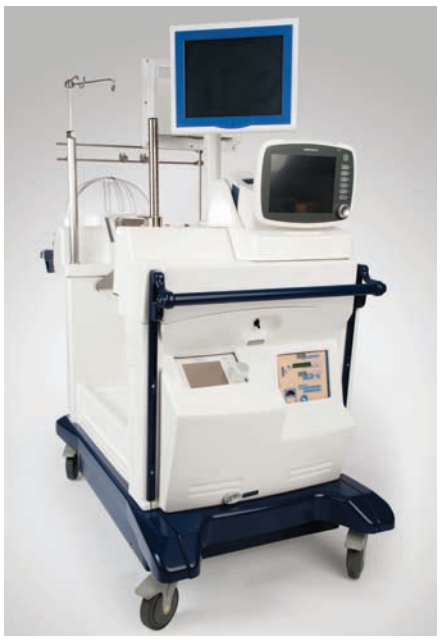
In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered 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.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018

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

Ex vivo lung perfusion device preserves donor organs



COURTESY XVIVO PERFUSION

The FDA approved the XVIVO Perfusion System, which maintains potential donor lungs for up to 4 hours.

BY ELIZABETH MECHCATIE

Frontline Medical News

A device that preserves less-than-ideal donor lungs until they are cleared for transplantation has been approved, the Food and Drug Administration announced.

The ex vivo perfusion device preserves donated lungs that initially do not meet all the criteria for a transplantable lung. The device does this by warming the donor lungs to "near normal body temperature," continuously flushing the lung with a sterile solution, and ventilating them, "which oxygenates the cells and makes it possible for the transplant team to examine the lungs' airways with a bronchoscope," according to the FDA statement.

The lungs can remain in the machine for up to 4 hours, providing time for the transplant team to evaluate the lungs to determine if they meet the criteria; donor lungs that meet the criteria are then transplanted into a patient.

The device warms the donor lungs to near normal body temperature, continuously flushing them with a sterile solution and ventilating them, which oxygenates the cells.

The device, the XVIVO Perfusion System (XPS) with STEEN Solution, is manufactured by XVIVO Perfusion.

"With this approval, there may be more lungs available for transplant, which could allow more people with end-stage lung disease who have exhausted all other treatment options to be able to receive a lung transplant," Christy Foreman, director of the Office of Device Evaluation in the FDA's Center for Devices and Radiological Health, Silver Spring, Md., said in the statement.

About 1 in 5 donor lungs meets the standard transplantation criteria. In the United States, 1,754 lung transplants were performed in 2012 and 1,616 potential recipients were on the lung transplant waiting list at the end of 2012, according to the FDA.

In two studies, outcomes for lung-transplant recipients were similar among those who received a donor lung preserved with the device and those who received donor lungs that were considered ideal and were preserved in cold storage.

"Both trials showed that recipients of the ideal and non-ideal lungs had similar survival rates up to 12 months after transplant and similar rates of organ rejection," the FDA statement said.

The manufacturer is required to conduct a long-term study of the effects of the device as a condition of approval.

emechcatie@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: This is exciting news given the shortage of available lungs that meet the current transplant criteria. Early studies showing similar 12-month survival rates and rates of organ rejection are encouraging. I would like to know how significant will the financial impact be using the device. I look forward to the results of long- term studies. Hopefully this will be a viable option for our patients.

IN THIS ISSUE

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

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Anticoagulation options in trauma are expanding

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – In the next 5-10 years, reaching for a powdered form of plasma may become the normative first-line treatment for trauma patients who present with severe bleeding. That's because the current standard of administering fresh frozen plasma is riddled with problems, Dr. Martin Schreiber said at the University of California, San Diego, Critical Care Summer Session.

For one thing, frozen plasma takes 35 minutes to thaw. "That's a problem, and the clotting factor function of plasma deteriorates as you freeze it and thaw it," said Dr. Schreiber, professor of surgery at Oregon Health & Science University, Portland. "Also, you need it in large volumes and that's not good for patients with congestive heart failure on Coumadin, and the availability is limited, especially in rural settings."

Enter lyophilized plasma (LP), a process developed by HemCon Medical Technologies in which whole blood is sterilely removed, and the plasma component is separated and turned into a powder. The powdered plasma is returned and reconstituted prior to transfusion. "You can put this stuff as a powder on a shelf in nearly any environment," Dr. Schreiber said. "It's good for at least 3 years, it survives a broad range of temperatures, and you can restore it to plasma within a couple of minutes."

COURTESY WIKIMEDIA COMMONS/DIVERDAVE/CREATIVE COMMONS

Fresh frozen plasma (shown) takes about 35 minutes to thaw. Lyophilized plasma, a powder, is reconstituted in minutes prior to transfusion.

An initial study of LP showed encouraging results with the use of a freeze-dried form of plasma for resuscitation (J. Trauma 2008;65:975-85). A later study by researchers including Dr. Schreiber evaluated the effects of the lyophilization process on plasma clotting factor levels in swine, by adding the antioxidant ascorbic acid (vitamin C) to the reconstitution solution, and by comparing the efficacy of LP with that of fresh frozen plasma and that of plasma and packed red blood cells in a 1:1 ratio (Arch. Surg. 2009;144:829-34). "What we found was that if we gave LP with packed red blood cells in a 1:1 ratio we had 14% less blood loss than if it's given as FFP with packed cells, which was significant," Dr. Schreiber said.

"The LP was better in terms of stopping hemorrhage. We also noticed that with the vitamin C, we suppressed inflammation and got reduced IL-6 [interleukin-6] expression. Now, the Germans, the Dutch, and the French are using LP in their military settings. Our special forces people are also using it. It's under current development for common use in your hospital in 5-10 years. I think this stuff is good anywhere. With LP we can always maintain a 1:1 ratio, and we don't have to worry about the thawing process."

Tranexamic acid, a synthetic derivative of lysine, is another anticoagulant therapy that is likely to be

Continued on following page

Crises inform critical care update

CHEST *from page 1*

trieved only in times of crisis, said Dr. Dichter, a member of the task force. He is medical director for intensive care at Unity Hospital, Fridley, Minn.

The task force heard from colleagues that the 2008 document helped them plan to scale up ICU capacity and manage ventilated patients during the 2009 Mexican influenza epidemic – plans that they did not need to implement but that gave them reassurance nonetheless.

Triage guidelines in the 2008 document helped Bellevue Hospital in New York plan for allocating scarce resources such as electricity from backup generators during 2012's Hurricane Sandy, a hospital physician reported at the College's 2013 annual meeting. "Simply knowing they had an approach in place to make those decisions if required allowed the staff to focus on dealing with the situation at hand effectively rather than being distracted by the uncertainty of what would happen if the generators failed," Dr. Dichter said.

The 2014 document's attention to evacuation of critically ill and injured patients should be of particular interest. "We have seen the challenge related to evacuating ICUs, particularly during the New York hurricane," he said.

Another highlight is a focus on developing the capacity to increase health care personnel and supplies when needed (also known as "surge response") to meet disasters of various sizes – small, medium, or large. The previous recommendations covered only the largest, "crisis" care.

The document provides advice for everyone from individual doctors to hospital administrators, regional health systems, and national governments. "While it is important for all health care workers to have a broad understanding of the issues of emergency preparedness, readers can focus on the areas more relevant to them by consulting the tables in each document" that identify the people for whom those recommendations are most relevant, he said.

The recommendations are based on expert consensus because there is no research to support evidence-based guidelines, the task force stated. That should change by the time the recommendations are updated again in the future, Dr. Dichter said. Groups such as the International Forum for Acute Care Trialists and the International Severe Acute Respiratory and Emerging Infection Consortium are starting to conduct research during pandemics and disasters.

And, of course, more crises will occur, providing experience that will help improve planning for the next inevitable disaster.

Dr. Dichter reported having no financial disclosures.

The 2014 update is available at: journal.publications.chestnet.org/article.aspx?articleid=1899971.

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VIEW ON THE NEWS

The consensus statement moves forward planning for critical care during pandemics and disasters in unprecedented ways, Dr. Christian Sandrock, FCCP, said in an editorial.

The principles behind recommendations for conservation of personnel and supplies (particularly scarce medications and oxygen therapy), substitutions where necessary, and triage "are very relevant today where the resource limitations in West Africa are hindering both patient care and outbreak management," wrote Dr. Sandrock (Chest 2014 [doi:10.1378/chest.14-1900]).

Emphases on technology and telemedicine, baseline education plus just-in-time training, and mental health support during disasters should help support health care workers on the front lines to deliver the best care possible, he added.

A goal of "a 20% increase in surge within the health-system resources to a 200% surge with regional and national resource support sets an international benchmark for health-system preparedness," Dr. Sandrock wrote.

Recommendations for coordinating patient flow and resources at a regional level have "not been described elsewhere," and the task force's vision of incorporating critical care expertise in large, central coordination of patient flow, resources, and care "sets a high but necessary benchmark for public health and government officials," he wrote.

Perhaps the greatest contribution of the document is its attention to potential health care inequities during disasters and the need for ethical and equal care, Dr. Sandrock suggested. The consensus statement provides "a foundation of disaster response for the critically ill that provides justice to the most adversely affected patients," which is an unparalleled accomplishment, he wrote.

Dr. Sandrock is in the division of pulmonary and critical care medicine at the University of California, Davis.

Nurse practitioners play bigger role in critical care

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Nurse practitioners are assuming expanded roles and responsibilities in the provision of critical care services, according to Thomas Farley, R.N., N.P.

At the University of California, San Diego, Critical Care Summer Session, Mr. Farley described the expanded role nurse practitioners (NPs) have played in critical care services for about a decade at the University of California, San Francisco (UCSF). In 2004, Dr. Michael Matthay, a pulmonologist, and Dr. Michael Gropper, a critical care anesthesiologist, spearheaded an effort to hire four NPs to work in the university's medical-surgical intensive care unit. "At the time, there were increasing limitations on physician trainees, both in the number of trainees and their work-hour restrictions that were becoming more tight," recalled Mr. Farley of the UCSF School of Nursing. "The goal was to provide critical care at the bedside 24 hours per day, which is in line with the Leapfrog Group recommendations for critical care services. At the time, they had 60 adult ICU critical care beds."

Today, 18 NPs work in adult ICUs at UCSF, with expansion to 76 adult critical care beds, including the medical-surgical ICU, cardiothoracic ICU, and neuro ICU. "Initially the NPs were integrated with medical residents," Mr. Farley said. "Now there are teams that don't have residents, so it's an NP paired with an attending physician, or sometimes a fellow. There are always two NPs on service. Usually, during the day we have four NPs on, with two on at night." The program was described in 2011 (ICU Director 2011;2:16-19).

Practice trends driving the need for NPs in critical care include the increasing demand for intensivists and a reliance on a team-based approach to care delivery, "understanding that a single provider cannot provide all the needs that any individual critical care patient has," Mr. Farley explained. "I think we're a little slow to incorporate the use of nurse practitioners on the West Coast. It's certainly been done for quite some time on the East Coast."

At UCSF, NPs work in teams that include an attending or a fellow, but not always a resident.

MR. FARLEY

He said that NPs are already incorporated into critical care delivery programs at Memorial Sloan Kettering Cancer Center and Columbia University, both in New York; Emory University, Atlanta; Henry Ford Hospital, Detroit; the Cleveland Clinic; and Vanderbilt University, Nashville, Tenn. Adopters out West include UCSF; UC Davis; UC Los Angeles; UC Fresno; and Oregon Health & Science University, Portland.

At UCSF, critical care NP duties include a consultative role to admitting services, a consultative role to bedside RNs, guidance of house staff, responding to code blue activations, assisting with rapid response consultations, serving on hospital-wide multidisciplinary committees, and precepting adult care NP students, as well as attending morning teaching and monthly morbidity and mortality conferences. Procedures performed include insertion of central venous catheters, arterial catheters, chest tubes, and PICC (peripherally inserted central catheter) lines; lumbar puncture; suture and drain removal; and airway intubation.

The use of NPs in critical care "works because we have appropriate conduits for collaboration and supervision that are explained, understood, and taken to heart," Mr. Farley said. "The NPs need to know that they have supportive attending physicians who will assist them when questions arise. We've also had buy-in from the ICU nurses."

A growing body of medical literature suggests that this trend is having an effect. A retrospective study of 600 admissions at two ICUs in New York found that patients managed by NP/PA teams had no worse outcomes, compared with those managed by physicians (Chest 2011; 139:1347-53).

In addition, a recent survey of critical care program directors at academic medical centers found that 86% believe NPs and other advanced practice providers contribute to the continuity of care, 78% believe they save time during rounds and evaluating new patients, and 73% believe they assist in maintaining work flow (J. Crit. Care 2014; 29:112-5).

In the years ahead, Mr. Farley predicted that NPs and other advanced practice providers "are certainly going to be in the ICU, probably even in greater numbers and perhaps in broader roles than they are now."

Mr. Farley said he had no relevant financial conflicts.

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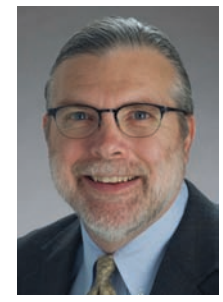
VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: The vast shortage of intensivists in this country and the growing need dictate nontraditional approaches to caring for ever-increasing numbers of critically ill patients. Mid-level providers, whether nurse practitioners (NP) or physician assistants (PA), can substantially extend the expertise of critical care specialists, allowing them to care for more patients. The University of Kansas, my own institution, can be added to the list, just to show that it is not only a bi-coastal phenomenon, and I'm certain other universities and nonteaching hospitals across the continent can either count themselves in now or will be doing so soon. It will remain important, though, to continue to train as many intensivists as possible; mid-level providers can extend critical care docs, but they cannot replace them."



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used with increasing frequency, he predicted. This agent "binds plasminogen so plasminogen can't break down fibrin so you can't get fibrinolysis," said Dr. Schreiber, who has been deployed three times as a combat surgeon.

"This drug has been around forever and is extremely inexpensive. It's approved by the FDA for use in tooth extraction and the oral form is approved for menorrhagia." Tranexamic acid has also been studied in 53 prospective, randomized studies involving some 3,800 subjects, mostly cardiac patients. "They show that if you use tranexamic acid, you use less blood. It reduces the amount of blood necessary for transfusing people in high-bleeding settings, but no difference in mortality, thrombotic events, myocardial infarction, or stroke. It does not seem to produce a hypercoagulable state."

One study of tranexamic acid use by British surgeons during Afghanistan combat operations found that soldiers who received tranexamic acid were seven times more likely to live, compared with those who did not receive the agent (Arch. Surg. 2012;147:113-9). "There was a survival of 85% in tranexamic acid group, compared with about 70% in those who did not receive it," said Dr. Schreiber. "This has resulted in a change in practice in civilian trauma centers where it is being used widely."

Another anticoagulant being used is the prothrombin complex concentrate known as Kcentra, which contains all four vitamin K–dependent coagulation factors. Distributed by CSL Behring, Kcentra is approved for warfarin reversal in adult patients with acute major bleeding and for those who require emergency surgery. The max dose is 50 units/kg. "That's about $4,445 for a 70-kg person," Dr. Schreiber said. "Why is it so good? It's rapidly available, you don't have to give a lot of fluid, there's no infectious risk, and you can very rapidly increase coagulation factor function. This is where we're headed in the future for trauma patients."

Dr. Schreiber said that he had no relevant financial conflicts to disclose.

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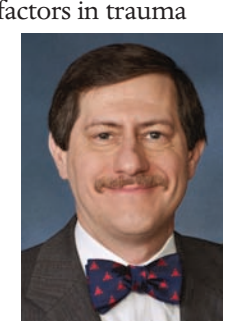
VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: Replacement of blood clotting factors in trauma (and other medical settings) has long been a challenge given the logistics of transfusion and shelf life of blood products. Advances in technology that have yielded powdered forms of blood clotting factors offer clinicians a greater degree of latitude in resuscitation of these patients.



Physicians in groups saw earnings grow

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians in medical groups and other organized systems of care delivery saw a slight increase in compensation, according to annual survey data released by the American Medical Group Association.

In general, findings show average percentage increases in compensation in 2013 were slightly higher than in 2012, with the overall weighted average increase in 2013 being 2.9%, up from 1.6% in the previous year. Results were based on a survey done on behalf of the American Medical Group Management Association (AMGA) by Sullivan, Cotter and As-

Climbing 8.2% to $569,073, cardiac/thoracic surgeons' compensation had one of the highest median total increases year over year.

sociates, with 289 medical groups representing about 73,700 providers submitting valid responses. AMGA released the results on Aug. 20.

Individual specialties showing the biggest median total compensation increase year over year include gastroenterology (a 9.0% increase to $471,336), cardiac/thoracic surgery (8.2% to $569,073), emergency medicine (5.2% to $316,739), and neurology (5.1% to $268,096). Total compensation includes the compensation of the individual provider, with base, variable, and administrative compensation, and all voluntary salary reductions.

Four specialties saw compensation decreases during this time period, including allergy/immunology (a 1.3% decrease to $267,338), rheumatologic disease (–0.5% to $239,112), cardiology-cath lab (–0.4% to $544,733), and endocrinology (–0.2% to $233,769).

Overall, AMGA reported that 68% of specialties reported increases in compensation in 2013, with primary care specialists reporting a 3.8% increase in 2013, up from 2.8% in 2012. Other specialists saw compensation increase on average 1.8%, up from 1.6%, and surgical specialists saw an average increase of 3.0%, up from 0.5%.

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Guideline adds clarity on perioperative beta-blockers

BY SHERRY BOSCHERT
Frontline Medical News

A new clinical practice guideline on cardiovascular evaluation and management of patients undergoing noncardiac surgery adds some clarity around the controversial issue of beta-blocker therapy and updates other aspects of care.

If a patient on beta-blocker medication needs noncardiac surgery, continue the beta-blocker, because there is no evidence of harm from doing so; but you risk doing harm if the drug is stopped, according to the new guideline from the American College of Cardiology (ACC) and the American Heart Association (AHA).

Surgeons will be happy to hear that, said Dr. Lee A. Fleisher, the chair of the guideline-writing committee, because that conforms to one of the Surgical Care Improvement Project's National Measures.

For patients at elevated risk of a cardiovascular event during noncardiac surgery who are not already on beta-blocker therapy, however, the new guideline steps back from the organization's 2009 position that beta-blockers not be started, and says instead that it's not unreasonable to start the drug, with a caveat. Be very cautious, and start the drug early enough before surgery that you can titrate it to avoid causing hypotension or a low heart rate.

"Make sure that you're giving the right amount and monitoring their blood pressure and heart rate," Dr. Fleisher, chair of the guideline writing committee, said in an interview. "Really think once, twice, and thrice about starting a protocol," added Dr. Fleisher, professor of anesthesiology and critical care at the University of Pennsylvania, Philadelphia.

The ACC and AHA commissioned a committee to review the evidence for and against beta-blockers in patients undergoing noncardiac surgery. A separate writing committee then considered the evidence review committee's report, reviewed the literature on other aspects of perioperative care for noncardiac surgery, and compiled a 102-page guideline with a 59-page executive summary.

The new guideline steps back from the 2009 position that beta-blockers not be started, and says instead that it's not unreasonable to start the drug, with a caveat. Be very cautious, and start the drug early.

The "2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery" will be published online on the ACC and AHA websites.

Dr. Fleisher described other highlights of the new guideline. For the first time, palliative care has been added as an option that may come out of the preoperative evaluation, he said. Patient categories of high risk and intermediate risk have been lumped together as having "elevated" risk for simplicity's sake because recommendations for the two separate categories were so similar.

The guideline now endorses two tools to choose from for preoperative risk assessments: the Revised Cardiac Risk Index (RCRI) and the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) risk calculator. "There have been a lot of comments that [the NSQIP] is a very useful tool to have shared decision-making conversations with patients," he said.

Another change applies to patients who receive second- or third-generation coronary stents. Instead of a wait of a year after stent implantation to perform noncardiac surgery, a 6-month wait may be reasonable if the risks of delaying noncardiac surgery outweigh the risks of interrupting dual-antiplatelet therapy for the noncardiac surgery.

In addition, the guideline incorporates findings from the recent POISE-2 study to say that aspirin can be stopped and clonidine is not useful in patients without stents undergoing noncardiac surgery (N. Engl. J. Med. 2014;370:1494-503).

A new statement in the guideline about troponin says to check troponin in high-risk patients with signs or symptoms of trouble but not to include troponin in routine screening.

The recommendations on beta-blockers, however, address the most controversial topic in the guideline, Dr. Fleisher said. "There is a lot of confusing evidence" on the use of beta-blockers, "so we've tried to clarify as much as we can."

The ACC and AHA funded the work. Dr. Fleisher reported having no financial disclosures.

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VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: The largest randomized controlled trial (RCT) ever undertaken in perioperative medicine, PeriOperative Ischemia Study Evaluation trial (POISE), showed that perioperative beta-blockade decreased cardiac risks but increased all-cause mortality and the risk of disabling stroke.

These findings called for a thorough review of previous guidelines and accepted practice.

Several editorials and comments followed the publication of POISE. As clinicians, we have to keep in mind that guidelines also advocate the careful assessment of patient- and surgery-specific risk factors in determining who should receive therapy that may benefit or, conversely, be exposed to harm by the introduction of beta-blockade before noncardiac surgery.

Apixaban gets green light for treating PE, DVT

BY ELIZABETH MECHCATIE
Frontline Medical News

The oral factor Xa inhibitor apixaban is now approved for the treatment of deep vein thrombosis and pulmonary embolism, and for reducing the risk of recurrent DVT and PE following initial treatment, the manufacturers have announced.

This approval is based on the results of the AMPLIFY and AMPLIFY-EXT studies, according to the statement issued by Bristol-Myers Squibb and Pfizer.

Apixaban, initially approved in 2012 and marketed as Eliquis, is already approved for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the prophylaxis of DVT, "which may lead to PE," after hip or knee surgery. The recommended dose for the treatment of DVT and PE is 10 mg twice a day for 7 days, followed by 5 mg twice a day. The recommended dose for reducing the risk for recurrent DVT and PE, after initial therapy, is 2.5 mg twice a day.

AMPLIFY was a noninferiority study of about 5,200 patients with symptomatic DVT or PE. It compared apixaban to standard care using enoxaparin. The primary efficacy endpoint, a composite of recurrent symptomatic VTE or VTE-related death over 6 months, was comparable in the two groups: 2.3% among those on apixaban and 2.7% among those on enoxaparin/warfarin, according to the prescribing information.

The primary safety endpoint, major bleeding, was 0.6% among those on apixaban vs. 1.8% among those on enoxaparin/warfarin, a significant difference. Rates of clinically relevant nonmajor bleeding were 3.9% among those on apixaban vs. 8% among those on enoxaparin/warfarin.

In Amplify-EXT, almost 2,500 patients who had received anticoagulant therapy for DVT and/or PE for 6-12 months and had not had a recurrent event were randomized to treatment with apixaban 2.5 or 5 mg twice a day, or placebo, followed for a mean of almost 1 year. The rate of recurrent VTE or all-cause death was 3.8% among those on 2.5 mg twice daily and 4.2% among those on 5 mg twice daily, vs. 11.6% among those on placebo.

The rate of bleeding-related adverse reactions was 13.3% among those on apixaban vs. 8.7% among those on placebo. The rate of major bleeding was 0.2% among those on the 2.5-mg twice-daily dose and 0.1% among those on the 5-mg twice-daily dose, vs. 0.5% among those on placebo.

The updated prescribing information is available at http://packageinserts.bms.com/pi/pi_eliquis.pdf. Serious adverse events associated with apixaban should be reported to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/medwatch.

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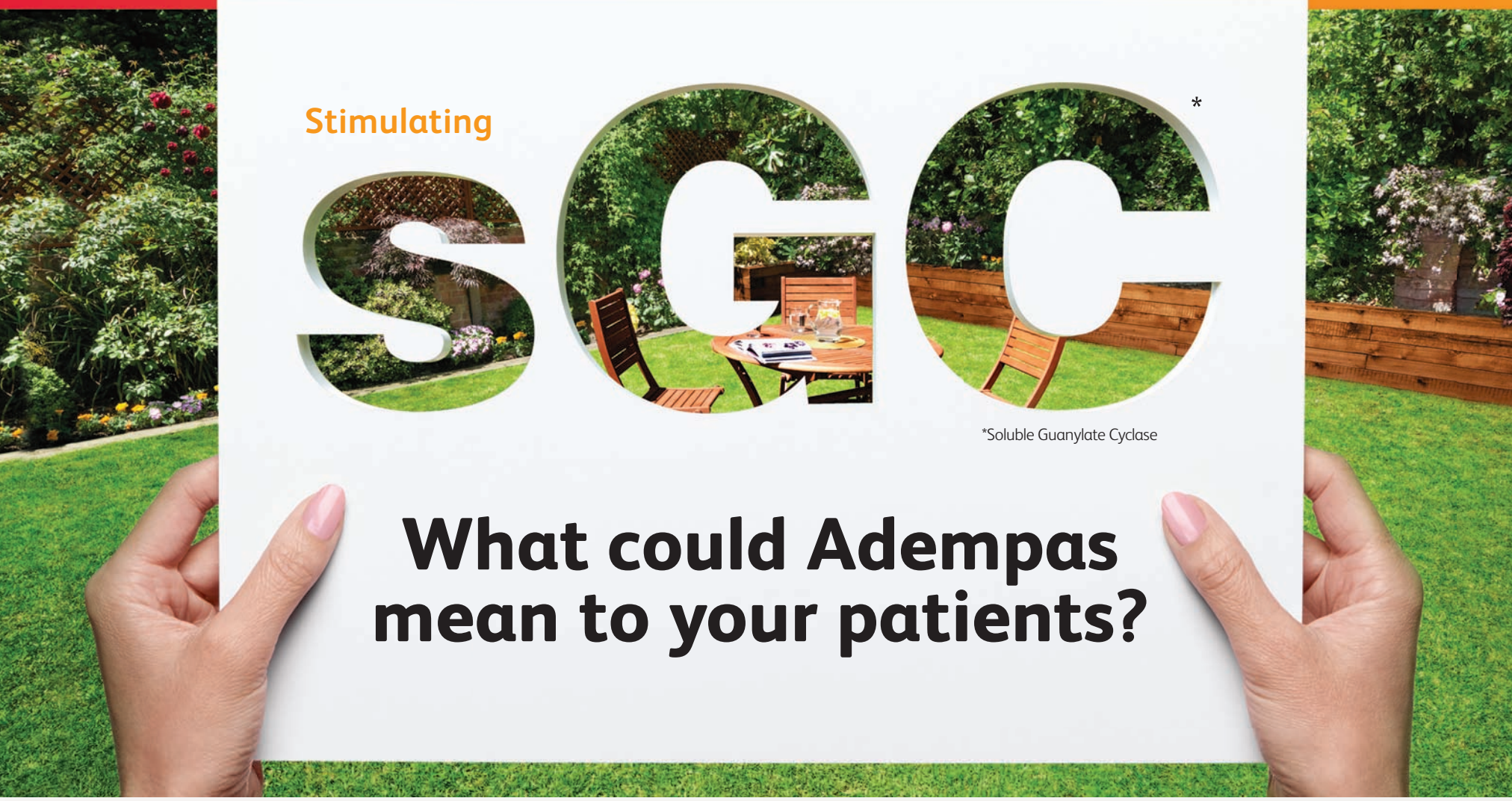
First and only treatment approved for both **PAH** and inoperable or persistent/recurrent **CTEPH** after surgery[†]



[†]INDICATIONS

- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.[‡]

  Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

[‡]Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets 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, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

Adempas-US.com

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Adempas could mean moving from the couch to the kitchen

Patients walked farther with Adempas at Week 12: results from Week 2 onward

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001) for PAH (WHO Group 1) patients.

WHO FUNCTIONAL CLASS

50%

more PAH patients improved WHO Functional Class vs placebo (p=0.0033; Adempas: n=53/254 [21%], placebo: n=18/125 [14%]) at Week 12.

Deteriorated

4% for Adempas (n=9/254)

14% for placebo (n=18/125)

Stable

76% for Adempas (n=192/254)

71% for placebo (n=89/125)

PATENT-1: 443 PAH patients were studied. (Adempas 2.5 mg n=254, 1.5 mg n=63, placebo n=126)

Baseline characteristics:

– PAH defined as: pulmonary vascular resistance (PVR) >300 dyn·sec·cm^{-5}, mean pulmonary arterial pressure (mPAP) >25 mm Hg

– Mean age: 51 years (approximately 80% female)

– PAH etiologies: idiopathic (61%), familial (2%), associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or anorexigen or amphetamine use (1%)

– Mean 6MWD was 363m

– Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

Patient population was: 50% treatment-naïve, 44% pretreated with an endothelin receptor antagonist (ERA), and 6% pretreated with a prostacyclin analogue (PCA). The majority of patients had WHO Functional Class II (42%) or III (54%) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Patients walked farther with Adempas at Week 16: results from Week 2 onward

46m improvement (mean) in 6MWD over placebo at Week 16 (95 % CI: 25m-67m; p<0.0001) for CTEPH* (WHO Group 4) patients.

WHO FUNCTIONAL CLASS

2x

as many CTEPH patients improved WHO Functional Class vs placebo (p=0.0026; Adempas: n=57/173 [33%], placebo: n=13/87 [15%]) at Week 16.

Deteriorated

5 % for Adempas (n=9/173)

7 % for placebo (n=6/87)

Stable

62 % for Adempas (n=107/173)

78 % for placebo (n=68/87)

CHEST-1: 261 CTEPH patients were studied. (Adempas n=173, placebo n=88)
Baseline characteristics:
*Inoperable or recurrent/persistent CTEPH after surgery.

– Mean age: 59 years (range: 18–80)

– Mean 6MWD was 347m

– Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed, but not nitric oxide donors, endothelin receptor antagonists, prostacyclin analogues, specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline)

Patient population was: 72 % inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] >300 dyn·sec·cm^{-5} and mean pulmonary arterial pressure >25 mm Hg measured at least 90 days after the start of full anticoagulation); 28 % recurrent or persisting pulmonary hypertension (PH) following PEA (PVR >300 dyn·sec·cm^{-5} measured at least 180 days following PEA). The majority of patients were WHO Functional Class II (31 %) or III (64 %) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

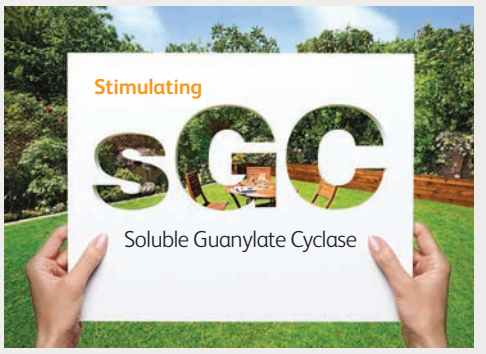
WARNINGS AND PRECAUTIONS

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients 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 Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.



FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

Adempas-US.com

More than 90% of Adempas patients survived at 2 years*

*Data from CHEST-2 and PATENT-2 open-label extension studies. Without a control group, these data must be interpreted cautiously.

PAH

93%

PROBABILITY OF SURVIVAL AT 2 YEARS

CTEPH

94%

PROBABILITY OF SURVIVAL AT 2 YEARS

At 1 year, probability of survival was 97% in both open-label extension studies.

WARNINGS AND PRECAUTIONS

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

Visit
Adempas-US.com
for more information

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100 Bayer Boulevard, Whippany, NJ 07981 USA

400-10-0003-14b September 2014

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[See Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1]*.

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

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

Adempas REMS Program

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

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

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

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

Other Risks Associated with Adempas

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

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Cessation by text? Interactive app helps smokers quit

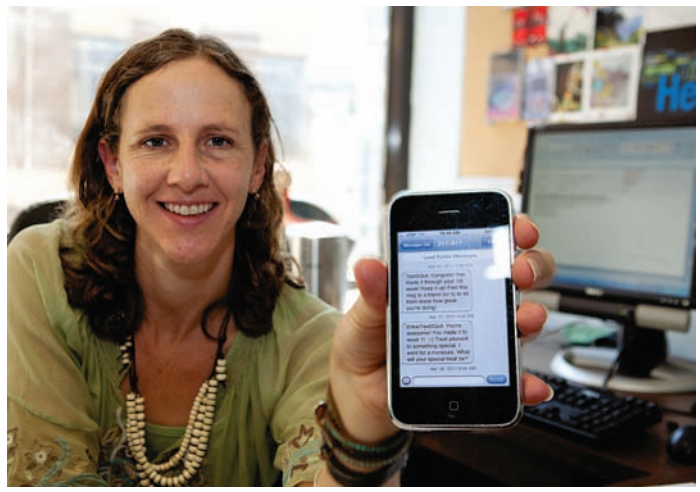
BY SHERRY BOSCHERT
Frontline Medical News

Text-messaging programs on phones seem to help smokers quit. The jury's still out on smartphone apps for smoking cessation when used by patients, but they may help nurses improve screening, several separate studies suggest.

The interactive text-messaging program Text2Quit helped U.S. smokers quit and stay off cigarettes in a 6-month randomized, controlled trial in 503 adults who smoked at least five cigarettes a day, owned a cell phone with an unlimited service plan for short text messaging, and had expressed an interest in quitting cigarettes. Participants already were avid texters, sending or receiving an average of 29 text messages per day before they enrolled in the study.

At the 6-month follow-up, 20% of 241 people in the Text2Quit group said they had not smoked in the prior 7 days, versus 10% of 262 people in the control group, reported Lorien C. Abroms, Sc.D., and her associates.

Laboratory analyses of saliva from 54 members of the intervention group and 32 in the control group showed that nearly a quarter of participants had lied about quitting. Text2Quit still was effective, however, with biochemically confirmed abstinence from smoking in 11% of the intervention group and 5% of the control group (Am. J. Prev. Med. 2014 June 5 [doi: 10.1016/j.amepre.2014.04.010]). Those biochemical quit rates are similar to rates reported in studies of other text-messaging programs for smoking cessation or of telephone quit-line counseling, she said.



COURTESY GEORGE WASHINGTON UNIVERSITY

Dr. Lorien C. Abroms shows a screen shot of smoking cessation messages from the Text2Quit app.

The results support a meta-analysis of five studies that found mobile phone–based interventions (predominantly text messaging) for smoking cessation increased 6-month quit rates (Cochrane Database Syst. Rev. 2012;11:CD006611 [doi: 10.1002/14651858]). Most U.S. studies, however, have been small, uncontrolled pilot trials with no biochemical verification of quit rates, said Dr. Abroms, who designed Text2Quit and receives royalties from sales.

What's involved?

Text2Quit costs $30 for a 4-month subscription unless you have a code from a sponsoring organization. When U.S. smokers call the national quit-line number (1-800-QUIT-NOW), residents of some states get offered Text2Quit. More than 50,000 smokers have enrolled since the program became available in 2011, reported Dr. Abroms of George Washington University, Washington. Other text-messaging programs are available, such as the free SmokefreeTXT program from the National Cancer Institute's smokefree.gov site.

People randomized to the control group in Dr. Abroms' trial initially were given a link to smokefree.gov, but after the launch of SmokefreeTXT in 2011, new control group members instead were given a link to the National Cancer Institute's "Clearing the Air" guidebook on quitting smoking.

Text2Quit consists of automated, bidirectional text messages, with extra support from e-mails and a web portal. The texts prompt users to track their smoking and report on their cravings and smoking status, with the messages to participants tailored by the reasons for quitting, money saved, and use of medications for smoking cessation. The frequency of texts peaked around the smoker's chosen quit date, with five texts on that date, approximately two per day in the following week, three per week in the next 2 months, and less than one per week after that.

Considering that an estimated 75% of adults around the world have access to cell phones, text-messaging interventions potentially could puff up the number of quitters, she said.

Apps reach far, but may say little

Smartphones aren't yet as ubiquitous but, still, an estimated 11 million U.S. smokers own a smartphone, Dr. Abroms wrote in a separate study of apps for smoking cessation. We don't yet know if any of the 400 smoking cessation apps that were available in 2012 work, but her analysis of 98 of the most popular smoking cessation apps found that they seldom include information and strategies that have been proven to help smokers quit.

She and her associates rated 47 apps for iPhones and 51 for Android phones on a 42-point scale, with a top score indicating adherence to the U.S. Public Health Service's Clinical Practice Guidelines for Treating Tobacco Use and Dependence. The average score was 13. No apps recommended calling a quit line, for example. Only 4% recommended using medications approved for smoking cessation. Only 19% offered practical counseling or advice on how to quit (Am. J. Prev. Med. 2013;45:732-6).

On the other hand, it's possible that national guidelines that were developed for clinical settings don't apply to mobile apps. If the apps somehow are effective, their reach could magnify any impact, Dr. Abroms suggested.

"Text messaging programs for smoking cessation have a reasonably good evidence base," according to Dr. Abroms. "The evidence for smartphone apps is still in its early stages. I would not recommend them as a stand-alone intervention, though many with tracking elements may be useful as part of a comprehensive program. Apps that include games could be good as a distraction from smoking."

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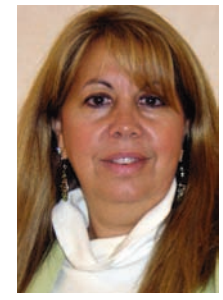
VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: Instant messaging and texting have become prominent communication and reminder tools with a high degree of integration in daily life. One can see the potential of their use in medicine, particularly in messaging wellness.



As apps and messaging use continues to grow and as the segments of society that are most comfortable with this technology age and become consumers of health services, these may be important tools for improving population health.

Treatment app boosts counseling rate

A separate study found that an experimental "decision support system" app, created for use by nurses on smartphones and tablets, improved rates of screening and counseling for tobacco use by prompting nurses to screen for tobacco use and offered guideline-based treatment recommendations, reported Kenrick Cato, Ph.D. of Columbia University, New York, and his associates.

DR. CATO

The 185 registered nurses who were enrolled in advanced practice degree programs handled 14,115 clinic visits, in which they asked patients about smoking status in 84% of visits and offered cessation counseling to 90% of those who expressed a willingness to stop smoking (Oncol. Nurs. Forum 2014;41:145-52).

That compares favorably with federal U.S. data suggesting that tobacco screening happens in approximately 60% of clinic visits, and fewer than 20% of patients get counseling on quitting, Dr. Cato said in a prepared statement released by the university. The federal Healthy People 2020 program aims for tobacco screening in 69% of office visits and counseling rates of 21%, he said.

If further development of the app confirms that it's useful, it could light a fire under tobacco screening.

Dr. Cato reported having no financial disclosures.

Corticosteroid adherence gets better in the bathroom

Seniors *from page 1*

Sinai, New York, and his coauthors (J. Intern. Med. 2014 Aug. 5 [doi:10.1007/s11606-014-2940-8]).

The team investigated adherence to inhaled corticosteroids among 358 elderly patients with asthma. They were a mean of 67 years old, with 31% older than 70 years. Most (84%) were women and many were Latino (38%). Black patients comprised 31% of the cohort and the others were non-Hispanic whites.

The majority had a low monthly income ($1,350 or less), and 25% were not fully literate in English. Many had comorbid psychological conditions, including depression (20%) and anxiety (21%).

Low health literacy was common (34%), although most (71%) did understand that they would always have asthma and that it could not be cured (81%). But half believed that they had the disease only when they were symptomatic. In a survey of medication beliefs, most did believe that the steroids were good for them and that their benefits outweighed the risks.

However, only 37% of the cohort reported good medication adherence. This proportion was significantly worse among blacks and Hispanics; those with lower incomes and lower education; those born in Puerto Rico and the Dominican Republic; and those with poor physical health, anxiety, or depression.

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For some older patients with asthma, integrating inhaled corticosteroid use into their daily routine can reduce forgetful nonadherence.

The authors identified six medication adherence strategies among the group: keeping the medication in a usual location (44%); integrating it into their daily routine (33%); taking it at a specific time of day (22%); taking it with other medications (13%); using it only when needed; (13%) and using other reminders (12%). Less than 2% reported using written notes as a reminder or having someone else remind them; 4% had no specific strategy.

The most common places to keep medicine were at the bedside (20%) and in the bathroom (9%). Those who integrated taking it with other daily routines did in the morning (12%) and at bedtime (8%).

Only three of the strategies were significantly associated with good adherence: keeping medication in the bathroom (16% adherent vs. 5% nonadherent); integrating it into a daily routine (morning 25% vs. 5%; evening 13% vs. 6%); and taking it at a specific time of day (29% vs. 17%).

Taking the medication only when needed was associated with significantly worse adherence.

After controlling for other variables, only leaving the medication in the bathroom significantly predicted good adherence (odds ratio, 3), compared with those who kept it somewhere else).

Those who integrated medication into other daily routines were also significantly more likely to be adherent (OR, 3.7) in a partially adjusted model, but not in a fully adjusted model. Still, the authors noted, this recommendation would be a good suggestion toward improving adherence.

Patients who used these two strategies were more likely to be white, have at least a partial education, and to have been born in the United States. Low income, limited English proficiency, low health literacy, poor physical and psychological health, and erroneous beliefs about asthma predicted poor adherence.

The team postulated that there are two types of nonadherence: simple forgetfulness or lack of understanding about its importance and deliberate nonadherence.

"The bathroom and daily routine strategies may address forgetful nonadherence. … Taking the medication only as needed, on the other hand, may indicate faulty disease or medication beliefs. … Taken together, these findings provide further evidence of the value of patient-centered care: Clinicians need to understand why patients do not use their medications appropriately before counseling patients on ways to improve adherence."

The study was supported by a grant from the National Heart, Lung, and Blood Institute. None of the authors had any financial disclosures.

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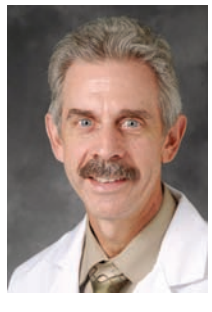
VIEW ON THE NEWS



Dr. Daniel Ouellette, FCCP, comments: My busy afternoon clinics are filled with patients with asthma who, despite using an extensive (and expensive) bronchodilator regimen, continue to wheeze and cough.

Do I "step-up" therapy, add prednisone, or recommend a novel agent or procedure? All too often, I wonder if they are using their inhalers correctly. I spend some time to teach them about the use of an increasingly varied array of devices. An underlying concern remains: Are they using their inhalers at all? Research suggests that they are not.

This recent study indicates that simple strategies will improve compliance. Next week, I will tell my patients to keep their inhalers in the bathroom, and incorporate them into their daily routine!

WHO urges indoor ban on e-cigarettes

BY GREGORY TWACHTMAN

Frontline Medical News

The use of electronic cigarettes, like that of their tobacco-containing cousins, should be banned in public indoor spaces, the World Health Organization recommends.

Users of electronic nicotine delivery systems devices (ENDS), such as e-cigarettes, should "be legally requested not to use ENDS indoors, especially where smoking is banned, until exhaled vapor is proved to be not harmful to bystanders and reasonable evidence exists that smoke-free policy enforcement is not undermined," according to a WHO report published Aug. 26.

The report is intended to provide a framework for governments to follow when developing regulations around e-cigarettes.

Users of such devices should be legally requested not to use them indoors, 'especially where smoking is banned, until exhaled vapor is proved to be not harmful to bystanders.'

The report recommends that manufacturers be prohibited from making any health claims related to ENDS, specifically identifying claims that e-cigarettes are smoking cessation products. The report notes that there is anecdotal evidence to suggest e-cigarettes have been effective in helping people quit smoking but "their efficacy has not been systematically evaluated yet." WHO recommends that approved and proven cessation products be tried first, with e-cigarettes being a last resort. Recent guidelines from the American Heart Association echoed that sentiment.

The WHO guidance is in line with recent recommendations made to the Food and Drug Administration from various medical societies in advocating for strict oversight in marketing to ensure that children are not targeted. The FDA is considering broadening its tobacco oversight to include e-cigarettes.

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AHA says restrict e-cigs, but notes potentially helpful role

BY DEEPAK CHITNIS
Frontline Medical News

The American Heart Association has released its recommendations regarding the sale and usage of e-cigarettes, cautioning that the devices should be regulated to avoid enticing children to smoke while also saying that e-cigarettes could be used as a way to help some current smokers quit.

The guidelines, published Aug. 25 in Circulation, state that clinicians "should not discourage" their patients from resorting to e-cigarettes if other approved forms of smoking cessation, such as the nicotine patch, have been exhausted. The AHA warned, however, that further studies are needed to fully understand the effects of e-cigarette usage, stressing that e-cigarettes have not been approved by the Food and Drug Administration as an acceptable smoking cessation device and could contain low amounts of toxic chemicals that would prove more harmful than helpful to patients in the long run.

"E-cigarettes have caused a major shift in the tobacco-control landscape," Aruni Bhatnagar, Ph.D., lead author of the guidelines and chair of cardiovascular medicine at the University of Louisville, Ky., said in a statement. "It's critical that we rigorously examine the long-term impact of this new technology on public health, cardiovascular disease, and stroke, and pay careful attention to the effect of e-cigarettes on adolescents."

For now, the AHA says that clinicians should tell their patients who use e-cigarettes to set a firm quit date, warning that any device that delivers nicotine into the body is harmful and likely lethal.

"Nicotine is a dangerous and highly addictive chemical no matter what form it takes – conventional cigarettes or some other tobacco product," Dr. Elliott Antman, AHA president, said in the statement. "Every life that has been lost to tobacco addiction" could have been saved, he noted.

To that end, the AHA also called for strong regulations regarding the potential marketability of e-cigarettes to youngsters. The group recommended a federal ban on the sale of e-cigarettes to minors. The AHA also recommended that all existing rules and regulations in place for tobacco-related products should apply to e-cigarettes.

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Smokers should not be discouraged from use of e-cigarettes as a quit tool.

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)

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

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

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

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

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

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

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

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

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

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

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance.

GSK
Research Triangle Park, NC 27709

Revised 12/2013 ANR:1BRS

ABIM answers MOC concerns of grandfathered physicians

BY ALICIA AULT
Frontline Medical News

Physicians who are grandfathered from maintenance of certification requirements may soon be listed differently on the American Board of Internal Medicine website.

The ABIM site currently reports publicly whether or not physicians are "Meeting Maintenance of Certification Requirements," and that status means grandfathered physicians do not appear to be meeting MOC requirements on the American Board of Medical Specialties' Certification Matters website.

" 'Not meeting MOC requirements' is, in essence, a scarlet letter meant to pressure grandparents into enrolling in the current flawed MOC system," Dr. Mack Harrell, president of the American Association of Clinical Endocrinologists, said in a June 30 letter to the ABIM.

At an August meeting, ABIM agreed that the language "is causing legitimate confusion." Grandfathered physicians are encouraged but are not required to participate in MOC, yet they are still being listed as either meeting or not meeting the MOC requirements, according to an Aug. 15 statement from the board.

The board is "exploring what changes to the reporting language can be made," according to the statement. The issue is making sure that "reporting of certification status is clear and consistent across the community of specialty boards."

The nature and timing of the change have not yet been decided by the board, ABIM spokesperson Lorie Slass said. "We want to work with ABMS to make sure there is consistency and clarity in web reporting."

' "Not meeting MOC requirements" is, in essence, a scarlet letter meant to pressure grandparents into enrolling in the current flawed MOC system.'

To help CHEST members negotiate the changes that have already gone into effect, the organization devotes an education page on chestnet.org to help its members stay current using plain language: "Did you know ABIM MOC Requirements changed in January 2014? Did you know the changes affect ALL of you?"

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Federal health IT chief DeSalvo feels meaningful use pain

FRONTLINE MEDICAL NEWS

Dr. Karen DeSalvo is the fifth person to serve as national coordinator for health information technology at the Department of Health & Human Services, but perhaps more than any of her predecessors, she is truly in the thick of the struggle to bring doctors, medical practices, and hospitals into the digital age.

Physicians face a major deadline this year: It's the last year to sign up for the meaningful use incentive payment program created by the Health Information Technology for Economic and Clinical Health Act (HITECH). If they don't participate, they lose out on the potential to recoup from the federal government at least a small portion of the money they've spent on electronic health record systems. And it's becoming inevitable that not participating could mean being left behind by insurers, hospitals, and patients.

That's causing a lot of anxiety. Dr. DeSalvo – a practicing internist – says that she feels doctors' pain. She recently completed a national listening tour and says that what she learned from those sessions will help inform how the Office of the National Coordinator moves forward.

— Alicia Ault

Fight or pay up? How to survive a billing audit

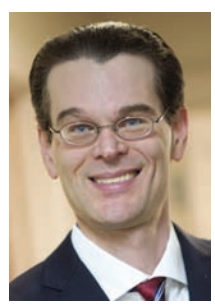
BY ALICIA GALLEGOS
Frontline Medical News

CHICAGO – The first rule of a billing audit, according to Dr. Brent Moody: "Don't take it personally."

Audits are about money, and "there's always going to be a winner and a loser," said Dr. Moody, an adviser to the American Medical Association's Relative Value Scale Update Committee (RUC). The RUC acts as an expert panel in developing recommendations to the government on the relative value of physician services under the Medicare physician fee schedule. He addressed the American Academy of Dermatology summer meeting.To raise the odds of landing on the winning side of an audit or billing investigation, Dr. Moody advised taking the following steps.

Consider legal counsel. The need for an attorney depends on the size, scope, and seriousness of the audit.

"You may be able to handle it on your own" if a small number of records are requested, he said. But a Recovery Audit Contractor (RAC) audit request for dozens or hundreds of chart records could indicate a more serious audit investigation. "If they come back to you with a big recoupment or a really broad request, you may want to think about getting legal help."



FCA violations or qui tam lawsuits 'are serious issues. You need legal help, and you need it right away.'

DR. MOODY

Legal counsel is strongly recommended if audit investigations evolve into allegations of False Claims Act (FCA) violations or qui tam lawsuits, said Dr. Moody. The federal FCA law sets criminal and civil penalties for falsely billing the government, overrepresenting the amount of a delivered product, or understating an obligation to the government. Qui tam lawsuits are civil claims under the FCA in which whistle-blowers are rewarded if the claims uncover fraud and recover funds for the government. Both types of cases can mean the involvement of federal authorities, seized documents or equipment, and potential criminal charges.

FCA violations or qui tam suits "are serious issues. You need legal help, and you need it right away," he said.

Decide whether to fight or pay. Complying with a recoupment will reduce hassle and more quickly resolve an audit. An appeal makes sense if the request is erroneous or unfair. Appealing within 30 days halts the recoupment but doesn't stop interest accrual.

A letter of rebuttal – a formal statement as to why the recoupment should not take place – is ideal when the wrong doctor or practice has been audited or the audit violates rules on look-back timelines. Health providers have 15 days to rebut upon notice of an impending recoupment action. Another option is pay the recoupment sum, but get the auditors to agree that no further look-backs will occur from a certain time frame.

Do your audit homework. Audit resources and information are available from the American Medical Association and state medical societies.

Be civil to your auditor. While challenging, remaining cordial and respectful to auditors during the audit process can ultimately work in the physician's favor, Dr. Moody said. "Talk to them and try to figure out exactly what they are looking for. You don't want to fight the wrong battle."

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Burnout is prevalent among transplant surgeons

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Nearly half of transplant surgeons in the United States show signs of burnout, suggests an online survey of members of the American Society of Transplant Surgeons. But several of the contributing factors identified are potentially modifiable.

The 218 surgeons completed online questionnaires, including a job content questionnaire, the Maslach Burnout Inventory–Human Services Survey, and questions about the frequency of and comfort in dealing with difficult or emotional patient interactions.

'The very low level of personal accomplishment is really kind of astounding.'

DR. JESSE

"Most research on burnout in surgeons has focused on the medical environment, if you will, so the type of supervision, decisional autonomy, the psychological job demands, work hours, nights on call, that type of thing," lead investigator Michelle T. Jesse, Ph.D., said in an interview at the 2014 World Transplant Congress, where the study was presented.

"We wanted to look at that as well, but we wanted to take it to the next level and look at some more interpersonal components – look at the components in the work environment, but also with the patients. That's really the new thing to this particular study," she said.

The surgeons were 48 years old, on average. Most of them were male

Continued on following page

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: Burnout in medicine is a prevailing theme in many specialties, and is particularly common in transplant surgeons, as recounted in this paper presented at the American Society of Transplant Surgeons. However, many of the same themes of psychological stress and depersonalization leading to potential burnout are likely present in other surgeons who deal with high-risk, emotionally charged diseases such as lung cancer for the thoracic surgeon. Increasing governmental regulation, demands for even more productivity due to diminished reimbursement, and less decisional authority has accelerated the problem of burnout into even younger surgeons.

Continued from previous page

(87%) and white (74%), and practiced in academic institutions (83%). They worked a mean of 70 hours per week.

Study results, reported in a poster session, showed the three components of burnout were prevalent: 40% of the surgeons had a high level of emotional exhaustion, 17% had a high level of depersonalization, and 47% had a low level of personal accomplishment.

"The high emotional exhaustion is concerning because that's really associated with most negative outcomes. And given what transplant surgeons do, the lives they save, the work they do, the very low level of personal accomplishment is really kind of astounding," Dr. Jesse commented.

"But a very small proportion had high depersonalization. So in other words, basically, these surgeons are not distancing themselves from their patients or their work; that would suggest they are invested in their work. They have not gotten to the point where they are emotionally forced to in essence separate themselves from the work and the patients, but they are not feeling like they are successful necessarily, they are stressed, and you see this when you talk to them in real time," she added.

Study results also revealed a variety of risk factors, according to Dr. Jesse, who is a senior staff psychologist with the Henry Ford Health System in Detroit.

Surgeons had higher levels of burnout if they had less decisional authority, they had poorer coworker support, their job was more psychologically demanding, they had greater discomfort dealing with difficult or emotional patient situations, and they had to deal with such situations more frequently.

Interventions could also enhance comfort with people, especially in difficult situations inherent to this specialty.

"This is the reality of their work, and helping them to develop the skills to deal and comfortably communicate with patients who are emotionally distressed, patients with whom they have to talk about DNRs [do not resuscitate orders] and end-of-life issues, things like that – we can definitely intervene there," Dr. Jesse maintained.

Some of the findings regarding personal accomplishment may be related to perfectionism, she noted, and mindfulness could be a helpful approach there. "That's been really effective at eliminating some burnout, and the beauty of mindfulness is minimalizing judgmental perspective reflected on oneself," she elaborated.

Dr. Jesse disclosed no conflicts of interest relevant to the research.

Clinics, EDs miss many flu vaccination opportunities

BY SHARON WORCESTER
Frontline Medical News

LAKE BUENA VISTA, FLA. – Nearly 44% of incompletely vaccinated inpatients with influenza had a missed opportunity for vaccination, according to a chart review at Children's Hospital Colorado.

Among 197 such children admitted with confirmed influenza in 2010-2014, 86 (44%) had a total of 507 medical visits during which influenza vaccine was available, Dr. Suchitra Rao of the University of Colorado, Denver, reported in a poster at the Pediatric Hospital Medicine 2014 meeting.

The majority of patients with missed opportunity visits were considered high risk for severe complications from influenza from factors such as age younger than 2 years, immunosuppression, pregnancy, or an underlying chronic pulmonary, cardiovascular, renal, hepatic, neurological, hematologic, or metabolic disorder, Dr. Rao reported.

VITALS

Key clinical point: Specialty outpatient visits offer an important opportunity for influenza vaccinations.

Major finding: A total of 44% of 197 patients had a total of 507 missed opportunities for vaccination.

Data source: A review of the charts of 197 incompletely vaccinated children with the flu.

Disclosures: The investigators reported having no relevant financial disclosures.

The bulk of missed opportunity visits occurred during September, October, and November (20%-23% each month) prior to onset of the influenza season, with declining percentages taking place between December and April. Most of the visits (45%) occurred at specialty clinics, followed by the emergency department or urgent care setting (22%).

"Subspecialty outpatient visits provide an excellent opportunity for influenza vaccination because they target high-risk patients and they represent the highest proportion of missed opportunities for vaccination," Dr. Rao and her colleagues wrote.

VIEW ON THE NEWS

Dr. Burt Lesnick, FCCP, comments: The federally funded Vaccine for Children program provides free influenza vaccine in most states. However, many states require that a specialist take shipment and administer all the childhood vaccines offered in order to get the influenza vaccine. Such roadblocks are common and need to be removed if we are to achieve our goal of universal pediatric influenza vaccination.

DR. LESNICK

Complications from flulike illnesses occur in 35%

BY TARA HAELLE
Frontline Medical News

One in three (35.3%) children developed complications with influenzalike illnesses, and children with neurologic or neuromuscular conditions were at highest risk for complications, according to a recent study.

The most common pediatric complication was pneumonia, seen in 26.1% of the study patients. Dr. Rakesh D. Mistry of the University of Colorado in Aurora, and his colleagues reported in the journal Pediatrics that the complication rate did not vary between influenza and other respiratory viruses. Seizures was another complication that was common, at 5.8%. Interestingly, children with neurological or neuromuscular conditions were also four times more likely to develop complications in general.

The researchers prospectively assessed 241 children aged 0-19 years who presented to a children's hospital emergency department with influenzalike illness – fever plus a cough or sore throat without another cause – from early winter 2008 to late spring 2010. The study included only children with moderate to severe symptoms (defined by physicians' decision to do venipuncture and respiratory viral testing) who did not already have severe complications (including seizures, encephalopathy, pneumonia, bacteremia, bacterial tracheitis, respiratory failure, myocarditis, or death.

Overall, 24.9% of the children had influenza, 28.2% had no virus detected, 14.5% had rhinovirus, 11.6% had respiratory syncytial virus, and the remainder had human metapneumovirus, adenovirus, or parainfluenza viruses. Among children with influenza, the risk of developing pneumonia was 7.6 times higher with the H1N1 strain than with other strains.

Asthma was the most common chronic medical condition in the study population but of note, 53.5% of patients in the study were identified as having a chronic underlying disease state. With the finding that children with neurological and neuromuscular disorders also are at higher risk for respiratory viral complications, the authors emphasized that children with chronic health problems need an increased focus by health care providers to provide yearly influenza vaccinations and early institution of antiviral treatment (Pediatrics 2014 Aug. 4 [doi:10.1542/peds.2014-0505]).

The Pennsylvania Department of Health supported the study in part. The authors reported no disclosures.

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Another breath of fresh air – we keep telling parents that *all* babies from 6 months, children, and young adults should get yearly flu shots – and this study again supports all the hard work we are doing!

New President to be inducted at CHEST 2014

Curtis N. Sessler, MD, FCCP, is the Orhan Muren Distinguished Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the Virginia Commonwealth University (VCU) Health System in Richmond, Virginia. Board certified in internal medicine, pulmonary diseases, and critical care medicine, Dr. Sessler is Director of the Center for Adult Critical Care, as well as Medical Director of Critical Care and Medical Director of the Medical Respiratory ICU at the Medical College of Virginia Hospitals of VCU.

DR. CURTIS N. SESSLER, FCCP

Dr. Sessler is an enthusiastic clinician and educator named to "top doc" lists and has received a variety of teaching awards at VCU, including the School of Medicine Educational Innovation Award. His research interests focus on ICU topics, including sedation and analgesia, mechanical ventilation, infection control, and procedural competency resulting in more than 300 published journal articles, book chapters, books, abstracts, and enduring products. He led a multidisciplinary group that developed the Richmond Agitation Sedation Scale (RASS), widely used in ICUs worldwide. Dr. Sessler has also served on a variety of multisociety task forces addressing research, training competency, workforce shortage, and reimbursement. He is Past President of the Virginia Thoracic Society and was a member of several committees for the US Food and Drug Administration, including chair of the Pulmonary and Allergy Drug Advisory Committee. Dr. Sessler is an active Fellow of CHEST and has served on the Board of Regents and as Chair of the Critical Care Section, Chair of the Council of Sections, Chair of the Critical Care Institute, and Program Chair for the 2003 CHEST annual meeting. He received the Roger C. Bone Memorial Lecture award in 2010. He is a member of the editorial board of the journal *CHEST*, also serving as co-section editor for Contemporary Reviews in Critical Care Medicine, and is Editor-in-Chief of CHEST SEEK Critical Care Medicine.

We asked Dr. Sessler for his thoughts on his upcoming CHEST presidential year.

► What would you like to accomplish as President of CHEST?

I am grateful for the opportunity to help lead this tremendous organization in the upcoming year. Working in ICUs most of my professional life has ingrained in me a strong belief in the power of the team, and I view my role as President as one of providing leadership and direction but also encouragement and empowerment of the many talented and dedicated member-volunteers and professional staff of CHEST – the TEAM. I am also indebted to and will continue to rely upon the wisdom and dedication of our current and past leaders of CHEST for their thoughtful counsel. CHEST is a global organization dedicated to excellence in education, knowledge creation and dissemination, and team-based clinical care in pulmonary, critical care, and sleep medicine.

The breadth of world-class CHEST activities and products designed to advance these goals is truly breathtaking. This starts with the flagship journal *CHEST*, which has achieved the highest readership and impact factor ratings ever; the SEEK series of board review books and apps that recently expanded to include Pediatric Pulmonary Medicine; authoritative clinical practice guidelines; the information-packed annual CHEST meeting and board review courses; and numerous simulation-based courses in bedside ultrasonography and pulmonary and critical care procedures, to name a few.

This past year has brought several exciting developments in the delivery of world-class education and training, starting with the opening of the new CHEST Global Headquarters in Glenview, Illinois – which is a combination of facilities for nearly 100 staff, and a state-of-the-art Innovation, Simulation, and Training Center – already the host site for many programs.

Second, in collaboration with the Spanish professional society, SEPAR, CHEST hosted the first CHEST World Congress in Madrid this past March. I am a clinician and educator at heart and am a strong supporter of continued excellence and innovation in meeting our members' needs for education, training, and knowledge creation and dissemination, and clinical practice. As an extension of my belief in teams, I strongly support the continued leadership role of CHEST in national and international issues related to pulmonary, critical care, and sleep medicine.

CHEST leadership actively collaborates with sister societies, here and around the world, on important issues, engaging in robust discussion and often leveraging the power of speaking with one voice. I consider these collaborative activities central to the well-being of our profession, and, most importantly, our patients.

Finally, CHEST members are, by nature, giving people, and regularly volunteer to help others. These important actions are often through service on committees and related activities at CHEST but also are evident in supporting the various core philanthropic missions of the CHEST Foundation. The number of people touched by the good works of the CHEST Foundation over the years is amazing, and I enthusiastically support those continued successes.

► What do you consider to be the greatest strength of CHEST, and how will you build upon this during your Presidency?

Two of the core values that we embrace at CHEST are collegiality and innovation. I believe these reflect some of our greatest strengths – the rich collaboration of dedicated people and a continual striving for cutting-edge advances. CHEST has a long history of blending the skills and can-do attitudes of dedicated volunteer members and a very talented professional staff. This partnership has resulted in tremendous accomplishments, ranging from world-class educational activities and products to opportunity and support for volunteer and pro-bono efforts. Additionally, this natural focus on nurturing positive relationships is linked to a welcoming and collegial atmosphere, a pleasure of which to be a part. I'm strongly committed to continuing the tradition of CHEST as a welcoming home to all members–a place for continued professional growth and good will.

CHEST is widely recognized as a leader in innovation, particularly within the context of education and training. One needs to look no further than our new LEED Silver-certified CHEST Global Headquarters in Glenview to see the central role of innovation in what we do. The Innovation, Simulation, and Training Center is a true state-of-the-art facility where hundreds of individuals have already participated in experiential learning since its opening this spring. In fact, CHEST is the first medical association to receive accreditation from the Society for Simulation in Healthcare. The synergy between our outstanding staff and volunteer member thought leaders promises to keep CHEST at the forefront of innovation in medical education, and I enthusiastically support this continued growth in cutting-edge education and training in pulmonary, critical care, and sleep medicine.

► What are some challenges facing CHEST, and how will you address these challenges?

All individuals and organizations face challenges, and it is important to recognize that very often such challenges represent important opportunities. When one considers the challenges facing CHEST, it is worth starting with the challenges that our members face in their daily professional lives. These include the uncertainty of an ever-changing health-care environment, evolving needs for continuing education, training and knowledge dissemination, and the rigors of work-life balance. Here CHEST can help by providing information and a forum for idea exchange and by building upon our profession-leading activities and products.

Further, we value our members as people and recognize the importance of tackling important practical issues like workplace stress and burnout, the business of medicine, and maintenance of certification. From the perspective of CHEST leadership, a key challenge is to examine the many opportunities in pulmonary, critical care, and sleep medicine and to prioritize those that align best with our mission and vision and strategic di-

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NETWORKS: Moral distress, fracking concerns, capnography

Palliative and End-of-Life Care

ICU resident moral distress rounds

Moral distress is a well-established concept in the literature yet is still under-recognized in medical education and resident training (Berger. *J Gen Intern Med*. 2013;29[2]:395). Resident burnout is an ongoing concern and addressing ways to minimize the strain of care in the ICU is one way to deal with it. Many encounter conflicts in the ICU relating to end-of-life care (EOL). This is also the place where conflicts between caregivers, families, and other clinicians arise. Establishing methods to address distress and clarify clinical ethics are essences of our EOL monthly sessions for trainees.

DR. MOKWUNYE

Once a month, the current set of residents, interns, and medical students rotating through the medical ICU have a sit-down lunch session with one of the members of the Center for Ethics Department and an internal medicine attending. Trainees are informed that this is a safe space in order to minimize any distress over speaking up. They are also informed that everyone will remain anonymous if any situation described requires further intervention ranging from Ethics to the Department Chair. Feedback from these sessions demonstrates trainees leave with the feeling of being heard, having their questions about EOL care and ethical decision making answered, and a sense of empowerment. Follow-up with residents highlights the promise of protection during problematic situations. Burnout may continue to be a concern, but these monthly sessions seem to offer solace and a chance to recharge.

Dr. Nneka O. Mokwunye, FCCP – Steering Committee Member; Olubukunola M. Tawose, JD; and Dr. Deborah Topol

Occupational and Environmental Health

Hydraulic fracturing—a concern for pulmonary physicians?

While a respiratory hazard to hydraulic fracturing (fracking) has not been demonstrated, concern remains that there may be an occupational risk with fracking from exposure to silica, air pollutants, and radiation.

To summarize, more than 52,000 shale gas wells have been drilled in the United States (Kovats et al. *Lancet*. 2014; 383[9919]:757). More than 200,000 workers are employed in the United States by well servicing companies (Esswein et al. *J Occup Environ Hyg*. 2013;10[7]:347). Plus, workers at drill sites are exposed to:

(A) crystalline silica: greater than 90% of sand mover operators are exposed to crystalline silica greater than the ACGIH TLV (Esswein et al); (B) outdoor air pollutants (diesel

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Workers who drill shale gas wells are exposed to silica, air pollutants, and radon, all of which could contribute to lung disease.

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exhaust, VOCs, ozone [Kovats et al]); and (C) radon. Hydraulic fracturing in a coal seam gas field in Australia was associated with peak outdoor (222)Rn levels of nearly 30 Bq/m^3 and was related to the number of gas wells within 3 km and wind speed (Tait et al. *Environ Sci Technol.* 2013;47[7]:3099). Radium 226 levels in Marcellus Shale brine can exceed 10,000 pCi/L (Brown. *Environ Health Perspect.* 2014;122[2]:A50), and radon gas is released at the wellhead. Many workers are temporary or subcontractors, and it is difficult to follow their respiratory status over a prolonged period of time.

The respiratory health effects of fracking remain unknown, but workers are exposed to silica, diesel exhaust, and volatile organic compounds, and, at some sites, radon. Studies of fracking workers are warranted to resolve the question of occupational risk for lung disease.

Dr. Richard B. Evans, MPH, FCCP
NetWork Vice-Chair

Sleep Medicine

Meeting future demands in specialty

One of the biggest challenges facing sleep medicine today is the growing schism between the number of trainees interested in pursuing a career in the specialty and the need of an aging population for competent providers of therapy for sleep disorders. This year's National Resident Matching Program results are particularly concerning; of 133 available fellowship positions, 27% went unfilled on Match Day; this is a marked increase from 12% in 2012 and 24% last year (available online at www.nrmp.org). While this increase is, in part, related to an increase in the number of accredited sleep medicine fellowships, there is a concomitant decline in applications, more pronounced among graduates of United States medical schools, though also present in our international colleagues. This may, in part, be related to the downsizing and closing of several high-profile clinical sleep programs around the country, signaling to our trainees that the financial future of the specialty may lie on shaky ground. Certainly, while there are new financial challenges for sleep medicine providers, they are not all too dissimilar from the pressures that providers in other specialties are facing with the changes in insurance coverage and the availability of research funding.


DR. SCHULMAN

Since it is clear that the number of patients with sleep disorders will continue to increase, we are faced with solving the problem of how to manage them. Sleep specialists will need to work with organizations like CHEST to increase the pipeline of physicians and nonphysician providers training in sleep medicine, but we will also need to improve the ability of providers who are not formally trained in sleep medicine to identify and manage certain patients with insomnia and sleep apnea, at the minimum. To meet this need, CHEST is working with members of the Sleep NetWork Steering Committee and the Association of Pulmonary and Critical Care Medicine Program Directors to identify sleep medicine core competencies that all pulmonary trainees should master; in addition, there will be several sessions at CHEST 2014 focused on developing solutions to this concerning problem.

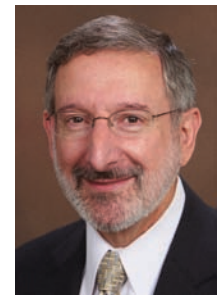
Dr. David Schulman, FCCP
NetWork Chair

Respiratory Care

Capnography update

Capnography, the noninvasive dynamic monitoring of CO_2, has gained popularity by being used by clinicians to: identify misplaced ET tubes or N/OG tubes, identify respiratory status during PCA use, measure $Paco_2$ when V_D/V_T is known, quantitate effectiveness of CPR, identify ROSC, and confirm apnea in brain death.

Measurements: The CO_2 sensor may be either mainstream (in line with the ET or trach tube) or sidestream (using tubing to transport samples of airway gases). The capnogram display is either CO_2 vs. time (timed) or vs expired volume (volumetric). The more common timed capnogram has five phases: zero CO_2 from inhalation (phase 0), zero CO_2 from expiratory dead space (phase I), rising CO_2 from alveoli emptying (phase II), plateau CO_2 near end exhalation (phase III), and rising CO_2 from final alveoli emptying (phase IV). End tidal CO_2 ($ETco_2$) is the maximum CO_2 at end exhalation and is less than $Paco_2$ per V_D/V_T.


DR. PATRICK

New applications: Volumetric capnography can be a guide to metabolic rate (Mehta et al. February 26, 2014. *Clin Nutr.* An Integrated Pulmonary Index (IPI™) combines $ETco_2$, Spo_2, respiratory rate, and heart rate as a "smart alarm." IPI values are 1=immediate attention needed to 10=normal (Alotaibi and Restrepo. *Chest.* 2014;145[3_Meeting Abstracts]:206A). Timed capnograms provide patient feedbackby capnometry-assisted hypoventilation "CATCH" (Ritz et al. Published online ahead of print. Aug 14, 2014. *Chest*).

Dr. Herbert Patrick, FCCP
NetWork Chair

Continued from page 29

rection of CHEST.

It will be my responsibility as the President and Chair of the Board of Regents to help set a course that focuses on the core missions of CHEST and is fiscally responsible. It will be important to listen to our members as to these needs and to seek the wise counsel of past, present, and future CHEST leaders.

► And finally, what is your charge to the members and new Fellows of CHEST?

First and foremost, congratulations to the new Fellows of CHEST! You are embarking on a wonderful partnership with a world-class professional society. My hope is that you, and all members of CHEST, find the relationship to be satisfying and so much more.

I have personally found that my many experiences with CHEST over the years have been among the most fulfilling of my professional life. I have made many lifelong friends around the country (and world) in the process. Like many lasting relationships, mine started with volunteering to become involved, in my case, serving on a Section (now NetWork) steering committee. I encourage you to take that first step of involvement in the annual meeting or service on a committee, then to accept chairing a committee, to mentor and encourage a younger colleague to become involved, and to "make a difference" through your service to the profession and to your patients.

I am highly committed to doing all that I can to encourage and support the professional growth and satisfaction of our member-volunteers. I'm eager to move forward together!

Cutting-edge education and Austin's charm

When you travel to Austin to attend CHEST 2014, October 25 - 30, you will not want to miss a minute of the cutting-edge education sessions and simulation training. And, you will also want to take time to take in the great city of Austin. Knowing that your time may be limited, we came up with a list of the best restaurants nearby the convention center and local destinations that you can explore within the short breaks in your schedule.

Close grub

Enjoy a walk, grab a cab, or hail a pedicab to enjoy these nearby eats:

- Iron Works BBQ (2-minute walk) – As a family-owned and operated business, this restaurant serves real Texas barbecue.
- Champions Sports Bar & Restaurant (6-minute walk) – This sports bar will offer a quick bite in a casual environment.
- Swift's Attic (9-minute walk) – Influenced by a passion for farm to table offerings, this restaurant and bar offer modern American small plates.
- The Driskill Grill (10-minute walk) – This luxurious, historic hotel was built in 1886. It serves American food in a beautiful setting.
- Easy Tiger (10-minute walk) – Order a sandwich, a snack, or a sausage from this bake shop and beer garden.
- Truluck's (10-minute walk) – This seafood, steak, and crab house was rated Best Food in 2012 by Open Table.
- Halcyon (12-minute walk) – This coffeehouse/bar/lounge offers good food and great coffee.
- Roaring Fork (3-minute drive) – Enjoy delicious, wood-fired steaks.
- Wink (6-minute drive) – Known for Austin-style hospitality, a commitment to local farms and gardens, and sustainable agriculture and fine dining cuisine.

Quick jaunts

Looking for a quick excursion during a break in your education schedule? These nearby activities will offer you a glimpse of Austin's charm and history:

- Texas Capitol Building (3-minute drive) – The Texas Capitol Building is the largest in gross square footage of all US capitol buildings, and it stands taller than the US Capitol Building in Washington, DC. Learn about Texas' part-time legislature that only meets for 140 days every other year, and explore this beautiful, historic site.
- Bullock Texas State History Museum (5-minute drive) – It features three floors of dynamic exhibits, a special effects Texas Spirit Theater, museum store, and café.
- University of Texas (5-minute drive) – Visit the main campus for the University of Texas, and enjoy the view from atop the University of Texas tower.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The Texas Capitol in Austin is the nation's largest state capitol building.

- Zilker Metropolitan Park (10-minute drive) – Visit Austin's largest and most popular park. The park offers hiking and biking trails, picnic tables, Barton Springs Pool, and Zilker Zephyr miniature train.
- Congress Avenue Bridge (8-minute walk) – Watch the largest urban bat colony in North America take flight every night under Congress Avenue Bridge.

Note: All estimated times assume you are starting at the Austin Convention Center.

We know you'll enjoy Austin's charm and CHEST 2014's extensive educational offerings. You'll receive relevant updates on patient care, and practice management strategies will offer insight, perspective, and inspiration you can seamlessly incorporate into your practice to stay at the forefront of clinical chest medicine.

Begin planning your trip to Austin now with the Austin Convention & Visitors Bureau's website, austintexas.org; and start planning your learning itinerary with the CHEST 2014 mobile-ready website or apps for iOS or Android. Find links to the mobile-ready website and apps, and learn more about CHEST 2014 at chestmeeting.chestnet.org.

Lounge in gratitude: Donors have VIP room at CHEST 2014

In recognition of your annual gift to the CHEST Foundation, we invite you to join your fellow members in our Donor Lounge to enjoy complimentary light refreshments, Internet and computer access, and a quiet atmosphere, all conveniently located in the Austin Convention Center. Meet with colleagues, check e-mail, call home, enjoy a hot cup of coffee. Staff will be on hand to answer questions and make your annual meeting as productive and hassle-free as possible.

Not yet a donor? Make a gift online today at www.chestnet.org/store.

Contributions to the CHEST Foundation help support education programs and research in pulmonary, critical care, and sleep medicine. These donations help advance breakthrough research and share new discoveries and expanded knowledge with doctors, patients, and families.

Our donors make it all happen, and this is one way we say **"Thank you!"**

Get MOC points at CHEST 2014

Do you need points toward your ABIM Maintenance of Certification (MOC)?

CHEST has three modules approved for CHEST 2014 – 1 each in Critical Care, Pulmonary, and Sleep, worth 10 points each. These modules will stimulate and challenge clinical thought processes to assist in self-assessment and implementation of new strategies. The case-based questions contain histories, laboratory results, and images to provide opportunities to evaluate current practice and identify areas for improvement.

Modules will be complimentary during CHEST 2014 and available during meeting hours in a dedicated MOC room.

This month in *CHEST*: Editor's picks

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

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration vs Conventional Transbronchial Needle Aspiration in the Diagnosis of Sarcoidosis. *By Dr. D. Gupta et al.*

Risk of Mycobacterial Infections Associated With Rheumatoid Arthritis in Ontario, Canada. *By Dr. S. K. Brode et al.*

Variation in Decisions to Forgo Life-Sustaining Therapies in US ICUs. *By Dr. C. M. Quill et al.*

Special Feature

Entrustable Professional Activities and Curricular Milestones for Fellowship Training in Pulmonary and Critical Care Medicine: Report of a Multisociety Working Group. *By Dr. H. E. Fessler et al.*

Declaring war against antibiotic resistance

BY DR. JEAN CARLET, MD; AND GLENN TILLOTSON, PHD, FCCP

The World Alliance Against Antibiotic Resistance (WAAAR)

The increase in antibiotic-resistant bacteria poses a major global health-care threat. In the face of an almost complete absence of new antibiotics in development, antibiotic resistance (ABR) has become one of the main public health problems of our time.

Antibiotics are a unique class of drugs because of their undoubted societal impact. Bacterial resistance can evolve rapidly, by acquiring and/or developing resistance mechanisms. The altered bacterial genetic material coding for resistance mechanisms can be readily transmitted between bacteria, extending the reach and impact of resistance. Ehrlich pointed out over a century ago (*BMJ.* 1913; 2[2746]:*353*) if we do not treat bacteria effectively initially, we will "face" the complexities of resistance. Treatment failures due to multidrug resistant (MDR) bacteria, once rare, notable, and limited to hospitals, now occur very commonly in hospitals and increasingly in the community. It is estimated that at a minimum 25,000 patients in Europe (ecdc.europa.eu/en/publications/Publications/0909) and 23,000 in the United States (cdc.gov/drugresistance/threat-report-2013/) die each year of infections caused by resistant bacteria. The cost of antibiotic resistance is tremendous, whether measured as the personal and societal burden of illness, death rates, or health-care costs. Recent estimates put the pure financial costs into the billions of dollars or Euros as patients stay longer in the ICU, hospital, or nursing facility, and the costs associated with isolation methods are also escalating. These estimates do not account for the personal financial impact of lost work time and caring for patients.

DR. CARLET

DR. TILLOTSON

Although it is a never-ending phenomenon, ABR is directly related to the volume and type of antibiotics used. We are using increasing amounts of antibiotics in health care and agriculture and discharging these active drugs into the environment. Similarly, use of antibiotics in humans is escalating and not well monitored. We must change how antibiotics are used and adopt proactive strategies, similar to those used to save endangered species. Preservation of the efficacy of antibiotics and to stabilization of antibiotic-susceptible bacterial ecosystems should be global goals.

Safeguarding and developing new antibiotics will require a concerted effort by patients and prescribers. The primary goal of WAAAR is to raise awareness about the urgency and magnitude of the threat and to promote an international dialogue across the entire range of prescribers to assist in improving antibiotic use. The Alliance, in particular through this declaration, is dedicated to lobbying actively for antibiotic preservation and to raising awareness among antibiotic prescribers, politicians and policy-makers, patient safety and advocacy groups, the pharmaceutical industry, international health organizations, and the general population. Individual actions, no matter how well intended, are doomed to failure unless there is an international dialogue, a common sense of purpose, and broad consensus on how best to proceed.

In parallel, the pharmaceutical industry is continuing to develop new agents for the growing number of MDR- and even pan-resistant bacteria. These efforts cost many millions of dollars and take time, so in the meantime, we need to improve what we do, how we do it, and how often we do it. Here are the key actions required:

- Promotion of awareness of all the stakeholders – including the general public – of the threat represented by antibiotic resistance.
- Organization, in each country, ideally by Ministries of Health or regulatory bodies, of a financed national plan for the containment of antibiotic resistance, with the participation of all stakeholders, including patient advocacy groups.
- Continuous access to antibiotics of assured quality, especially in middle and low income countries

Continued on following page

NAMDRC report: A guide to control COPD readmissions

BY DENNIS DOHERTY, NAMDRC PRESIDENT; AND PHIL PORTE, NAMDRC EXECUTIVE DIRECTOR

With the Medicare Hospital Readmission Program slated to expand to include all cause COPD readmissions October 1st, there are several key approaches that physicians and hospitals should utilize to manage COPD-related discharges. CMS data indicate between 75% and 83% of these discharges **do not** result in a readmission within 30 days. Hospitals and physicians should use available resources to identify those at highest risk for readmission, and then focus on and aggressively manage this high risk subpopulation.

Prior to discharge:

► Coordination with the health-care team, including discharge planners, respiratory therapists, physician assistants, and others, along with patients' families, should be integral to every COPD-related discharge.

►Ensure appropriate treatment for COPD exacerbations while hospitalized. GOLD Guidelines (Schnell et al. *BMC Pulm Med*. 2012;12:26) recommend steroids, antibiotics for most patients, along with bronchodilators. Appropriate long-acting maintenance therapy should be prescribed.

►Educate patients on inhaler techniques, managing supplementary oxygen, drug regimens to improve respiratory status, pharmacologic and nonpharmacologic (eg, purse-lipped breathing) regimens and continuation of smoking cessation counseling.

►Reconcile medications, and ensure that the patient has access to these medicines at the time of discharge.

►If spirometry has not been done to confirm the diagnosis of COPD, or has not been done recently, spirometry testing should be arranged shortly after the patient stabilizes from the COPD exacerbation to help stratify the severity of their disease (GOLD Grade classification).

►Assess activities of daily living (ADLs); a growing body of evidence indicates that patients who can demonstrate at least 4 ADLs are significantly less likely to experience readmission, while those who demonstrate two or less run notable risk for readmission

►Assessment of comorbid conditions

►Referral to pulmonary rehab services

► Proper handoff – immediate communication of the action plan designed for the patient to those caring for the patient in an outpatient setting, eg, primary care provider and/or specialist (pulmonologist, cardiologist, diabetologist, etc), and ensure follow-up within a reasonable time period after discharge

Following discharge:

There are now data indicating that the majority of COPD readmissions within 30 days are for diseases other than COPD (Schnell et al. *BMC Pulm Med*. 2012;12:26). Therefore, home health care (agencies, DME providers, respiratory therapists, etc) is integral to successful management and must be included in any genuine effort to manage patients following discharge. A well-cited article from the *New England Journal of Medicine* shows that Medicare beneficiaries are often not seen in the 30 days after hospital discharge (Jencks et al. *N Engl J Med*. 2009;3360[14]:1418). Effective January 1, 2013, two transitional care CPT codes are now available for physician/physician office billing and include certain contact that is not face-to-face. The codes are **99495** and **99496**. Be aware that these codes are only billable by the **first** physician who submits a claim, regardless of specialty, patient need, etc. Therefore, it is possible that a patient with several comorbid conditions may be contacted by a physician who is not managing the COPD component of illness. That physician may submit a transitional care code claim, precluding all other physicians from submitting subsequent bills.

Telehealth/telemedicine:

There are several aspects to the telehealth component of managing patients with COPD after discharge. First, there is a range of options of "what to monitor," who reviews that information to ensure the focus on the declining patient, and what action can/should be taken to optimize care to avoid rehospitalization.

DME programs, home health care, and specialized contractors:

Sophisticated suppliers, home health agencies, and independent contractors have shown a certain level of promise in assisting hospitals address readmissions. Ideally, this care begins before discharge and is integrated immediately into the continuum of care as an outpatient. Unfortunately, the Medicare fee-for-service payment system does not incentivize this care model, leaving hospitals to make important financial determinations regarding the extent to which they need to invest their own resources to partner with companies that can assist in patient management after discharge.

(Read the full report, "Hospital Readmissions – Managing COPD Patients Post Discharge," at www.namdrc.org/pubs/Hospital-Readmissions.pdf.) For more information about NAMDRC, go online or call the Executive Office at 703/752-4359. NAMDRC's mission is to improve access to quality care for patients with respiratory disease by removing legislative and regulatory barriers to appropriate treatment.

Continued from previous page

► Integrated surveillance of ABR and antibiotic use

► Improved use of diagnostic tests that provide clear directions sooner to the prescriber

► Antibiotic stewardship (prudent, controlled, and monitored approaches to the use of antibiotics) and not just simply using fewer antibiotics

► Educational efforts for change in the medical curriculum

► Containment of bacterial transmission and prevention of infection

► Basic and applied research and development of new antibiotics

► Request for UNESCO to include antibiotics in the Intangible Cultural Heritage list.

As members of CHEST, we are responsible for treating a large proportion of infections in both the hospital and the community. We have members in over 100 countries who, individually, could stimulate support in their individual nation so as to enhance the efforts of WAAAR.

Please, help us to act now, by supporting this declaration. Wherever you practice, take a few moments to contact Professor Jean Carlet to confirm your support for WAAAR. E-mail jeancarlet@gmail.com.

Dr. Jean Carlet is Former Head of the Research Programs and Medical Director, Quality and Safety Improvement for the French Health Authority (HAS); currently, he is a Consultant for the WHO. Glenn Tillotson PhD, is with Transcrip Partners and is a Visiting Distinguished Scientist, Public Health Research Institute, Rutgers University, NJ.

FROM THE EVP/CEO Revenue beyond membership dues

BY PAUL A. MARKOWSKI, CAE

As fiscal year 2013-2014 came to a close and the new fiscal year began, all eyes were focused on our financials. I'm happy to say we finished the year strong, putting us in excellent position to continue the work toward our mission to champion the prevention, diagnosis, and treatment of chest diseases. Once more, I'm struck by the diversity of our revenue sources. Whereas many organizations rely heavily on membership dues to support operational expenses, CHEST has a healthy mix of revenue streams from multiple sources—sources that bring in income while directly advancing our brand and mission.


MR. MARKOWSKI

The journal *CHEST* connects clinicians around the world to the latest evidence-based medicine and research related to chest diseases. While *CHEST* performs the critical role of disseminating clinical information, it also generates strong revenue to support our work. During the past fiscal year, *CHEST* reached all-time highs in both subscription and advertising revenue. The strong

CHEST has a healthy mix of revenue streams from multiple sources—sources that bring in income while directly advancing our brand and mission.

sales can be partly attributed to the quality of content published in *CHEST*, which is reflected by the most recent impact factor. Impact factor is a ratio of the number of citations to a journal's articles in the previous 2 years, divided by the number of citable articles published in that 2-year period. Simply stated, a high impact factor indicates a high average number of citations—a testament to the quality of papers published. The 2013 Journal Citation Reports data from the ISI Web of Knowledge show the *CHEST* impact factor is an impressive 7.132, the highest in the journal's history. In addition, *CHEST* ranks 2 of 27 journals in the Critical Care Medicine category and 3 of 53 in the Respiratory Systems category, representing the highest ranking the journal has held in both categories. *CHEST* revenue is important to our bottom line; but, perhaps more important, is the quality of its content, which sets *CHEST* apart from other journals and makes it one of our primary vehicles for achieving our mission. We're fortunate to have a journal so successful on both levels.

Another strong revenue producer is our Professional Representative Education Program, or PREP. PREP is an unbranded, disease-state training program we coordinate and offer across clinical areas to educate industry partners about disease states, thereby advancing their knowledge and understanding to build confidence for engagement with health-care teams. During the past fiscal year, we trained more than 1,300 industry representatives, including those who concentrate on chest-related areas of atrial fibrillation, venous thromboembolism, pulmonary hypertension, idiopathic pulmonary fibrosis, and COPD. We also have partnerships with other associations, offering PREP in their disease-state areas:

- Society of Interventional Radiology
- American Society of Clinical Oncology
- American Association of Neurology
- American College of Obstetrics and Gynecology

While educating industry representatives and helping them advance health care, PREP generated its highest profit level to date. This year, we're expanding our programs with the American Society of Clinical Oncology and the American Association of Neurology to offer PREP training for prostate cancer and multiple sclerosis, so our growth in this area promises to continue.

A new revenue resource we have available is our Innovation, Simulation, and Training Center. When we're not holding our own education programs and meetings in the center, the space is available to rent. We recently hosted SimGHOSTS (Gathering of Healthcare Simulation Technology Specialists) for 4 days in August. SimGHOSTS is a training and community-building event for over 180 professionals, serving the technical needs of simulation centers across North America and beyond. Their event director and attendees alike gave glowing feedback on our training center and the quality of the program delivered. This is an exciting new opportunity for CHEST to take in revenue while supporting the advancement of other organizations' missions and initiatives.

An area for revenue growth we're starting to explore more is industry partnerships to promote disease awareness months and patient education materials. We currently have patient education materials for asthma, COPD, cough, DVT and blood clots, lung cancer, pulmonary fibrosis, sarcoidosis, shortness of breath, and sleep apnea. Now, we're working with Sunovion to launch a campaign, targeted toward both consumers and clinicians, to raise the awareness of COPD treatment options within the Hispanic community. "Tome Un Respiro" (Take a Breath) is the first-ever campaign dedicated to COPD awareness that is designed specifically for Latinos with culturally attuned and Spanish-language messages. This campaign is an excellent opportunity for us to make a positive impact in the Hispanic community, and I'm looking forward to watching its development. Activity will ramp up in November.

We're working on a campaign, targeted toward both consumers and clinicians, to raise the awareness of COPD treatment options within the Hispanic community. 'Tome Un Respiro' ('Take a Breath') is designed with culturally attuned and Spanish-language messages.

We remain focused on our mission to champion the prevention, diagnosis, and treatment of chest diseases. We're fortunate our work to achieve our mission also helps generate the revenue needed to advance it. This financial stability keeps us positioned to be the global leader in promoting best patient outcomes.

As always, feel free to connect with me if you want to discuss this further. You can also follow me on Twitter (@PMarkowskiACCP), or look for me at CHEST events. Next month I'll be at CHEST 2014, October 25-30, in Austin, Texas, and I hope to see you there.

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

South Florida Critical Care Medicine - Nocturnist

An MHS representative will be attending the CHEST2014 Conference, visit us at booth#740

About the Opportunity:
Memorial Healthcare System's Intensivist program is expanding. The program is currently comprised of 21 full time intensivists, providing 24/7 ICU coverage at multiple locations within The Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple Board Certifications including infectious diseases, pulmonology, surgery and neuro-critical care. This is a full-time employed position with competitive benefits and compensation package, "sovereign immunity", paid CME, state of the art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds etc)

Qualifications & Responsibilities:
The program is seeking four (4) dedicated critical-care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12 hour in–house shifts, 7pm to7am – averaging approximately 15 shifts per month. The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence based care. Candidates must be BC/BE.

About Memorial Healthcare System:
Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial's patient, physician and employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

About South Florida:
South Florida offers quality of life, is rich in cultural and recreational amenities, and offers pristine beaches, top-rated golf courses, museums and world-class dining. The greater Ft. Lauderdale area offers numerous communities in which to raise a family. In addition, Florida has no state income tax.

To inquire about this opportunity, visit www.memorialphysician.com

Live Work Play

Memorial Healthcare System

Lahey Hospital & Medical Center

Department of Pulmonary & Critical Care Medicine Presents

State of the Art Thoracic Ultrasound, Endobronchial Ultrasound TBNA, and Navigation Bronchoscopy: Enhancing Your Diagnostic Yield in Mediastinal Diagnosis, Staging and Approach to the Peripheral Nodule
Featuring EBUS Simulation Training - 2014

Saturday, November 8, 2014
Lahey Hospital & Medical Center
Burlington, MA 01805

Course Director: Carla Lamb, M.D.

This course will serve as an introduction to endobronchial ultrasound and airway navigation system applications for pulmonologists and thoracic surgeons. The course will employ lectures by experts and a hands-on workshop will familiarize the participants with currently available ultrasound and navigation technology for use by pulmonologists and thoracic surgeons. Activity approved for 8.25 AMA PRA Category 1 credit™

Information:
Lahey Hospital & Medical Center CME Office
Phone: 781.744.8969
Email: **cme@lahey.org**
Brochure and On-line Registration:
https://cmetracker.net/LAHEY/Catalog

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Interested physicians should contact: Kimberly Salvail, Huntsville Hospital – **kimberly.salvail@hhsys.org** or 256-265-7073.

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Hospital employed joining four Pul/CC physicians with 1-8 call in desirable Bend, Oregon with unlimited recreational and cultural amenities including world class skiing in community of 100,000 population associated with a modern 260 bed hospital.

Excellent salary, signing and production bonus and benefits. 800-831-5475 **donohueandassoc@aol.com**

HATTIESBURG CLINIC

Hattiesburg Clinic, P.A. ~ Critical Care / Intensivist Physician

Hattiesburg Clinic, P.A.
Department of Pulmonary & Critical Care Medicine

Hattiesburg Clinic is seeking a BE/BC Critical Care Medicine physician who is committed to excellence in patient care in an intensive care hospital setting. The physician would share responsibilities in a 42 bed critical care unit and on-call with a group of Intensivists comprised of seven Pulmonary and Critical Care physicians. Preferred candidates will have skills and expertise in inpatient medicine.

Hattiesburg Clinic is one of the largest physician-owned and directed multi-specialty group practices in the Southeast, with 250 physicians and over 90 physician extenders. Our primary hospital, Forrest General, is a state-of-the-art facility in a rapidly growing community with high patient demand located in Southeast Mississippi.

Hattiesburg is located in South Mississippi, just hours away from New Orleans and the Alabama and Florida coastal areas. We are home to two universities, a DO medical school and a new family residency program. Our weather is mild year round and we have an abundance of outdoor recreational opportunities, as well as a variety of shopping and dining options.

The Clinic offers a competitive salary with excellent benefits, including relocation assistance.

If you are searching for a unique opportunity to be a part of our expansion please send your CV to:

Glenda Sharp
Hattiesburg Clinic, P.A.
415 South 28th Avenue
Hattiesburg, MS 39401
Office – 601-579-5008
Cell – 601-606-5941
Glenda.sharp@hattiesburgclinic.com

For more information please visit our website: http://www.hattiesburgclinic.com

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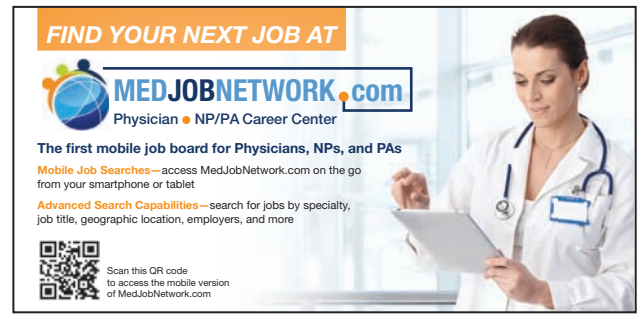

Florida

We are currently seeking a Board Certified Pulmonologist/Intensivist or Intensivist to join a single specialty practice in Central Florida. The role would primarily entail working 7 nights on with 7 nights off providing coverage at Florida Hospital Celebration Health in the Intensive Care Unit.

Please contact:
Jacqueline Blanco via email
Jacqueline@floridalungdoctors.com
or call 407-507-2636.

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CHEST Physician

CLASSIFIEDS

For Deadlines and More Information, Contact:
John Baltazar
Tel: (917) 488-1528
jbaltazar@americanmedicalcomm.com

FRONTLINE MEDICAL COMMUNICATIONS

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PROFESSIONAL OPPORTUNITIES

Arcadia California

Positions available in the largest single specialty pulmonary critical care group in the San Gabriel Valley.

A growing practice in need of highly qualified pulmonary critical care physicians to practice high-quality medicine in a community hospital.

The hospitals are STEMI receiving centers, stroke centers, bariatric centers of excellence plus neurosurgical intervention and cardiac surgery.

We offer an excellent practice of high-level medicine in a stimulating environment that believes in family values.

Arcadia is considered an American top 10 city. Salary is competitive with opportunities for bonuses and early partnership.

Email your CV to:

davidratto@gmail.com
and
ekatagihara@gmail.com

PENNSYLVANIA

Three physicians private pulmonary, critical care and sleep medicine practice seeking a fourth associate. Community hospital in western suburbs of Philadelphia. Competitive salary, fast tract to partnership. On call and work schedule will be shared.

Please contact us at
padh309@comcast.net
or call 610-394-9861

MID-ATLANTIC

Kaiser Permanente's, Mid-Atlantic Medical Group seeks a BC Sleep Medicine/BC Pulmonologist to join our Suburban Maryland group on a full-time basis.

MAPMG offers a satisfying practice, without the hassles of running an office, and freedom from insurance billing.

Kaiser Permanente's integrated EMR system is an excellent approach to providing care.

Salary and benefits are extremely competitive.

Please contact:
Terry Janes at
terry.r.janes@kp.org
or call (301) 816-6597

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THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER
EDUCATION • RESEARCH • HEALTHCARE

CRITICAL CARE/PULMONARY/SLEEP FACULTY POSITION

The Division of Pulmonary, Critical Care and Sleep Medicine at the University of Mississippi Medical Center is currently seeking faculty at all levels for the Divisions of Critical Care, Pulmonary and Sleep Medicine. Divisional activities are located in the Conerly Critical Care Hospital, the University Hospital, and the G.V. "Sonny" Montgomery Veterans Affairs Hospital. The division has active programs in critical care, eICU, cystic fibrosis and interventional pulmonary medicine. The Pulmonary Division has a strong fellowship program. Collaboration with basic sciences and the National Heart Lung and Blood Institute-sponsored Jackson Heart Study is encouraged. Jackson, Mississippi, the state capital, is a family friendly city with a temperate climate, allowing year-round water and sporting activities.

Please forward your CV to
John Spurzem, M.D.
Professor of Medicine and Interim Director
Division of Pulmonary, Critical Care and Sleep Medicine The University of Mississippi Medical Center
2500 N. State St., Jackson, Mississippi, 39216
Phone 601-984-5650 or email
jspurzem@umc.edu
EOE, M/F/D/V

Alabama

Forbes Top Ten Smartest City Seeks a Pulm/CC Physician Immediately!

- Established, four physician practice
- Highly competitive salary w/productivity incentive
- Partnership track w/401k, paid vacation and CME allowance
- 1:5 Call
- EMR
- 101 open ICU beds
- 881 bed Level I Trauma/ Regional Referral Center

Interested physicians should contact:
Kimberly Salvail, Huntsville Hospital –
kimberly.salvail@hhsys.org
or 256-265-7073.

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SLEEP STRATEGIES OSA, insomnia are often bedmates

Strategies *from page 1*

ist in the same patient, resulting in misdiagnosis and incorrect therapy when the two coexisting conditions are not recognized and addressed concurrently.

Consider an overweight, 45-year-old man with hypertension, presenting with difficulty falling asleep and early morning awakening, along with mild snoring reported by his girlfriend. Assuming that both disorders are present in this individual, failure

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to treat the sleep-disordered breathing may result in an inability to fully control insomnia and ongoing fatigue. Alternatively, failure to recognize the coincident insomnia will likely result in patient frustration with CPAP that further disrupts sleep without "fixing" the complaint, leading to poor CPAP compliance or even rejection of PAP therapy altogether. To effectively treat such patients, providers must understand the frequency of the concurrence of these conditions, as well as diagnostic and treatment strategies that optimize outcomes.

Insomnia and OSA are the two most common sleep disorders; this simple fact makes their co-occurrence likely. However, rates of the co-existing conditions surpass the prevalence that would be suspected based upon the prevalence of each individual disorder. Several studies have examined patients with sleep apnea for comorbid insomnia, revealing that 40% to 55% of individuals with OSA have significant insomnia complaints (Lavie. *Sleep Med.* 2007;8: S21; Krakow et al. *Chest.* 2001;120[6]:1923); these complaints are typically divided into sleep-onset insomnia, sleep-maintenance insomnia, and early morning awakening. Most studies used patient-reported symptoms, using the Insomnia Severity Index Questionnaire (Bastien et al. *Sleep Med.* 2001[4];2:297), as well as patient estimation of sleep latency, nighttime awakenings, time awake in bed, and frequency of early awakenings.

While one would expect individuals with sleep apnea to have sleep maintenance difficulties due to apneic events, many patients also experience sleep-onset problems, which cannot be explained by the presence of OSA alone. It may be that patients change their sleep habits due to OSA, and this leads to an independent insomnia disorder.

Among insomnia patients recruited for research, 30% to 67% were diagnosed with frank OSA, with an AHI or RDI greater than five events per hour (Lichstein et al. *J Consult Clin*

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A CPAP mask is likely no friend of patients with sleep-onset insomnia.

Psychol. 1999;67[3]:405; Stone et al. *Psychol Aging.* 1994;9[2]:231). A greater percentage may have more subtle forms of respiratory abnormalities during sleep; one study demonstrated that 91% of insomnia patients had some degree of sleep-disordered breathing with 41% of patients having upper airway resistance syndrome (Krakow et al. *Biol Psychiatry.* 2001;49[11]:948).

Correctly diagnosing the patient with coexisting OSA and insomnia can be challenging because such patients may present with atypical symptoms, though they can be more severely affected (and have worse outcomes) when compared with individuals who only have one of the two disorders. Such patients have more pronounced sleeping difficulties, including longer sleep latencies, shorter sleep times, and lower sleep efficiency when compared with individuals with only OSA.

Complicating matters, when compared with pure OSA patients, significant anxiety, depression, and pain exists in this population, making it difficult for the clinician to identify whether the insomnia is a manifestation of the psychiatric or pain syndrome instead of an independent sleep disorder needing dedicated attention (Smith et al. *Sleep Med.* 2004;5[5]:449; Krell et al. *Sleep Breath.* 2005;9[3]:104). Insomnia is often thought to be secondary to OSA in these patients, preventing the clinician from fully recognizing the role of a separate disorder in the patient's poor sleep quality.

Additionally, patients with pronounced insomnia may deny sleep-related breathing disturbances or downplay them as extremely mild, often not complaining of daytime sleepiness to the same degree as patients with OSA. A recent paper underscored the difficulty of diagnosing both conditions concomitantly by dubbing the condition "complex insomnia" (Krakow et al. *Biol Psychiatry.* 2001;49[11]:948).

Though there are effective treatments for both OSA and insomnia, the likelihood of successful therapy for either disease diminishes if the coexisting disease process is not addressed. While middle-of-the-night insomnia may improve with long-term CPAP use, sleep-onset insomnia rarely improves with CPAP therapy (Björnsdóttir et al. *Sleep.* 2013;36[12]:1901). Imagine the patient with severe insomnia attempting to adjust to the use of PAP lying awake in bed for several hours, growing increasingly frustrated with the PAP machine and mask.

CPAP adherence has been shown to be diminished in individuals with untreated insomnia, especially those with sleep-onset insomnia and early morning awakenings (Wickwire et al. *Sleep Med.* 2010;11[8]:772). The most effective therapy for insomnia is cognitive behavioral therapy (CBT-I) administered by an experienced clinician. While pharmacologic therapy for insomnia may be effective in the short-term, the use of narcotics or benzodiazepines can worsen sleep apnea by prolonging the duration of apneic events and raising the arousal threshold.

Opting to treat the insomnia in these patients without concomitant OSA therapy may be no better. Studies have also shown an incomplete response to insomnia therapy in individuals with co-morbid untreated sleep-disordered breathing (Krakow et al. *Sleep Breath.* 2004;8[1]:15). This is important because individuals with insomnia, perceiving no benefit from CBT-I, may begin using hypnotic medications with respiratory depressant effects, worsening the unrecognized sleep apnea.

While the individual treatments for OSA and insomnia are well delineated, the treatment algorithms for the concomitant disease processes are still being developed. At present, sequential treatment of the two disorders is favored, based on current literature.

Several studies have tested treatment for sleep-disordered breathing in individuals with insomnia who have completed CBT-I but did not

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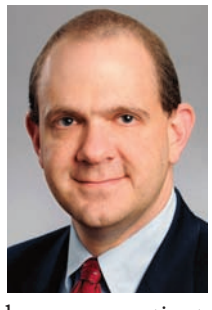
EDITOR'S COMMENT



This month, Drs. Zeidler and Martin remind us that our clinical tendency for diagnostic parsimony can occasionally impede our ability to successfully treat our patients. Given the commonality of insomnia and sleep apnea, it is certainly sensible to assume that a significant percentage of patients followed in our clinics have both disorders. Medical trainees espouse the benefits of Occam's razor, which they incorrectly assume requires them to come up with a single underlying disorder that explains the entirety of the patient's findings and complaints. Many of us carry this tenet with us throughout our careers, ascribing new or atypical patient symptoms to their known diagnoses. In fact, Occam's razor is more accurately described as recommending a paucity of assumptions be made, not a paucity of diagnoses. Perhaps your sleep apnea patient who cannot fall asleep despite adequate control of his sleep-disordered breathing is reporting a typical manifestation of his undiagnosed insomnia instead of an atypical manifestation of his sleep apnea.

When we encounter patients reporting complaints that don't entirely fit their diagnoses, or those who fail to respond to appropriate interventions for those diagnoses, it is a good opportunity to take a "diagnostic timeout" to reconsider our assumptions and reexamine the entirety of the patient's story. By doing so, we can improve our diagnostic yield and optimize patient satisfaction and outcomes.

Dr. David Schulman, FCCP
Section Editor

Poor sleep quality linked to elderly suicide risk

BY MICHELE G. SULLIVAN
Frontline Medical News

Elderly patients who report poor sleep quality face a significantly increased risk of suicide for up to a decade, whether or not depression is also present.

Even after controlling for comorbid depression, investigators found that impaired sleep was associated with a 20% increased risk of suicide in these patients.

Results of the prospective observational study suggest that regularly asking about sleep quality might help improve suicide risk assessment, Rebecca A. Bernert, Ph.D., and her colleagues reported online Aug. 13 in JAMA Psychiatry (doi: 10.1001/jamapsychiatry.2014.1126).

Older adults tend to seek more physician care in the final weeks and months before a suicide than do other at-risk populations (73% and 45%, respectively).

"Furthermore, at least one psychological autopsy study indicates that disturbed sleep is visible to friends and family members in the weeks and months preceding death," wrote Dr. Bernert of Stanford (Calif.) University and her coauthors.

The cohort comprised 420 subjects who were a subpopulation of the Established Populations for Epidemiologic Studies of the Elderly study. This project followed 14,500 older adults from 1981 to 1993; its purpose was to identify predictors of mortality, hospitalization, and placement in long-term care facilities and to investigate risk factors for chronic diseases. From this group, 400 controls were matched to 20 subjects who had committed suicide.

Sleep was evaluated with a five-item Sleep Quality Index (SQI) constructed by the investigators. Other measures included assessments of depression, cognition, and physical function.

Subjects were a mean of 75 years old at baseline; 60% were white, 19% were African American, and 1% were Asian, American Indian, or Hispanic. The methods of suicide included firearm (62%), cutting (10%), hanging (9%), poisoning (5%), drowning (5%), lethal jump (5%), and suffocation (5%).

The mean SQI scores were significantly higher among those who committed suicide than among the controls (10 vs. 8). Individuals who committed suicide also reported higher scores on all of the SQI subsets: difficulty falling asleep, difficulty staying asleep, early morning awakening, daytime sleepiness, and nonrestorative sleep.

In the univariate analysis, the total sleep score was a significant predictor of suicide (higher score odds ratio, 1.39) over the 10-year follow-up period, as were difficulty falling asleep and nonrestorative sleep (OR, 2.24 and 2.17, respectively).

After controlling for the presence of baseline comorbid depression, the investigators found that the relationship between overall sleep quality and suicide remained significant (OR, 1.2). Difficulty falling asleep and nonrestorative sleep lost their significance in the multivariate analysis.

Those who committed suicide had higher scores on all of the SQI subsets, including difficulty falling asleep, difficulty staying asleep, and early morning awakening.

The authors proposed that sleep-related deficits in cognitive and emotional processing might be a key factor in suicide among such patients.

"Research indicates that sleep fragmentation results in increased emotional reactivity, intensifying negative emotional responses while blunting positive affect," they noted. "Similarly, sleep deprivation among healthy adults is associated with amplification of amygdala activation, as well as increased reactivity to negative emotions such as anger and fear. Notably, a night of recovery sleep following sleep deprivation reverses this effect, decreasing amygdala activation and reducing such emotional reactivity.

The authors cited several limitations of their study. The measures of sleep quality were self-reported rather than measured objectively. Also, diagnostic information that might influence sleep quality, such as chronic pain and substance use, was not included. Finally, because 19 of the 20 decedents in the study were male,"the present results should be interpreted as primarily applicable to men and chiefly white men," they wrote.

The study was sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention. Neither Dr. Bernert nor her coauthors reported any financial conflicts.

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achieve full remission of insomnia symptoms; a significant number of these patients demonstrated improvement in residual insomnia symptoms, daytime functioning, and quality of life (Krakow et al. *Sleep Breath*. 2006;10[1]:16). Limited data exist on implementation of insomnia therapy in the treated OSA patient with residual insomnia complaints, though both behavioral CPAP adherence programs, which incorporate CBT-I principles, and the use of a hypnotic sleep aid during CPAP titration and early therapy have been beneficial (Collen et al. *Chest*. 2009;135[3]:704; Lettieri et al. *Chest*. 2009;136[5]:1263). To date, no randomized controlled study of concurrently initiated CBT-I and CPAP therapy has been completed, although there are two ongoing trials evaluating the efficacy of early CBT-I alongside CPAP initiation in individuals with both insomnia and OSA (Novel Treatment of Comorbid Insomnia and Sleep Apnea in Older Veterans and Multidisciplinary Treatment for Obstructive Sleep Apnea and Insomnia, both available online through clinicaltrials.gov).

Both chronic insomnia and OSA are common diseases associated with significant patient consequences, including daytime sleepiness, cognitive decline, decreased productivity, and increased cardiovascular morbidity and mortality. Effectively treating the patients who have both disorders relies on our ability to identify each disease separately while having a healthy suspicion for their coexistence. In so doing, we can improve patient management and near- and long-term outcomes of this difficult problem.

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