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HOT patients need to be screened for smoking and substance use issues, and followed up and counseled, Dr. Mary Baker said.

Burn risk doubles in smokers on HOT

BY WHITNEY MCKNIGHT
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Smokers offered home oxygen therapy were at twice the risk for burn injuries, based on data from a retrospective study.

Even so, almost all the home oxygen therapy (HOT) patients who were burn victims were discharged with a prescription for oxygen, including the 15% of patients who had incurred similar injuries at least once, and in some cases, three times.

"I have a problem with this," said Dr. Mary Baker, a critical care fellow at Indiana University and a medical ethics fellow at the university's Richard M. Fairbanks Burn Center at Wishard-Eskenazi Health, both in Indianapolis. Dr. Baker presented the findings at the annual meeting of the American College of Chest Physicians.

"Should we be prescribing oxygen to patients who smoke? Maybe the bigger question is [whether] it is ever ethically defensible to take oxygen away once someone has sustained a combustion injury from smoking while using HOT," she said.

Dr. Baker and her colleagues conducted a chart review of patients admitted to a single site for home oxygen–related burns between 2008 and 2013. They found that 55 of all such burn unit

See **Burn risk** • *page 6*

Sedation protocols linked to fewer ventilator days

Sedation in 24 hours affects extubation.

BY WHITNEY MCKNIGHT
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Patients given propofol-based sedation in the intensive care unit were more likely to have daily dose optimization, stay at their target Richmond Agitation Sedation Scale rate, and be intubated for fewer days, compared with patients given benzodiazepine-based regimens, a retrospective study has shown.

Being on propofol at the time of extubation, however, was associated with a significantly higher risk of being reintubated.

"The most important take-away here was that being on any sedative within 24 hours of extubation meant you had a high rate of failing that extubation," Dr. Steven J. Campbell said at the annual meeting of the American College of Chest Physicians.

In 2013, the American College of Critical Care Medicine updated its guidelines for sedation in the ICU. The changes reflected the new paradigm to use the least amount of se-

See **Sedation protocols** • *page 5*

INSIDE

CRITICAL CARE COMMENTARY

A Nebraska experience with Ebola

BY DR. CRAIG A. PIQUETTE, FCCP, AND DR. ANDRE KALIL

The ease of international travel now brings new threats to our EDs and clinics, diseases that we learned about but thought we would never see. That is the challenge to which we in critical care must respond. Intensivists and infectious disease specialists at the University of Nebraska Medical Center/Nebraska Medicine, Omaha, recently cared for three patients in our biocontainment unit, and we would like to share some insights about the preparation for and care of those patients.

The Nebraska Medicine Biocontainment Unit was established in 2005, in the wake of the anthrax attack and 9/11. The staff of the unit was drawn from volunteers across all areas of the hospital, including

See **Ebola** • *page 8*

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet 2403 mg/day in the three phase 3 trials had a higher incidence of elevations in ALT or AST (≥3× ULN) than placebo patients (3.7% vs 0.8%, respectively). Elevations ≥10× ULN in ALT or AST occurred in 0.3% vs 0.2% of patients in the Esbriet 2403 mg/day group and placebo group, respectively. Increases in ALT and AST ≥3× ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet 2403 mg/day in the three phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Most photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Instruct patients to avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: In clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported by patients in the Esbriet treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% vs 5.8% of patients in the 2403 mg/day group compared with the placebo group, respectively; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event vs 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea (36% vs 16%), rash (30% vs 10%), abdominal pain (24% vs 15%), upper respiratory tract infection (27% vs 25%), diarrhea (26% vs 20%), fatigue (26% vs 19%), headache (22% vs 19%), dyspepsia (19% vs 7%), dizziness (18% vs 11%), vomiting (13% vs 6%), anorexia (13% vs 5%), gastroesophageal reflux disease (11% vs 7%), insomnia (10% vs 7%), weight decreased (10% vs 5%), and arthralgia (10% vs 7%) in the Esbriet and placebo treatment groups, respectively.

Drug interactions: Pirfenidone is metabolized primarily (70% to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.

The concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors (eg, enoxacin) is not recommended because it significantly increases exposure to Esbriet. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of Esbriet and avoided during Esbriet treatment. If fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of Esbriet (ie, CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during Esbriet treatment.

The concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of Esbriet, and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to Esbriet treatment and avoid concomitant use of Esbriet and a strong CYP1A2 inducer.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to InterMune at 1-888-486-6411.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

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BRIEF SUMMARY

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

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*, which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
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Brisbane, CA 94005 USA

Reference: 1. ESBRIET full Prescribing Information. InterMune, Inc. October 2014.

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Fewer ventilator days

Sedation protocols *from page 1*

dation for the shortest amount of time possible. The updated guidelines also suggest not relying on benzodiazepines as a first-line sedative. "We've seen a shift away from benzodiazepines in recent years, and that when patients are given (benzodiazepines), they stay in ICUs longer and have longer ventilation times," Dr. Campbell of Ohio State University said.

To examine how the updated sedation protocols have affected the multiple ICUs in the university system, and to assess the relationship of the changes with reintubation risk, Dr. Campbell and his colleagues retrospectively analyzed data on 988 intubated patients and 6,359 ventilator days recorded at the medical center during a 10-month period in 2013, after the new protocols were in place.

Considering either single sedation drips or combined sedation drips in the 988 unique intubations, about 69% of patients received at least 1 day of propofol, and roughly a third were given at least 1 day of a narcotic.

For 373 patients, the most commonly used drip was propofol only. Propofol combined with a narcotic was used in 141 patients, whereas a combination of the two with a benzodiazepine was used in 140 patients.

A quarter of all intubated patients received at least 1 day of a continuous benzodiazepine drip, although only 7% of these received this sedation regimen as a first-line agent. Data were not presented on what previous benzodiazepine sedation rates were at the center before the protocol change.

The number of ventilator days for the propofol-only group was between 5.6 days plus or minus another 5.8 days. The total ventilator days for the propofol/narcotic/benzodiazepine group came to 10.5 days, give or take another 8 days.

"It intuitively makes sense that the more drips the patients were on, the more they would be on a ventilator," Dr. Campbell said.

However, for patients given benzodiazepines only, the number of ventilator days was 4.3, plus or minus 4.2 days. Dr. Campbell theorized this was attributable to there being a number of patients withdrawing from alcohol and so needing to rely on an infusion of the benzodiazepine to help them through the process.

Propofol-based regimens were associated with improved dose optimization compliance if patients were eligible (*P* less than .0001).

Patients given narcotic drips were more likely to meet their targeted RASS levels of –1 to +1, compared with either benzodiazepines or propofol, although propofol patient RASS targets were higher than those of the benzodiazepine group (43% for narcotics, 22% for benzodiazepines, and 37% for propofol, *P* less than .0001).

The study also found a relationship between failed extubation rates and sedative use. There were 953 patients extubated in all. Seven percent of the extubated patients who had received continuous sedation on the day of extubation had to be reintubated within 48 hours. A significant risk of reintubation was found for patients who'd been given propofol alone since nearly half of that cohort were among those reintubated ($P = .01$).

Although Dr. Campbell and his colleagues wrote in their study that this could have been due to lower levels of sedation to begin with, and so these patients being more likely to have earlier extubation, or the respiratory physiology of this group may have been altered by the propofol.

The researchers were not able to determine precisely when the sedation was terminated in each patient, only that it had occurred within a 24-hour period prior to extubation.

Dr. Campbell also noted that dexmedetomidine was not widely used as an alternative sedative at the site ICUs. "I suspect it's because it's still one of the newer agents," he said.

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RAPID: Characteristics impact response to A1-PI therapy

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Higher baseline alpha-1 proteinase inhibitor level, higher body mass index, and female gender may be associated with improved response to alpha-1 proteinase inhibitor augmentation therapy, according to an analysis of data from RAPID.

VITALS

Key clinical point: A1-PI augmentation is effective across a wide range of subgroups with A1-PI deficiency.

Major finding: The decreased rate of change in adjusted P15 lung density vs. placebo in those with high functional, antigenic, or intermediate functional A1-PI levels who were treated with A1-PI augmentation was 1.08 g/L per year, 1.23 g/L per year, and 1.38 g/L year, respectively.

Data source: An analysis of data from the 180-patient RAPID study.

Disclosures: This study was funded by CSL Behring. Dr. Stocks reported receiving funds as an investigator for the commercially sponsored clinical trial.

Better responses to therapy in the trial, as compared with placebo and as measured by mean computed tomography–assessed rate of change in adjusted P15 lung density at total lung capacity, occurred among the 79 female subjects (1.45 g/L per year), and among the 60, 58, and 59 patients with high functional, antigenic, or intermediate functional alpha-1 proteinase inhibitor (A1-PI) levels, respectively (1.08, 1.23, and 1.38 g/L per year), Dr. James Stocks reported at the annual meeting of the American College of Chest Physicians.

The differences in the rate of change with treatment vs. placebo in these subgroups were statistically significant, said Dr. Stocks of the University of Texas Health Science Center at Tyler.

Greater differences in favor of A1-PI – with a trend toward statistical significance – were also seen in the 21 patients with a body mass index of 30 kg/m^2 or greater (2.21 g/L per year); the 86 patients under age 54 years (0.96 g/L year); the 87 patients with a carbon monoxide diffusion capacity at or below the median at baseline (0.90 g/L per year); the 8 patients with lower exercise capacity, defined by 400 m or less walked (0.99 g/L per year); and the 88 patients with St. George's Respiratory Questionnaire symptoms scores at or below the median at baseline (0.93 g/L per year), he said.

RAPID (Randomized, Placebo-Controlled Trial in Alpha-1 Proteinase Inhibitor Deficiency) – the single largest clinical trial of A1-PI augmentation therapy – included 180 A1-PI–deficient patients and demonstrated that weekly intravenous A1-PI therapy at a dose of 60 g/kg per week for 2 years slows progression of emphysema. The annual rate of decline in CT-measured lung density was 34%, compared with placebo. Those findings were reported in May 2013.

According to the current analysis, A1-PI augmentation appears to be efficacious across a wide range of subgroups, Dr. Stocks said. Those with higher BMI may have experienced greater benefit because of receiving a greater amount of A1-PI as a result of weight-based dosing. Younger patients may have experienced greater benefit because of being in the earlier stages of disease, with less emphysematous lung damage and lung density loss.

"It is important to note that were no multiplicity adjustments made in the analysis, and no tests for interaction within a subgroup were significant, so no subgroup could be said to be particularly favored as being suitable for treatment with A1-PI," he said. It does appear, however, that earlier treatment may help to reduce overall progression of emphysema in affected patients, and that baseline factors such as higher baseline A1-PI, BMI, and gender may impact treatment benefit, he said.

This study was funded by CSL Behring. Dr. Stocks reported receiving funds as an investigator for the commercially sponsored clinical trial.

Smokers on HOT

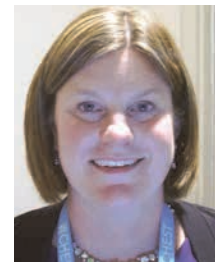
Burn risk *from page 1*

admissions were smokers, representing 4% of the center's annual admissions rate and twice that of the national burn rate for smokers in general. Nearly all the patients, a balance of men and women with a median age of 61 years, were using HOT for chronic obstructive pulmonary disease.

"The location of the burns, probably not surprisingly, was the face. Probably the most common was the nasal cannula," Dr. Baker said.

Although nearly three-quarters of the 55-member cohort had less than a 5% total body surface–area burn, Dr. Baker said that in a patient population with baseline respiratory compromise and respiratory failure, this was an alarming rate of morbidity, particularly since half of the injured were intubated, and bronchonscopic exam revealed a third of these patients also had inhalation injuries.

"And here's the kicker," said Dr. Baker. "Eight deaths over 5 years. This is huge. So when these [individuals] get burned, it's often really bad. Several of them had house fires, and we were able to find in the chart where other people [in the home] were burned and admitted to the hospital."



DR. BAKER

Still, after a median 5-day stay, almost all of the patients who survived were discharged with prescriptions for HOT, including the so-called "repeat offenders." Because nearly half of all surviving patients with smoking-related HOT injuries were discharged to a higher level of care, this cohort tended to have higher health care utilization rates as well, Dr. Baker noted.

A surprise finding was that more than a quarter of the cohort had either current or concomitant problems with substance abuse. "We were not expecting that, and it has not been previously reported," Dr. Baker said.

The data demonstrate the need to screen HOT patients for whether they smoke and whether they have substance use issues, she said. If either condition applies, then faster follow-up and, potentially, counseling could be offered, including better education about the risks of oxygen therapy. "Currently, we have no formalized way to educate patients on the dangers of those tanks in the home," said Dr. Baker.

The data raise questions about the risk-benefit ratio of prescribing any breathing aid to COPD patients who are also smokers.

"I don't know how much sense it makes to keep throwing these inhalers, which cost hundreds of dollars a month, at people who continue to smoke," Dr. Baker said in an interview. "We take all comers, and we think oxygen therapy helps, and prolongs life, but when you factor in smoking, we don't really know what the risks and benefits are."

A large study population would be needed to determine the risks and benefits, she added.

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VIEW ON THE NEWS

Dr. Vera A. DePalo, FCCP, comments: A couple of truths exist: Oxygen therapy trials have demonstrated the benefit of supplemental oxygen, and supplemental oxygen and smoking can result in fire and burns. This article and the retrospective data presented highlight the dangers when patients continue to smoke and use home oxygen therapy. They also highlight the ethical overlay of the decision-making process when the patient is not willing or not able to stop smoking, but needs oxygen. Many of us have been in the position of weighing the patient's need for oxygen and the potential for fire and burns.

Counseling patients on the importance of smoking cessation, offering aides and programs for smoking cessation, outlining the potential harmful consequences of oxygen use while smoking, and in some cases engaging the patient in signing care contracts to not smoke while using home oxygen therapy can be important tools in addressing these dangers.

The data presented here will be another tool in making the case for the importance of smoking cessation and in engaging the patients in helping to avoid this harm. This will continue to be a decision-making challenge for us.

IN THIS ISSUE

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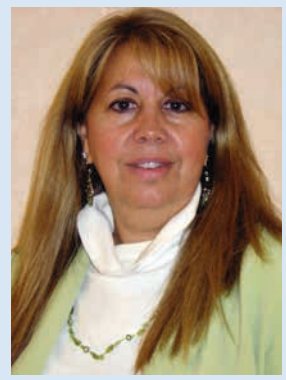

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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e-Cigarettes with nicotine aid smoking cessation

BY MIKE BOCK
Frontline Medical News

VITALS

Key clinical point: Electronic cigarettes with nicotine appear to help smokers stop smoking long term, but more data are needed.

Major finding: Smokers who use e-cigarettes containing nicotine are significantly more likely to quit than those who switch to e-cigarettes without nicotine. In addition, smokers who use e-cigarettes with nicotine and do not quit altogether succeed in cutting their cigarette consumption by half.

Data source: A meta-analysis of two randomized controlled trials that analyzed data from 662 current smokers.

Disclosures: Dr. McRobbie has undertaken educational sessions sponsored by Pfizer and Johnson & Johnson. Dr. Chris Bullen and Dr. McRobbie also were investigators on a study of e-cigarettes from an e-cigarette manufacturer (Ruyan Group) funded by the University of Auckland (New Zealand). Dr. Peter Hajek has provided consultancy to GSK, Pfizer, and Johnson & Johnson.

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Electronic cigarettes that contain nicotine are more effective than e-cigarettes without nicotine in helping smokers quit, and smokers attempting to quit are able to achieve a 50% or greater reduction in smoking with the use of e-cigarettes containing nicotine.

About 9% of smokers who used e-cigarettes that contained nicotine were able to stop smoking at up to 1 year, compared with about 4% of smokers who used nicotine-free e-cigarettes, according to a small-scale data review published in the Cochrane Database of Systematic Reviews (2014 Dec. 16:CD010216 [doi:10.1002/14651858.CD010216.pub2]).

"There is evidence from the pooled results of two trials that electronic cigarettes with nicotine, compared with [e-cigarettes without nicotine], helped smokers to stop smoking long-term; they also increased the number of people who did not quit altogether to halve cigarette consumption," wrote Dr. Hayden McRobbie of the Wolfson Institute of Preventive Medicine, Queen Mary University of London, and his colleagues.

Of the smokers included in the review who were not able to quit conventional cigarettes, 36% who used e-cigarettes with nicotine reported reducing the number of conventional cigarettes consumed by about half, compared with 28% of users who were given e-cigarettes without nicotine.

A team of researchers from New Zealand and the United Kingdom reviewed data from two trials of 662 current smokers to evaluate the efficacy of e-cigarettes use for helping smokers achieve long-term abstinence. E-cigarettes are electronic vaporizing devices that heat a liquid, usually consisting of propylene glycol and glycerol and often containing nicotine, into an aerosol for inhalation.

There is little clinical information on the amount of nicotine typically ingested from an e-cigarette, as the devices typically are not regulated by government health agencies. No serious adverse effects related to e-cigarette use were reported from either of the studies.

Although this is the first meta-analysis on e-cigarette use and the effects on smoking cessation, the authors said that more data are needed for it to become clinically useful.

"Given the variety of electronic cigarette products on the market and the product evolution, future studies need to select electronic cigarettes with good nicotine delivery that are representative of the best current standard in terms of reliability and user satisfaction," Dr. McRobbie and his associates wrote.

In addition, data were limited by the small number of trials and the small sample of participants from the studies. Also, there were few biochemical data on the participants or the sensorimotor effects of using electronic cigarettes.

"Data are also needed on the proportions of smokers who successfully quit smoking with the help of [e-cigarettes] and who continue to use [e-cigarettes] long-term and the proportion who eventually become nicotine-free," the authors concluded.

Dr. McRobbie has undertaken educational sessions sponsored by Pfizer and Johnson & Johnson. Dr. Chris Bullen and Dr. McRobbie were also investigators on a study of e-cigarettes from an e-cigarette manufacturer (Ruyan Group) funded by the University of Auckland (New Zealand). Dr. Peter Hajek has provided consultancy to GSK, Pfizer, and Johnson & Johnson.

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e-Cigarettes not first line for smoking cessation in cancer

BY GREGORY TWACHTMAN
Frontline Medical News

Given the lack of evidence to support the use of e-cigarettes as a smoking cessation product, two cancer organizations have advised against recommending e-cigarettes as a smoking cessation approach for patients with cancer.

"Given the overall lack of evidence supporting the use of ENDS (electronic nicotine delivery systems) as a proven cessation aid for smokers in general, and the absence of any data on the potential adverse effects of inhaling ENDS aerosol by cancer patients undergoing treatment, [clinicians] would be wise to refrain from recommending ENDS as a first-line therapy for smoking cessation," the American Society of Clinical Oncology and the American Association of Cancer Research said in a joint policy statement in Clinical Cancer Research (2015 Jan. 8 [doi:10.1158/1078-0432.CCR-14-2544]).

To better understand the health impact and role of ENDS in smoking cessation, the organizations advise research that examines key design features of ENDS; product testing standards; the effects of acute and chronic ENDS product use, including second- and third-hand exposure; health benefits of transitioning from traditional tobacco products to ENDS; abuse potential; and research on understanding how products are used in general and their potential to be a smoking cessation product.

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The policy statement also reiterated recommendations previously made to the Food and Drug Administration on how to regulate ENDS.

"Rapid elimination of combustible tobacco products would dramatically reduce the burden of tobacco-related death and disease," Thomas Brandon, Ph.D., Moffitt Cancer Center of Tampa, and his colleagues write. "The AACR and ASCO support every effort to reduce the use of combustible tobacco, and we support careful consideration of ENDS as potentially harmful, and potentially beneficial, products in this regard."

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Nebraska experience

Ebola *from page 1*

the ED and ICU and included specialists in infectious diseases, epidemiology, and infection control from the School of Public Health. The medical director is an infectious disease specialist, and intensivists were not involved in the training of the staff. The staff was trained in decontamination techniques and the transport and care of patients in strict isolation and was fully prepared for the patients sent to us. The acuity of the patients dictated that a team approach to the physician care of these patients be taken. The intensivists were brought in to obtain central venous access, manage fluid and electrolytes and nutrition, as well as any critical care issues that arose. The infectious disease specialists focused on treatment of the virus, health-care worker protection, equipment decontamination, and investigational new drug applications for the US Food and Drug Administration.

DR. PIQUETTE

That the Ebola virus is transmitted through contact with secretions is well known. The initial symptoms have been well documented (Bausch et al. *Antiviral Res.* 2008;78[1]:150) and should be a warning to those who have been exposed to seek medical attention. Those with fever should be quarantined and monitored closely for nausea, vomiting, and diarrhea. There appears to be a window of time during which if patients are hydrated and electrolytes monitored closely, the outcomes are improved. These are the patients who should be isolated in our critical care units and given the care that intensivists can deliver. Our biocontainment unit works successfully because the staff is highly trained in isolation procedures and the care of critically ill patients. Teamwork is essential for the care of these patients.

Isolation of patients with exposure to the Ebola virus and new onset fever maintains public safety and provision of proper personal protective equipment (PPE) gives the caregiver the confidence to treat this deadly disease. The key to maintaining isolation is careful attention to the donning and doffing of PPE. All caregivers going into the unit had to change into scrubs and put on the PPE one would use for universal precautions, including a surgical mask, isolation gown, and gloves. For added protection, everyone wore slip-on rubber shoes with shoe covers that were removed on leaving the unit and dipped in bleach solution. Entering the "hot zone" where the patient was located required additional PPE and another team member to observe the donning process to make sure there were no breaks in the PPE. Doffing was also a two-person job, requiring decontamination at each step with alcohol hand gel and new gloves. Resources from the University of Nebraska biocontainment unit are available outlining each step of this process (The Nebraska Ebola Method – For Clinicians. Accessed on iTunes U, Dec. 17, 2014).

Each patient that came to our biocontainment unit had a central venous catheter placed, even though some had previously established peripheral access. The reasoning was that these patients were malnourished prior to transfer to the biocontainment unit and would likely not be able to tolerate enteral nutrition for at least 7 days after arrival. The access also afforded us the ability to draw blood for monitoring of electrolytes without needing to do venipuncture, which minimizes health-care workers' risk of exposure. The process for placement of the central line was different only in the PPE that was required. The PPE required to enter the hot zone included goggles, N-95 face mask, hood, and full face shield, an impervious surgical gown, and boot covers that came up above the calf. Two pairs of gloves were worn with the second pair duct-taped to the cuff of the surgical gown. A third pair of gloves was used to enter the room and position the patient. These were removed, and alcohol sanitizer was used on the second pair of gloves prior to donning a sterile surgical gown and gloves over the PPE worn into the room. The internal jugular vein was the site selected for placement and located using ultrasound guidance. Two nurses were available in the room continuously to provide assistance. An antibiotic-coated quadruple lumen catheter was placed over a guide wire after confirming intravascular placement of the wire with the ultrasound. The lumen was flushed with saline solution and capped and an occlusive dressing placed over the site prior to breaking the sterile field. There were no complications with any of these procedures. There were no alterations in the procedure despite the patients' infection with the Ebola virus.

DR. KALIL

One issue we addressed early on was whether we would allow trainees under our supervision to become involved in direct patient care. Once it became known that we would be caring for these patients, a discussion was held with the faculty who would be responsible for these patients to determine if the fellows on critical care rotations should be involved in direct patient care. Given the uncertainty regarding the care of these patients and the additional scrutiny that these patients were under, it was decided that fellows should not be responsible for direct patient care. This was discussed with the fellows, and they were told that they could assist and be involved indirectly by assisting with documentation and writing orders from the nursing station outside the hot zone and interact with the patient and direct caregivers via closed circuit video link. Fellows were allowed to opt out if so desired, but all volunteered that they wanted to be involved in any way allowed. Over the course of the care of the three patients, seven of nine fellows participated in indirect patient care in some manner. Fellows were trained in donning and doffing PPE in preparation for entering the biocontainment unit.

A major issue that the biocontainment unit had to address prior to arrival of patients was what to do in the event of acute decompensation requiring advanced cardiac life support with CPR. Given the mortality reports from West Africa, the physician staff of the biocontainment unit discussed the risks of caregiver exposure if CPR was done, and it was determined that the risk was too high and the likelihood of survival if CPR was needed was too low. Initially, the physicians discussed this with each patient and next of kin and recommended that the patient be placed on DNR [do not resuscitate] status. As we gained experience, we realized intubation and mechanical ventilation could be done safely under controlled circumstances, and we developed a policy for intubation and

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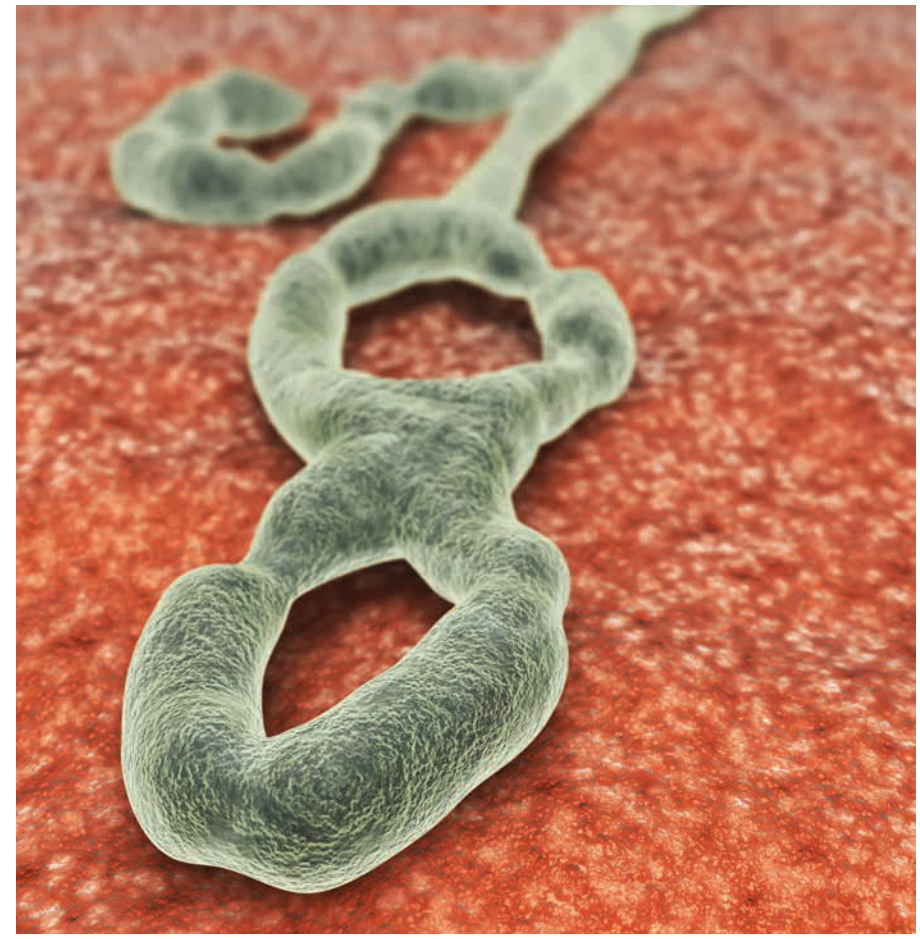

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A major issue that the biocontainment unit had to address was what to do in the event of acute decompensation requiring advanced cardiac life support with CPR.

Continued from previous page

critical care support but no CPR.

It seems clear from the general experience that patients with the Ebola virus who receive standard critical care therapies early following the onset of fever have better outcomes than did those who received this care late. If the virus is not treated and supportive critical care is not given in the first 6-8 days, multisystem organ failure ensues, and mortality is high

Our biocontainment unit works successfully because the staff is highly trained in isolation procedures and the care of critically ill patients. Teamwork is essential.

despite the best medical efforts. Patients may develop hypoxemic respiratory failure, liver failure, and renal failure, in addition to their nausea, vomiting, diarrhea, and delirium. It seems rational but somewhat unclear that these patients develop a syndrome similar to severe sepsis, with an eventual capillary leak syndrome, and that careful attention to volume status early on can help patients avoid the multisystem organ failure. Unfortunately, optimal antiviral therapy has not been determined, but we will learn more as we gain additional experience and perform clinical trials with potential therapies.

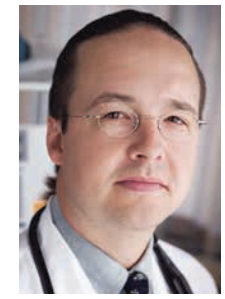
The lessons we have learned thus far are as follows:

1. Assemble and train a team of nurses, respiratory therapists, and industrial hygienists who can operate all aspects of biocontainment.
2. Assemble a group of physicians who can provide care for these patients, including intensivists and infectious diseases specialists.
3. Adhere to guidelines for donning and doffing PPE, and designate donning and doffing partners to assist and monitor every step.
4. Consider central venous access in all patients.
5. Establish policy for resuscitation.
6. Establish a role for residents and fellows, and if there is a role in indirect or direct patient care, provide proper training.
7. Treat as severe sepsis, monitoring volume status and electrolytes carefully.

Dr. Piquette is Associate Professor of Medicine and Pulmonary-Critical Care Medicine Fellowship Program Director, Division of Pulmonary, Critical Care, Sleep, and Allergy; Dr. Kalil is Professor, Infectious Diseases Division; Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska.

EDITOR'S COMMENT

In this first installment of my tenure as the section editor of Critical Care Commentary, I am extremely grateful to Dr. Piquette and Dr. Kalil for providing their first-hand insights on treating critically ill patients with the Ebola virus within one of the United States' most advanced biocontainment units. While optimal Ebola therapies are yet to be fully elucidated, these early experiences highlight several issues this infection – and other, future epidemic illnesses – may superimpose upon routine ICU care.



The incremental precautions required when performing invasive procedures in highly contagious individuals such as these, while extensive, are not necessarily surprising. However, these early experiences with the Ebola virus have required unique reflections on our self-imposed limits to providing care. What is the point at which the potential benefit to the patient with the Ebola virus becomes outweighed by the risk of harm to the physicians providing their care? It has convincingly been argued that our sacred oath of "Primum non nocere" requires us to be stewards in preventing harm to ourselves as well as to our patients. Withholding cardiopulmonary resuscitation and restricting the roles of trainees in the care of these patients are provocative examples of our competing interests and certainly merit further considerations.

Because this is my first commentary in *CHEST Physician*, I would like to take this opportunity to thank Dr. Peter Spiro for his astute author selection and insightful editorial comments during his 3-year term as editor of this section. I sincerely hope that my selections in the coming years measure up to the high standards he has firmly established. Readers with comments and/or suggestions should feel free to contact me at any time via e-mail (lmorrow@creighton.edu) as I sincerely welcome your criticisms and collaborations. I look forward to serving both our readers and CHEST in the years to come.

Dr. Lee E. Morrow, FCCP
Section Editor

ICS/LABA betters LABA in moderate and severe COPD

BY SHARON WORCESTER
Frontlline Medical News

AT CHEST 2014

AUSTIN, TEX. – Exacerbation rates were lower and lung function improved when patients with moderate or severe chronic obstructive pulmonary disease received combined treatment with the inhaled corticosteroid (ICS) budesonide and the long-acting beta$_2$-agonist (LABA) formoterol, as compared with patients given formoterol alone.

In a post hoc analysis of pooled data from three randomized double-blind studies, exacerbation rates were lower in the 197 patients with moderate airflow limitations and in the 975 patients with severe airflow limitations who received combination therapy, compared with the 211 and 963 patients, respectively, who received only formoterol.

The differences were seen regardless of whether antibiotics were used, regardless of airflow limitation severity, and despite an overall lower exacerbation rate in those with moderate vs. severe disease, Dr. Donald Tashkin reported at the annual meeting of the American College of Chest Physicians.

The lowest rate of exacerbations, 0.4 per patient-treatment-year, was among those in the combination therapy group who were not treated with antibiotics – suggesting infection was not a factor in the exacerbation. The exacerbation rate was 0.7 per patient-treatment-year in those with moderate airflow limitation who received only formoterol.

The respective exacerbation rates in patients with severe airflow limitation were 0.8 for those who received combination therapy and 1.0 in those who received only formoterol. The corresponding rates for exacerbations among those who were additionally treated with antibiotics were 0.5 vs. 0.8 and 0.9 vs. 1.2, said Dr. Tashkin of the University of California, Los Angeles.

The lowest rate of exacerbations was among those in the combination therapy group who were not treated with antibiotics – suggesting infection was not a factor in the exacerbation.

Further, an overall greater percentage of patients receiving combination therapy met responder criteria for at least a 100-mL improvement in predose forced expiratory volume in 1 second (FEV_1).

The rates were 47% vs. 39% for combination vs. formoterol alone in patients with moderate airflow limitation, and 34% vs. 29%, respectively, in patients with severe airflow limitations, he said.

The pooled data for this analysis were from two 12-month trials and one 6-month trial of COPD patients aged 40 years or older with at least one COPD exacerbation in the past year.

Two of the trials (the 12-month SUN study and the 6-month SHINE study) were pivotal randomized, placebo-controlled, double-blind, double-dummy trials that led to the approval of the budesonide/formoterol combination therapy, and the third was a non–placebo-controlled study, Dr. Tashkin noted.

Moderate disease was defined as FEV_1 percent predicted of at least 50%, and severe disease was defined as FEV_1 percent predicted of less than 50%. Exacerbations were defined as COPD worsening that required treatment with oral corticosteroids and/or hospitalization.

Combination therapy was administered twice daily via pressurized metered-dose inhaler at a dose of 320 mcg budesonide/9 mcg formoterol; formoterol-only therapy was administered twice daily via dry-powder inhaler at a dose of 9 mcg.

This study was supported by AstraZeneca. Dr. Tashkin reported receiving consulting fees and/or serving on a speakers bureau or advisory committee for AstraZeneca, Sunovion, Theravance, Pearl, Boehringer Ingelheim, and Forest, and receiving research funding or grant money from Sunovion, Pearl, and GlaxoSmithKline.

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

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

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

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

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

Once-daily ANORO ELLIPTA

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

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

WARNING: ASTHMA-RELATED DEATH

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

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

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

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

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

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

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

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

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

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

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

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

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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ICD-10 Cometh

BY DR. MICHAEL E. NELSON, FCCP

For all patients covered by the Health Insurance Portability and Accountability Act (HIPAA), ICD-9 CM coding will be replaced by the International Classification of Diseases, 10th Edition, Clinical Modification/Procedure Coding System, ICD-10 CM and ICD-10 PCS, on October 1, 2015. ICD-10 CM will be used in all health-care settings, and ICD-10 PCS will be used for procedure coding in US hospitals. Hopefully, all are aware of this change and have taken steps to have their practices ready. This article is the first in a series that will provide a list of ICD-10 CM codes commonly used for pulmonary, critical care, and sleep medicine. It will review the structure of the ICD-10 CM codes and provide a list of the codes for asthma. Future articles will highlight other code groups.

By way of review, Table 1 provides an overview of the major differences between ICD-9 CM and ICD-10 CM codes sets.

Table 1

ICD-9	ICD-10
Codes are 3 to 5 characters in length	Codes are 3 to 7 characters in length
Approximately 13,000 codes	Approximately 68,000 codes
First character may be numerical or alphabetical (V or E); second through fifth digits are numerical	First digit is alphabetical; second and third characters are numerical; fourth through seventh characters are alphabetical or numerical
Nonspecific and no laterality	Specific and has laterality (right and left)

The expanded characters in the ICD-10 code set are structured as follows:
Characters 1-3 – Category
Characters 4-6 – Etiology, anatomic site, severity, other clinical descriptors
Character 7 – Extension

The codes may also have Include notes and Exclude notes. Include notes are provided to further define, or give examples of, the content of the category. Excludes1 are codes that may NOT beused with the code group listed. Excludes2 are codes that are not part of the code group listed but could exist with the group. There are additional instructions and explanations of code structure at the CMS website www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html.

The ICD-10 CM codes for asthma are listed below.

J45 Asthma

Includes: allergic (predominantly) asthma
allergic bronchitis NOS
allergic rhinitis with asthma
atopic asthma
extrinsic allergic asthma
hay fever with asthma
idiosyncratic asthma
intrinsic nonallergic asthma
nonallergic asthma

Use additional code to identify:
exposure to environmental tobacco smoke (Z77.22)
exposure to tobacco smoke in the perinatal period (P96.81)
history of tobacco use (Z87.891)
occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-)
tobacco use (Z72.0)

Excludes1: detergent asthma (J69.8)
eosinophilic asthma (J82)
lung diseases due to external agents (J60-J70)
miner's asthma (J60)
wheezing NOS (R06.2)
wood asthma (J67.8)

Excludes2: asthma with chronic obstructive pulmonary disease (J44.9)
chronic asthmatic (obstructive) bronchitis (J44.9)
chronic obstructive asthma (J44.9)

J45.2 Mild intermittent asthma
J45.20 Mild intermittent asthma, uncomplicated
Mild intermittent asthma NOS
J45.21 Mild intermittent asthma with (acute) exacerbation
J45.22 Mild intermittent asthma with status asthmaticus

J45.3 Mild persistent asthma
J45.30 Mild persistent asthma, uncomplicated
Mild persistent asthma NOS
J45.31 Mild persistent asthma with (acute) exacerbation
J45.32 Mild persistent asthma with status asthmaticus

J45.4 Moderate persistent asthma
J45.40 Moderate persistent asthma, uncomplicated
Moderate persistent asthma NOS
J45.41 Moderate persistent asthma with (acute) exacerbation
J45.42 Moderate persistent asthma with status asthmaticus

J45.5 Severe persistent asthma
J45.50 Severe persistent asthma, uncomplicated
Severe persistent asthma NOS
J45.51 Severe persistent asthma with (acute) exacerbation
J45.52 Severe persistent asthma with status asthmaticus

J45.9 Other and unspecified asthma
J45.90 Unspecified asthma
Asthmatic bronchitis NOS
Childhood asthma NOS
Late onset asthma
J45.901 Unspecified asthma with (acute) exacerbation
J45.902 Unspecified asthma with status asthmaticus
J45.909 Unspecified asthma, uncomplicated
Asthma NOS

J45.99 Other asthma
J45.990 Exercise induced bronchospasm
J45.991 Cough variant asthma
J45.998 Other asthma

IOM recommends social factors to include in EHRs

BY ALICIA AULT
Frontline Medical News

Electronic health records should be equipped to record and track 12 social and behavioral determinants of health, an Institute of Medicine committee has recommended.

In addition to measures that are routinely collected now – race/ethnicity, tobacco use, alcohol use, and residential address – the committee advocated that electronic heath records (EHRs) should be able to capture the following information:

- Educational attainment,
- Financial resource strain,
- Stress,
- Depression,
- Physical activity,
- Social isolation,
- Intimate partner violence (for women of reproductive age), and
- Neighborhood median household income.

These measures can "provide crucial information about factors that influence health and the effectiveness of treatment."

Additionally they will allow collection of data for researchers and policy makers, and will help inform innovations that might improve health outcomes or reduce costs, according to the report.

The panel aimed for what it called a "parsimonious panel of measures," to help reduce the data collection burden for patients and health care providers, committee cochair Dr. William W. Stead, McKesson Foundation Professor of Biomedical Informatics and professor of medicine at Vanderbilt University, Nashville, Tenn., said during a press briefing discussion of the committee recommendations.

The IOM report will be used by the Office of the National Coordinator for Health Information Technology (ONC) to determine what it should require from certified EHRs and from physicians who are participating in Medicare's meaningful use incentive payment program.

Physicians will be required to document social and behavioral determinants under Stage 3 of meaningful use, which begins in 2017.

Dr. Stead said that the speed of inclusion of the social and behavioral determinants in EHRs will partly be determined by whether the ONC follows the panel's recommendations and requires them as part of meaningful use.

He noted that in the past, EHR vendors and health care systems have been told by the ONC that they need to obtain certain types of information, "but then had to figure out on their own how to capture that information.

"There's no reason why this (process) needs to take years," Dr. Stead commented.

With the IOM recommendations, "we're building the interoperability in from the beginning by providing a concise set of standard questions," he said.

It will likely take less time to get the determinants into EHR packages than for it will for health systems and physicians to figure out how to build the data collection into their workflow, Dr. Stead said.

The committee acknowledged that it will take more time during a patient encounter to collect these data. But, wrote the panel in the report, "the committee concluded that the health benefits of addressing these determinants outweigh the added

Continued on following page

Recommendations for core domains and measures

Domain/measure	Measure	Frequency
Alcohol use	3 questions	Screen and follow up
Race and ethnicity	2 questions	At entry
Residential address	1 question	Verify every visit
Tobacco use & exposure	2 questions	Screen and follow up
Census tract-median income	1 question	Update on address change
Depression	2 questions	Screen and follow up
Education	2 questions	At entry
Financial resource strain	1 question	Screen and follow up
Intimate partner violence	4 questions	Screen and follow up
Physical activity	2 questions	Screen and follow up
Social connections and social isolation	4 questions	Screen and follow up
Stress	1 question	Screen and follow up

Source: Institute of Medicine

FRONTLINE MEDICAL NEWS

Continued from previous page

burden to providers, patients, and health care systems."

Additional recommendations that were within in the IOM report include the following:

- That the ONC's EHR certification process be expanded to include appraisal of a vendor or product's ability to acquire, store, transmit, and download self-reported data germane to the social and behavioral determinants of health.
- That the National Institutes of Health develop a plan for advancing research using social and behavioral determinants of health collected in electronic health records.
- That the Health & Human Services department convenes a task force within the next 3 years, and as needed thereafter, to review advances in the measurement of social and behavioral determinants as well as make recommendations for new standards and data elements for inclusion in electronic health records.

The committee's work builds on draft recommendations published in April 2014. The committee was sponsored by a number of federal agencies and health care foundations.

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VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: While physicians might agree that the recommendations of the Institute of Medicine (IOM) might enhance medical care, it is naive to believe that this administrative burden will not make it increasingly difficult for physicians to meet Stage 3 of meaningful use should these requirements be added by the Office of the National Coordinator for Health Information Technology (ONC). Assuming that EHR vendors will incorporate this information into their software, the time required to elicit and record this information is not insignificant and will put further strain on the already busy clinician. In addition, there is a major assumption that the patient will actually provide this information willingly and that there would be implied consent to allow this information to be shared with the federal government, anonymously or otherwise. Should the ONC adopt these recommendations from the IOM, one would hope that EHR vendors are required to add this to their software at no additional cost to physicians. Also, each question might have a button for "patient declined to answer." George Orwell might have been more prescient than credited.

Staff who listen to patients make fewer errors

BY LUCAS FRANKI
Frontline Medical News

Hospital patients who are treated with respect by staff are less likely to experience a preventable medical error, according to a study by Consumer Reports.

About a quarter of 1,200 patients who responded to a *Consumer Reports* survey felt hospital staff did not treat them as adults involved in their own care. A third felt their wishes for treatments were not respected, and a similar proportion reported that staff would interrupt them. Around 20% said they experienced discrimination. Overall, patients unhappy with their care were more likely to experience a drug error, rehospitalization, or a hospital-acquired disease. The full report, "How Not to Get Sick(er) in the Hospital," is featured in the February 2015 issue of *Consumer Reports*.

EHRs need to focus on patient care, not payment

BY GREGORY TWACHTMAN
Frontline Medical News

FROM ANNALS OF INTERNAL MEDICINE

Electronic health records need to focus less on reimbursement and more on narrative entries and designs that improve patient care, a policy statement from the American College of Physicians says.

Documenting clinical information into EHRs via drop-down lists, check boxes, macros, and templates can be distracting and disruptive to vital clinical thinking and storytelling, wrote Thomson Kuhn of the ACP and his colleagues.

The authors warned against "overstructuring the clinical record and overloading it with extraneous data," and further devaluing the importance of narrative entries (Ann. Intern. Med. 2015 Jan. 13 doi:10.7326/M14-2128).

Complex and contradictory drivers are influencing the development of EHRs, so now seems a good time to reconsider how information is being documented, Dr. Peter Basch, who is one of the authors, the medical director of ambulatory EHR and health IT policy at MedStar Health of Washington, D.C., and the chair of the ACP Medical Informatics Committee, said in an interview.

On the one hand, the Office of the National Coordinator for Health Information Technology "calls for leveraging health IT to improve the consistency of documentation. At the same time and previous to that, the [Health & Human Services Office of Inspector General] has implied that seeing the same or very similar phrases in clinical documentation, whether in the same patient over a period of time or in different patients, could be evidence of note-cloning, and thus billing fraud," he said.

The focus on reimbursement in the design of EHRs limits market creativity and makes it difficult to introduce solutions that simplify the clinical documentation process, he added.

"Regulations should be clear and should address clinical workflow without adding burden for documentation solely for the purpose of obtaining reimbursement," the policy statement notes.

The ACP is calling on health care delivery organizations, medical societies, and others to define standards for clinical documentation, something that will allow the sharing of data. "No one format is appropriate for all specialties or clinical situations, but each organization or practice should develop 'chart etiquette' principles and policies based on a well-defined set of standards."

With standardization, common forms such as prior authorizations would "no longer be unique in their data content format requirements."

Other researche needed includes identifying best practices, developing automation tools that enhance document quality without facilitating improper behavior, improving medical education around health information technology, and finding effective ways to disseminate professional standards of clinical documentation and best practices, the authors conclude.

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VIEW ON THE NEWS

Dr. Thomas Sequist comments: To get the most out of electronic health records, their design needs to be focused on the entirety of the patient experience.

The true power of EHRs may be in moving from documenting isolated clinical transactions to describing whole-patient care from multiple viewpoints. Ideally, this process will shift providers from perceiving electronic documentation as a distraction from high-quality care to seeing it as a core component of such care.

EHR developers should work with customers to build products that document integrated care episodes in a manner that supports and does not impede the clinical cognitive process as well as the patient experience.

Dr. Thomas Sequist is chief quality and safety officer at Partners HealthCare and professor at Harvard Medical School, Boston. He made his comments in an editorial that accompanied the policy statement (Ann. Intern. Med. 2015 Jan. 13 doi:10.7326/M14-2913).

Physician suicide: Common and closeted

BY DOUG BRUNK
Frontline Medical News

One day in 1986, a medical school classmate handed Dr. Robert P. Bright a gun that she intended to use to kill herself. She asked him to hold on to it for her and to keep quiet about her sense of hopelessness.

"She didn't want anybody in the medical school to know; it was all hidden and hush-hushed," recalled Dr. Bright, who is now a psychiatrist at the Mayo Clinic, Scottsdale, Ariz. "I was trying to juggle that with the issue of safety."

He honored his classmate's request for confidentiality, but he sought advice from the medical school dean about what to do. Before long, his classmate sought help from a psychiatrist and got better with medication and psychotherapy. "It turned out well, thank goodness," Dr. Bright said.

Similar stories of despair among medical students and physicians don't always end well. The American Foundation for Suicide Prevention estimates that 300-400 U.S. physicians commit suicide each year, about one per day. Suicide deaths are 250%-400% higher among female physicians, compared with women in other professions, and 70% higher among male physicians, compared with men in other professions. Major depression is a common risk factor, along with bipolar disorder and substance abuse.

The American Foundation for Suicide Prevention estimates that 300-400 U.S. physicians commit suicide each year.

Depression and other mood disorders may be underrecognized and inadequately treated in physicians because they may be reluctant to seek treatment, may attempt to diagnose and treat themselves, or may seek and receive "VIP treatment" from health care providers, according to a review article coauthored by Dr. Bright (Current Psych. 2011;10:16-30).

"Physicians struggling with these things are very much in the closet about it," he said. "It's a sad reflection on the stigma that's still in our country that people can't come forth and say, 'I'm struggling with depression or anxiety.' "

Researchers led by Dr. Katherine J. Gold at the University of Michigan used data from the National Violent Death Reporting System to evaluate suicide among physicians and found that job stressors "may impact physician identity and be a particular risk factor for which more attention is warranted" (Gen. Hosp. Psychiatry 2013;35:45-9).


DR. REYNOLDS

Work dissatisfaction sent Dr. Pamela Wible into a tailspin early in her career. In 2004 she found herself in a suicidal state for about 6 weeks, "I stayed at home, crying myself into my pillow and I never sought help from my colleagues," recalled Dr. Wible, a family physician in Eugene, Ore., who currently leads training sessions in medical student and physician suicide prevention. "I was not depressed before entering the medical profession, but [I had developed] constant thoughts of 'Can I just disappear? What's the easiest way to do this?' I got to a place of complete surrender but I didn't have the gun. I didn't have the stockpile of pills. I didn't have a follow-through on the plan."


DR. WIBLE

Instead of taking her own life, she "had an epiphany" and changed the way she practiced medicine. She said that owning her own clinic empowered her to "become the doctor I had originally described on my personal statement when I entered medical school."

According to Dr. Charles F. Reynolds III, a psychiatrist at the University of Pittsburgh, reluctance to seek treatment can also be driven by concerns about the amount of time that treatment could take.

"As physicians, we often don't appropriately take care of ourselves when it comes to issues like depression," said Dr. Reynolds, who also directs the National Institute of Mental Health–sponsored Center of Excellence in the Prevention and Treatment of Late Life Mood Disorders. "We may still see it as a character weakness rather than as a medical illness that can be diagnosed and appropriately treated. Concerns about privacy also figure into the concerns of some physicians as well."

Practicing in a rural area or small community can also be an obstacle to treatment, not only because of limited access to psychiatrists, but because the "patient" may be the only physician in town.

"As much as there's stigma for everybody being voluntarily or involuntarily admitted [for suicidal ideation], it's a little different when you're a provider within the hospital where you're seeking care," Dr. Bright noted.

He said that if he had the opportunity to counsel physicians experiencing suicidal thoughts, he would "remind them of the medical nature of depression, that the brain is just another organ and the organ is not making chemicals just like the pancreas doesn't make insulin in diabetes," he said. "I'd also encourage them to get the treatment that they need. I would encourage compassion for themselves that they would give to anybody else in the same situation."

He said that he would advise them to find a mental health provider "that they trust with confidentiality, and to reach out to other people for support. I would also let them know about the physician assistance programs that are available. There's one through Vanderbilt (the Vanderbilt Center for Professional Health, Nashville, Tenn.) and several others that specialize in working with physicians who are struggling with mental health or substance abuse or disruptive behavior."


DR. BRIGHT


DR. MOUTIER

Dr. Reynolds' core message to distressed physicians is that "you're a better doctor for your patients, and a better father or mother for your family, if you're taking good care of yourself," he said. "It's hard for you to take care of your patients if you're not also taking care of yourself, if you're burning out. Get help. Treatment works."

Dr. Christine Moutier, chief medical officer of the American Foundation for Suicide Prevention, added that troubled physicians "should feel no shame for the fact that they're in distress. Any of us can get there through a whole variety of different pathways that life presents. There's science and data to support this experience as commonplace and having underpinnings that are of no fault to anyone. That's the reality."

Dr. Wible, who has lost several colleagues and physician friends to suicide, said that she hopes for a more transparent discussion of the topic by the medical profession. She presented on the topic at the 2014 annual scientific assembly of the American Academy of Family Physicians.

"The talk before mine was on Ebola, and every seat was taken" in the 900-seat room. When it came time for her presentation, "I maybe had 100 people in the room. Now, are physicians more likely to die from Ebola or from suicide? We are in a state of denial. If we don't talk about suicide, we will continue to lose one or two medical students or doctors every day. The sooner we talk about this and connect with each other outside of a PowerPoint presentation, the sooner we're going to solve this."

After a physician in a large clinical department at the University of Pittsburgh took his own life several years ago, the chair of that department invited Dr. Reynolds to speak with his staff. The meeting "was primarily educational in nature, so we talked about the topic, to try to destigmatize and to educate people about the need for appropriate help-seeking," recalled Dr. Reynolds, who is a former president of the American College of Psychiatrists. "If the leadership of a medical institution appropriately sanctions help-seeking behavior and treatment of mental disorders like depression, that's going to make it okay for people to reach out and seek help rather than pushing it under the rug, so to speak. If the leadership says 'this is a key thing and we don't think you can function adequately as a medical student or as a physician if you're not taking appropriate care of yourself,' that helps to shift the culture."

The ripple effect of that kind of message from health care administrators can't be underestimated, said Dr. Moutier, who helped launch a suicide and depression awareness program at the University of California, San Diego (Acad. Med. 2012;87:320-6). She encouraged health care leaders to

Continued on page 22

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Continued from page 20

stage periodic grand rounds and lectures for their medical staff about physician well-being, burnout, and the risk of suicide. "If the leader is uncomfortable talking about these things, that's a sign they should get a little education for themselves about [these topics]," she said.

Dr. Reynolds noted that certain state medical licensure boards including those for Arkansas and Pennsylvania have incorporated destigmatizing language into relicensure exams. "Some of them previously would ask questions such as whether the applicants had a history of a mental disorder like depression," he said. "What you're beginning to see now increasingly is that the state medical board will ask more generic questions, like 'Do you have any conditions that would interfere with the practice of your specialty in medicine?' This is a good thing."

He said that he is optimistic about the future of physician well-being, noting that the University of Pittsburgh and other medical schools have incorporated wellness principles into first-year curriculum. "We underscore the importance of students becoming sensitive to one another, learning how to recognize depression in each other and creating a culture in which students can encourage each other to engage in appropriate help-seeking," Dr. Reynolds explained. "I think we are witnessing a shift in the culture of institutional medicine as we bring along new generations of physicians who are better educated about mental disorders and their treatment and issues related to suicide as we reach out to students, make counseling services available to them, educate them about these issues. That supports a cultural shift that gradually erodes the issue of stigma that has so long plagued appropriate help-seeking in medical institutions."

Still, Dr. Wible said that she worries about the disaffected colleagues who reach out to her almost every day. "Just yesterday I got an e-mail from a physician in Oklahoma who told me they just lost three physicians to suicide in 1 month who were on probation with the medical board," she said. "These are not defective physicians. These people need to be helped."

Dr. Wible said that she favors holding periodic panel discussions on the topics of depression and physician suicide for medical students and physicians alike. "Let other physicians who've been depressed and suicidal sit in front of the room on the first week of medical school, or in a hospital once in a while, mandatory, where you listen to other well-respected physicians say, 'yeah. I cried myself to sleep after I lost this patient,' or 'I had suicidal thoughts during a malpractice case.' There are lots of reasons why physicians could be sad. They need to start talking about it publicly. Other medical students and physicians would then feel comfortable to raise their hands in the audience and say, 'I felt the same way.'"

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Suggested resources

American Foundation for Suicide Prevention (www.afsp.org/). 24-hour crisis line: 1-800-273-TALK (8255). In 2008 the AFSP released a documentary about the problem of physician depression and suicide titled "Struggling in Silence," which aired on public television stations nationwide and is available on DVD for $24.99.
Center for Patient and Professional Advocacy (www.mc.vanderbilt.edu/centers/cppa/index.php)
Depression and Bipolar Support Alliance (www.dbsalliance.org).
Federation of State Physician Health Programs (www.fsphp.org).
Vanderbilt Center for Professional Health (www.mc.vanderbilt.edu/cph).
The Mayo Clinic Program on Physician Well-Being (http://www.mayo.edu/research/centers-programs/physician-well-being-program/overview).
ePhysicianHealth.com, a program of the Ontario Medical Association (http://php.oma.org/ePhysicianHealth.html)
The Academic Medicine Handbook: A Guide to Achievement and Fulfillment for Academic Faculty, New York: Springer, 2013 (http://www.springer.com/medicine/internal/book/978-1-4614-5692-6)

SGR repeal faces the hurdle of how to pay for it

BY GREGORY TWACHTMAN

AT A HOUSE ENERGY AND COMMERCE HEALTH SUBCOMMITTEE HEARING

WASHINGTON – With bipartisan agreement to repeal and replace the Medicare Sustainable Growth Rate formula on the table, the next battle facing passage of the legislation will be how to pay for it.

At a 2-day hearing in January in which legislators on the House Energy and Commerce Health Subcommittee heard testimony from policy analysts, the American Medical Association, the American Hospital Association, and AARP, Republican leadership of the House Energy and Commerce Health Subcommittee made it clear that a permanent SGR fix would not move forward without offsets to cover the estimated $140 billion price tag for the agreement.

Finding the offsets "will not be easy, but it is a task we must embrace," Subcommittee Chairman Joseph Pitts, (R-Pa.), said in opening the hearings. "Some argue that SGR reform does not need to be paid for. I respectfully disagree."

Rep. Pitts noted that 98% of enacted SGR patches, spanning 120 of the 123 months worth of so-called "doc-fix" legislation, have been paid for with offsets.

Democrats on the subcommittee were critical of that hard line, noting that the House recently passed a bill to change definition of full-time employment in the Affordable Care Act to 40 hours a week, a bill estimated to cost more than $50 billion, without any cost offsets. They also suggested to look elsewhere in government to find the offsets.

"A fix to the SGR that harms Medicare beneficiaries because of the insistence of offsets that reduce benefits and limit access is not an acceptable tradeoff," said the subcommittee's ranking member, Rep. Gene Green (D-Tex.).

Witnesses who testified agreed that SGR reform should not be passed without offsets, though the common message was not to put the burden on beneficiaries through higher premiums or reduction of services.

Cost-saving reforms

Alice Rivlin, Ph.D., director of the Engelberg Center for Health Care Reform at the Brookings Institution, Washington, and cochair of the delivery system reform initiative at the Bipartisan Policy Center, offered potential cost-saving reforms, including income-adjusting premiums, accelerating of payment reform, rewarding seniors for choosing generic drugs, more competitive bidding, and accelerating the time frame for higher payments to providers participating in alternative payment mechanisms highlighted in the legislation to 2018 and offering those incentives to all Medicare providers.

The recommendations "would move to make Medicare a more efficient program," Dr. Rivlin, founding director of the Congressional Budget Office, said.

Dr. Rivlin also said that strengthening accountable care organizations (ACOs) would help with finding savings offsets, including setting lon-

REP. PITTS

DR. McANENY

ger-term savings goals rather than resetting baselines every year or eliminating historical or "after-the-fact" attribution of beneficiaries to ACOs.

"The long-term promise of these models won't be realized if unrealistic short-term pressures for savings make it unlikely that many providers can succeed," she said. "These are all fixable problems that can be addressed as part of SGR reform."

Better care coordination

Better care coordination also could save Medicare money and contribute to SGR reform funding, according to Marilyn Moon, Ph.D., a fellow at the American Institutes for Research in Washington.

Dr. Moon said that incentives should emphasize performing the right care at the right place and at the right time. To that end, the notion of bundled payments needs to be carefully examined because of the potential influence of the entity in charge of payments.

For example, if a hospital is the lead organization in charge of distributing bundled payments in a coordinated care system, it might be inclined to keep patients in house rather than send them to a more appropriate setting.

There are "a lot of things that need to be worked out," she said, adding that the SGR legislation could be a good vehicle for it.

Medical associations weigh in

Dr. Barbara L. McAneny, chair of the American Medical Association Board of Trustees, said that her organization needed more guidance from the subcommittee before leaders could recommend specific offsets.

"Within the health care sector, so many people are struggling now just to keep their doors open to their patients, that for us from within the health care sector to really come up with a specific pay-for may not be as useful until there are some guidelines set up by Congress," Dr. McAneny testified. "What are the rules of this particular budgetary process? How do we fit those things within that? I think the AMA stands ready to assist by weighing in on any given suggestions, but I think we are very uneasy and feel that we don't really have the ability to give you specific pay-fors."

Her testimony drew sharp criticism from Rep. Larry Bucshon (R-Ind.).

"I would just implore you to really reconsider that and the AMA reconsider and maybe help us rather than waiting for other options and coming out and saying up or down, we disagree or we agree," Rep. Bucshon said. "If you are going to offer an opinion at the end, then you should be part of the offering solutions on the front side. … If you are just going to wait and be a critic and not offer solutions yourself, to me that's not very helpful."

Others testifying before the subcommittee noted that despite the committee being open to all avenues to finance the SGR bill, Medicare would likely bear some of those costs.

"The [American Hospital Association] cannot support any proposal to fix the physician payment problem at the expense of funding for services provided by other caregivers," AHA President and CEO Richard Umbdenstock testified. The AHA "cannot simply oppose payment cuts without supporting other solutions."

Mr. Umbdenstock highlighted four solutions that the AHA supports: combining Medicare Part A and Part B with a unified deductible and coinsurance; higher premiums for beneficiaries coming into Medicare as well as means-testing for premiums; altering incentives to first-dollar coverage for Medigap so that beneficiaries will be more aware of how they are choosing the health care they need; and medical liability reform.

These suggestions have general bipartisan support and "would not only generate savings, but also put the Medicare program on firmer financial footing for years to come," he said.

Eric Schneidewind, president-elect of AARP, suggested that maybe Congress does not need to fully fund the SGR bill.

"In light of current and future savings in the Medicare program, Congress would be justified in not fully offsetting the cost of a permanent repeal at this time," Mr. Schneidewind said. He also added that legislators could consider expansion of competitive bidding for durable medical equipment, equalize payments based on physician site of services, be more aggressive in collecting overpayments to Medicare Advantage plans, increasing transitional care and chronic care management, and encourage the use of all highly skilled clinicians.

But what likely would be consid-

ALICIA AULT/FRONTLINE MEDICAL NEWS

ered more controversial were Mr. Schneidewind's suggestions related to drugs.

"AARP believes that any discussion of budget offsets for Medicare reimbursement reform should include savings from prescription drugs," he said. "We urge you to give strong consideration to the following prescription drug proposals that could save at least $150 billion."

Those proposals included offering Medicaid-level drug rebates to beneficiaries who are eligible for both Medicare and Medicaid, giving the secretary of Health & Human Services the power to negotiate drug prices, reduce the exclusivity period for biologics, prohibit pay-for-delay agreements (when a brand-name drug manufacturer pays to delay the launch of a generic equivalent), and prohibit the use of Risk Evaluation and Mitigation Strategies (REMS) to block generic and biosimilar drug development.

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Multiple patient types moving forward, one Adempas

In pulmonary arterial hypertension (PAH), (WHO Group 1)

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

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II-III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

In inoperable and persistent/recurrent chronic thromboembolic hypertension (CTEPH), (WHO Group 4)

46m improvement (mean) in 6MWD over placebo at Week 16 (95 % CI: 25m-67m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 261 adult patients with persistent/recurrent CTEPH after surgery or who were inoperable. The primary endpoint was change from baseline in 6MWD at 16 weeks.

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.

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.

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

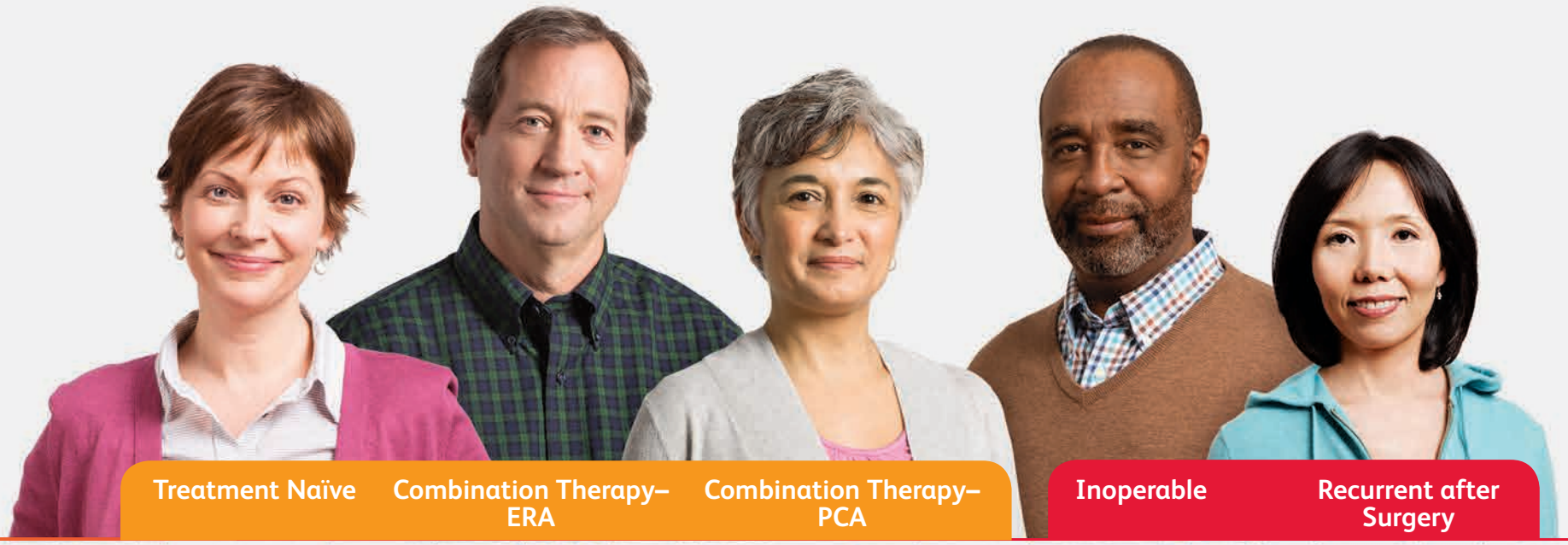
Important requirements of the Adempas REMS program include the following:

- 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.

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

PAH (WHO Group 1)

CTEPH (WHO Group 4)



WARNINGS AND PRECAUTIONS (continued)

- 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.

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.

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PP-400-US-1451 January 2015

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.

See what Adempas could do for your patients.

Visit Adempas-US.com

†Soluble Guanylate Cyclase

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

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

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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The high cost of treatment-resistant hypertension

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – Prepare for sticker shock: Researchers have put a price tag on direct medical expenditures for treatment-resistant hypertension, and it's a big one.

Indeed, apparent treatment-resistant hypertension (aTRH) is associated with an estimated $11.3-$17.9 billion per year in direct medical expenditures above and beyond expenditures for nonresistant hypertension in the United States, Steven M. Smith, Pharm.D., reported at the American Heart Association scientific sessions.

This is a conservative estimate based on an assumed 5% prevalence of aTRH among U.S. adults with hypertension, which may be a low figure, according to Dr. Smith of the University of Florida, Gainesville.

He presented an analysis of data on direct medical expenditures and health care utilization for 43,476 patients with hypertension in the nationally representative U.S. Medical Expenditure Panel Survey, of whom 1,924 met the criteria for aTRH as defined by a requirement for drugs from at least four antihypertensive medications classes in order to achieve blood pressure control.

While aTRH is known to be associated with higher rates of major adverse cardiovascular events and increased mortality relative to nonresistant hypertension, the financial costs associated with this condition haven't previously been carefully examined.

Mean annual health care expenditures for individuals with aTRH were $20,018, more than twice the $9,814 figure for patients with nonresistant hypertension.

But patients with aTRH were older, heavier, less likely to have a high income, and differed in additional ways from the much larger group with nonresistant hypertension.

Resource use: Treatment-resistant vs. nonresistant hypertension

	Apparent treatment-resistant hypertension		Nonresistant hypertension		Incidence rate ratio*
Office visits (annual)	15.18		9.56		1.17
ED visits (annual)	0.49		0.28		1.36
Inpatient visits (annual)	3.42		1.27		1.57
Length of stay (days)	0.54		0.22		1.96
Number of prescription drug fills (annual)	69		30		1.74

Frontline Medical News

*Adjusted for patient demographics, chronic comorbidities, physical activity, smoking, and insurance status.

Note: Based on data for 43,476 patients from the Medical Expenditure Panel Survey.

Source: Dr. Smith

In a multivariate analysis adjusted for these potential confounders, aTRH was associated with $2,413 in excess annual medical expenditures and $1,253 in excess total prescription expenditures, for a total of $3,647 excess total annual health care expenditures per person, compared with subjects with nonresistant hypertension, Dr. Smith said.

New preventive strategies are clearly in order, he concluded.

He reported having no financial conflicts regarding this study, which was conducted without industry funding.

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Edoxaban approved for atrial fib, DVT, and PE

BY ELIZABETH MECHCATIE
Frontline Medical News

Edoxaban, a selective factor Xa-inhibitor, has been approved by the Food and Drug Administration for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, with a statement in the boxed warning that it should not be used in patients with normal renal function.

The warning reflects the results of a subgroup analysis in the pivotal trial, which found that the 60-mg dose was superior to warfarin in terms of reducing the stroke risk in mildly renally impaired patients, but was worse in patients with normal renal function. This was the main focus of a meeting of the FDA's Cardiovascular and Renal Drugs Advisory Panel meeting in October, in which the panel voted 9-1 to recommend approval of edoxaban for this indication, but had mixed opinions on whether approval should be limited to patients with mild to moderate renal impairment.

The approved prescribing information recommends that a patient's creatinine clearance should be checked before edoxaban is prescribed. "Patients with creatinine clearance greater than 95 mL/min have an increased risk of stroke, compared to similar patients given warfarin," and should be treated with another anticoagulant, the FDA said in the statement announcing the approval. The recommended dose for those with a creatinine clearance between 50 mL/min and 95 mL/min is 60 mg once a day; for those with a creatinine clearance of 15-50 mL/min, the recommended dose is 30 mg once a day, according to the prescribing information.

Edoxaban, the fourth novel oral anticoagulant drug approved by the FDA, will be marketed as Savaysa by Daiichi Sankyo. It was also approved to treat deep vein thrombosis and pulmonary embolism following 5-10 days of initial therapy with a parenteral anticoagulant. The recommended dose for this indication is 60 mg once a day. For patients with a creatinine clearance of 15-50 mL/min, or who weigh up to 60 kg (about 132 pounds), or who are taking "certain P-glycoprotein inhibitors," the 30-mg/day dose is recommended.

FDA NEWS

Approval for the nonvalvular AF indication was based on ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) study, comparing once-daily edoxaban (60 mg and 30 mg) to warfarin in 21,015 patients with nonvalvular AF, at a moderate to high risk of thromboembolic events (N. Engl. J. Med. 2013;369:2093-104). Over a median of almost 3 years, both doses were noninferior to warfarin in the primary efficacy endpoint, the occurrence of first stroke or of a systemic embolic event. Overall, major bleeding events were significantly lower among those on the 60-mg and 30-mg doses, compared with those on warfarin. However, the rate of ischemic stroke was higher relative to warfarin in patients with a creatinine clearance over 95 mL/min.

About half of the edoxaban dose is eliminated by the kidneys, and patients with a creatinine clearance above 95 mL/min have lower plasma edoxaban levels, according to a statement in the clinical trials section of the prescribing information, which adds: "Given the clear relationship of dose and blood levels to effectiveness in the ENGAGE AF-TIMI 48 study, it could be anticipated that patients with better renal function would show a smaller effect of Savaysa, compared to warfarin than would patients with mildly impaired renal function, and this was in fact observed."

Approval of the DVT and PE indication was based on the Hokusai-VTE study of about 8,200 people comparing edoxaban to warfarin, which found that the edoxaban 60 mg once a day was noninferior to warfarin in the rate of symptomatic venous thromboembolism (3.2% vs. 3.5% in those on warfarin). The rate of major or clinically relevant nonmajor bleeding events was 8.5% among those on edoxaban vs. 10.3% in those on warfarin (N. Engl. J. Med. 2013;369:1406-15).

Bleeding and anemia were the most common adverse events among patients with nonvalvular atrial fibrillation in clinical trials, and "as with other FDA-approved anticlotting drugs, bleeding, including life-threatening bleeding, is the most serious risk with Savaysa," the FDA statement said. Among those treated for DVT and PE, the most common adverse events were bleeding, rash, abnormal liver function tests, and anemia.

Savaysa is the fourth novel oral anticoagulant to be cleared by the FDA, after dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis).

Serious adverse events associated with edoxaban should be reported to the FDA's MedWatch *program or at 800-332-1088.*

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Overanticoagulation in AF boosts dementia risk

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – Patients with atrial fibrillation who frequently have a supratherapeutic international normalized ratio are at sharply increased risk for developing dementia, according to a large observational study.

"We postulate that the mechanism is an accumulation of microbleeds in the brain," Dr. T. Jared Bunch said at the American Heart Association Scientific Sessions.

"In patients with hypertension, a condition that's extremely common with atrial fibrillation, these repetitive small bleeds are preferentially in the hippocampus, where memory is stored," added Dr. Bunch, who is medical director for heart rhythm services at the Intermountain Medical Center Heart Institute in Salt Lake City.

VITALS

Key clinical point: The more time patients with atrial fibrillation who are on warfarin plus aspirin spend with a supratherapeutic INR, the greater their risk of developing dementia.

Major finding: Atrial fibrillation patients on warfarin plus an antiplatelet agent who had an INR above 3.0 on at least 25% of occasions had a 5.8% incidence of dementia during follow-up, compared with a 2.7% incidence in those with a high INR less than 10% of the time.

Data source: This was a retrospective, case-control study involving 1,031 patients with atrial fibrillation on warfarin plus aspirin or another antiplatelet agent followed for a mean of more than 4 years.

Disclosures: This study was funded internally by Intermountain Healthcare. Dr. Bunch reported having no financial conflicts.

He presented a study of 1,031 patients with atrial fibrillation (AF) in Intermountain's centralized anticoagulation service. All were on dual therapy with warfarin plus aspirin or, much less commonly, another antiplatelet agent. At baseline, their average age was in the early- to mid-70s, and none of the subjects had a history of stroke or any notes in their medical record suggestive of early cognitive decline. At this dedicated anticoagulation center, their INR was measured on a weekly or biweekly basis, as a result of which their average time spent in the therapeutic range of 2.0-3.0 was relatively high at nearly 70%.

The increased risk of dementia in patients with AF has previously been recognized. The association is stronger in patients under age 75 than in those who are older. But the mechanism has been unknown. Dr. Bunch and coinvestigators decided to test their hypothesis that the mechanism involves microbleeds secondary to long-term overanticoagulation by dividing the patients into three groups based upon their percentage of INR measurements above 3.0 during a mean follow-up of more than 4 and up to a maximum of 10 years: 240 patients had a supratherapeutic INR 25% of the time or more; 374 did so less than 10% of the time; and 417 had an elevated INR 10%-24% of the time.

Continued on following page

Continued from previous page

The incidence of dementia diagnosed by a consultant neurologist during follow-up was 5.8% in the group with an INR above 3.0 at least 25% of the time, more than twice the 2.7% rate in patients with a high INR less than 10% of the time. In the middle group, the incidence of dementia was 4.1%. In a multivariate Cox regression analysis, having an INR above 3.0 on at least 25% of occasions was independently associated with a 2.59-fold increased risk of developing dementia, making it by far the most potent risk factor.

The next step in their research will be to perform serial brain imaging and volumetric scans, Dr. Bunch said. Also, he and his coworkers are 3 years into an ongoing study looking at the incidence of dementia in AF patients on the various novel oral anticoagulants, where INR is a nonissue. Their hypothesis is the dementia risk will be lower than in patients on warfarin. Dr. Bunch has particularly high hopes for AF patients on apixaban (Eliquis) because it's known to have a reduced risk of large bleeds, stroke, and GI bleeding; the hope is it will cause fewer cerebral microbleeds as well.

DR. BUNCH

In an interview, the cardiologist said he believes his study showing an increased risk of dementia in AF patients with supratherapeutic INRs on warfarin plus antiplatelet therapy holds several important lessons for AF patients and physicians alike.

For patients, the message is don't just start taking aspirin on your own because you've read it's good for your heart or may reduce cancer risk; consult your physician.

And for physicians, it's important to ask all patients on warfarin if they're using aspirin; many don't ask. Also, periodically reconsider the need for dual therapy with warfarin and aspirin.

"We find the risks of stroke and bleeding change dynamically over time, so the initial therapy for stroke prevention may not be the ideal therapy after 5-10 years," Dr. Bunch said.

Lastly, for patients who are overanticoagulated on a substantial percentage of their INR measurements, it's essential to consider a change in strategy.

Either follow their INRs more closely and adjust warfarin dosing accordingly, or switch to one of the novel, more predictable oral anticoagulants, he concluded.

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Riociguat benefits hypertension subgroup

BY BRUCE JANCIN
Frontline Medical News

LAS VEGAS – Patients with pulmonary hypertension due to systolic left ventricular dysfunction show marked hemodynamic and quality of life improvements in response to oral riociguat if they have low baseline pulmonary vascular resistance, but not if their baseline pulmonary vascular resistance exceeds 240 dyn s/cm^5, Dr. Marc J. Semigran reported at the annual meeting of the Heart Failure Society of America.

This was the key finding of a prespecified secondary analysis of the Left Ventricular Systolic Dysfunction Association With Pulmonary Hypertension Riociguat Trial (LEPHT).

LEPHT was a phase-IIb, double-blind, placebo-controlled study in which 201 affected patients were randomized to 16 weeks of oral riociguat or placebo.

This previously reported study (Circulation 2013;128:502-11) did not meet its primary endpoint because patients on riociguat at 2 mg t.i.d. did not experience a significantly greater decrease in mean pulmonary artery pressure than with placebo. However, the researchers hypothesized that the response to riociguat would differ based upon baseline pulmonary vasomotor tone, and this hypothesis was testable in the secondary analysis, explained Dr. Semigran, medical director of the heart failure and transplantation program at Massachusetts General Hospital, Boston.

Riociguat (Adempas) is a first-in-class oral stimulator of soluble guanylate cyclase. It is approved for two indications: chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension, both of which are uncommon conditions.

The LEPHT study was part of an ongoing program to win an additional indication for a much more common condition: pulmonary hypertension caused by systolic left ventricular dysfunction.

For the analysis, Dr. Semigran and coworkers divided the LEPHT population into two subgroups: the 92 patients with a low baseline pulmonary vascular resistance (PVR) of 240 dyn s/cm^5, and 109 others with a PVR above that threshold. Ischemic etiology of heart failure and diabetes mellitus were both more common in the high PVR group.

While both groups showed a significant reduction in systemic vascular resistance over 16 weeks in response to riociguat at 2 mg t.i.d., only patients in the low baseline PVR group experienced significant reductions in pulmonary capillary wedge pressure (–6.55 mm Hg) and mean arterial pressure (–8.8 mm Hg). Moreover, improvements in stroke volume (+17 mL) and cardiac index (+0.6 L/min/m^2) in response to riociguat were confined to the low-baseline-PVR group.

The lower baseline PVR group may have less advanced disease, making them better candidates for therapy, he concluded.

The LEPHT study was sponsored by Bayer. As principal investigator, Dr. Semigran received a research grant from the company.

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Introducing a better bleeding risk score in atrial fib

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – The ORBIT-AF bleeding risk score is a simple, user-friendly new tool for assessing the risk of major bleeding in patients with atrial fibrillation on oral anticoagulation, Emily C. O'Brien, Ph.D., announced at the American Heart Association scientific sessions.

This novel score offers significant advantages over existing bleeding risk scores, including HAS-BLED and ATRIA. Those scores were developed on the basis of small numbers of bleeding events, they show inconsistent performance, and their calculation requires data that are often not readily accessible in busy daily practice, according to Dr. O'Brien of the Duke Clinical Research Institute in Durham, N.C.

The new score was derived from the ORBIT-AF registry, the largest prospective U.S. registry of patients with atrial fibrillation (AF).

The score was constructed using data on 7,411 AF patients in community practice settings at 173 U.S. sites. All subjects were on oral anticoagulant therapy at baseline. During 2 years of prospective follow-up, 581 patients (7.8%) experienced a major bleeding event as defined by International Society on Thrombosis and Haemostasis criteria.

After sifting through numerous potential candidate variables, Dr. O'Brien and her colleagues settled upon five they identified as the most potent and practical baseline predictors of major bleeding risk while on oral anticoagulation.

Then they packaged them in a convenient acronym: **ORBIT**, for **O**lder than 74, **R**enal insufficiency with an estimated glomerular filtration rate below 60 mL/minute per 1.73 m^2, **B**leeding history, **I**nsufficient hemoglobin/hematocrit or anemia, and **T**reatment with an antiplatelet agent.

The two strongest predictors – renal insufficiency and bleeding history – were awarded two points each; the others are worth one point each.

The observed major bleeding rate among patients enrolled in the ORBIT-AF registry rose with an increasing risk score.

The same was true upon application of the ORBIT bleeding score to an independent study sample comprised of participants in the ROCKET-AF randomized clinical trial.

Dr. O'Brien also compared the performance of the ORBIT bleeding score to that of two existing bleeding risk scores – HAS-BLED and ATRIA – in the ORBIT-AF and ROCKET-AF cohorts. The simpler, more user friendly ORBIT bleeding score had a C-statistic of 0.67, similar to the 0.64 for HAS-BLED and 0.66 for ATRIA.

Thus, the ORBIT bleeding score is a practical new tool for use alongside the CHA2DS2-VASc stroke risk score to support clinical decision making regarding whether or not to place an individual AF patient on oral anticoagulation, Dr. O'Brien concluded.

She reported having no financial conflicts regarding this study. The ORBIT-AF registry is sponsored by Janssen.

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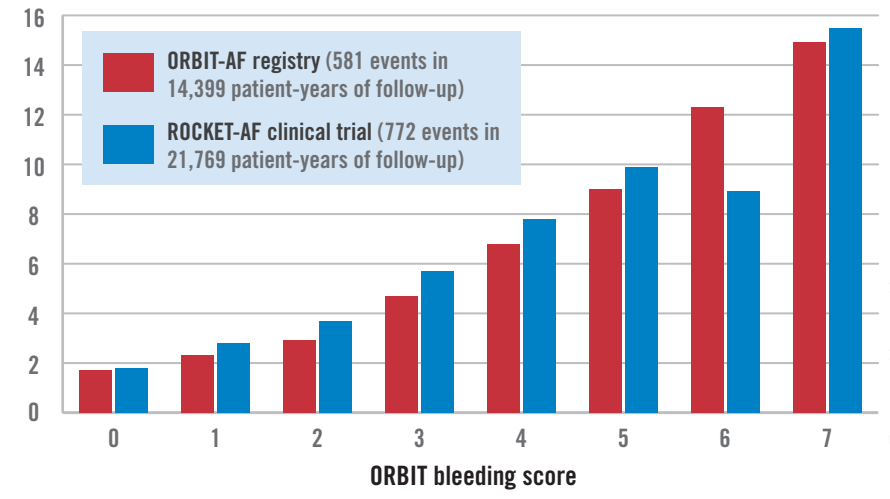
Major bleeding events per 100 patient-years



Note: The ORBIT-AF bleeding score was constructed using data from 7,411 patients.
Source: Dr. O'Brien

NETWORKS: Airways disorders, clinical research, critical care, diffuse lung disease

Airways Disorders

The changing paradigm of asthma management: biologics and beyond

More than 30% of asthmatics have poor response to treatments and 5%-10% have severe asthma that requires additional therapies. The last few years have seen a rise in publications on novel therapies for asthma. These include newer versions of inhaled therapies, biologics, nondrug therapy, and bronchial thermoplasty (BT).

IgE was the first molecule to be successfully targeted by monoclonal antibodies and led to FDA approval of omalizumab in 2003 for treatment of allergic asthma. Two studies published last year (*N Engl J Med*. 2014;371:1189) showed that anti-interleukin-5 antibodies (mepolizumab) decreased both the rate of asthma exacerbations and maintenance dose of systemic glucocorticoids in patients with uncontrolled eosinophilic asthma. Several other biologics targeting interleukin-13 (lebrikizumab), alpha-subunit of interleukin-4 receptor (dupilumab), and alpha-subunit of interleukin-5 receptor (benralizumab) are in different phases of investigation. Five-year follow-up of AIR2 trial evaluating BT showed sustained reduction in asthma exacerbations with an acceptable safety profile (*J Allergy Clin Immunol*. 2013;132[6]:1295). Additional work is being done to identify predictors of positive response to BT. Efforts are also underway to identify biomarkers, including IgE, FeNO [fractional exhaled nitric oxide], blood eosinophils, serum periostin, and YKL-40, which may guide individualized treatment in asthma.

DR. KHURANA

Indeed, personalized medicine has the potential to offer highly effective treatment with more favorable therapeutic risk-benefit profile in this difficult to treat population. If done right, it holds the promise of improved patient care and lower health-care utilization. Careful patient selection, however, remains key to achieving successful outcomes.

Dr. Sandhya Khurana, FCCP
Vice Chair

Clinical Research

Challenges in PAH research: time for a paradigm shift?

Pulmonary arterial hypertension is relatively rare, yet its impact on society is significant, killing patients at a productive age and at a tremendous financial cost. Thankfully, the care and the quality of life of patients with PAH have improved over the past 20 years, thanks to an explosion of knowledge from translational research and the advent of new therapeutic agents.

However, given the rarity of the disease, and the multiplicity of PAH WHO groups that are distinct from each other, recruitment of enough subjects in each group that would make current and future trial results meaningful and applicable to bedside, is a significant hurdle.

Many patients are impaired physically and find it difficult to travel from communities to PAH centers. Moreover, PAH experts may not trust the diagnostic findings of such community patients as they may be misdiagnosed or inappropriately started on PAH oral therapy. Among recent efforts to bridge the care gap, perhaps a new paradigm should emerge in which a "telemedicine" network would connect the community physicians to the PAH experts, thus allowing their patients to access trials and expertise without


DR. BENCHEQROUN

the need for geographic relocation. This would require a standardization of definitions, diagnostic and therapeutic modalities, aggressive education efforts, and reporting of results in a template manner. Investment from the industry to establish such an ambitious yet sorely needed endeavor would be a welcome collaboration. A desirable side benefit would also be to identify patients with early disease who could benefit from transplantation and optimize their care.

Dr. Hassan Bencheqroun, FCCP
Steering Committee Member

References

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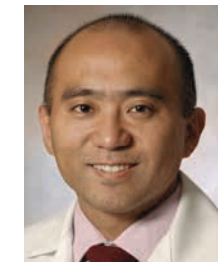
2. Sutendra and Michelakis. *Sci Translational M.* 2013;5 (208):1.
3. McLaughlin et al. *Chest.* 2013;143(2):324.
4. Corris and Degano. *Eur Respir Rev.* 2014;23(134):488.

Critical Care

Albumin in septic patients

NetWork steering committee members are participating in a pro/con debate for the journal *CHEST* regarding the intense debate for albumin resuscitation in critical illness. While there is agreement that in critically ill patients, serum albumin concentration is inversely related to risk of death, landmark papers challenged the value of infused albumin in that setting (*BMJ* 1998;317:235).

Recently, data suggest that albumin may benefit certain subgroups and reopened the debate. The SAFE study demonstrated albumin safety but no mortality benefit, as compared with saline in resuscitation in critically-ill patients (although a recent post hoc analysis suggested sicker patient survival [*N Engl J Med.* 2004;350(22):2247; *Intensive Care Med.* 2011;37:86]). A later study suggested that albumin administration is associated with improved organ function in critically ill patients, restricting positive fluid balance and leading to a better tolerance to enteral feeding (*Crit Care Med.* 2006;34[10]:2536).


DR. KAKAZU

Recently, the ALBIOS trial compared 20% albumin plus crystalloid to crystalloid alone in patients with severe sepsis or septic shock (*N Engl J Med.* 2014;370[15]:1412). Daily albumin administration was given for 28 days or until ICU discharge to maintain a serum albumin of 30 g/L. Primary endpoints showed no difference; however, there were significant improvements in mean arterial pressure, discontinuation of vasoactive drugs, and lower medi-

Continued on page 37

Sneak preview: Get a glimpse of our new membership structure

In May 2015, CHEST will transition from the current membership categories to a new structure that puts you in control of the value and benefits you derive. Currently, members belong to categories corresponding to title and stage of career. Under the new structure, you decide your membership level based on how you want to engage with CHEST.

The new structure will provide a rich array of benefits and value in three member categories:

Basic Membership

Annual dues: $295

Benefits:

- Online access to the journal *CHEST*
- Discounts for courses and products
- Free access to clinical practice guidelines
- CHEST Career Connection access
- Opportunity to join CHEST NetWorks
- Access to the e-Community portal

Enhanced Membership

Annual dues: $395

- All the benefits of Basic Membership
- Print access to the journal *CHEST*
- Opportunity to become/remain an FCCP
- Leadership opportunities
- Invitation to networking events

Premium Membership

Annual dues: $495

- All the benefits of Enhanced Membership
- Enhanced discounts
- Advanced access to course registration
- Advanced access to hotel reservations
- Invitation to VIP events

This new structure will take effect May 2015. The good news is you won't have to do anything. You will be placed into the category that best aligns with your current level of engagement.

Discounts on dues will be available for all clinicians-in-training, nonphysician/nondoctoral clinicians, retired clinicians, and chest physicians who live outside the United States or Canada.

If you decide you want more from membership, you can always upgrade to a higher category by calling CHEST Customer Support (224/521-9800).

Learn more about how this new membership structure will make your tomorrow greater than today by allowing you to collaborate more, engage more, and achieve more.

Find more information about the new membership structure at chestnet.org/tomorrow.

CHEST Clinical Trials Registry

Are you a clinical trials investigator with unused capacity? Would you like to refer patients to participate in ground-breaking clinical trials?

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

Ongoing groundbreaking research could have a measurable impact on patient care, but a lack of clinical trial participants is significantly slowing research and threatening the development of new treatments. Recruiting and retaining trial participants are the greatest challenges to developing the next generation of treatment options.

Participation in clinical trials provides an opportunity to advance and accelerate medical research and contribute to an improved health outlook for future generations.

You can use our registry to get immediate information on how you can be involved in a clinical trial.

For more information about the clinical trials registry, access chestnet.org/Guidelines-and-Resources/Clinical-Trials/Clinical-Trials-Registry.

This month in *CHEST*: Editor's picks

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

A Scoping Review of Patient Discharge From Intensive Care: Opportunities and Tools to Improve Care.
By Dr. H. T. Stelfox et al.

Is a Raised Bicarbonate, Without Hypercapnia, Part of the Physiologic Spectrum of Obesity-Related Hypoventilation?
By Dr. A. R. G. Manuel et al.

Factors Predictive of Airflow Obstruction Among Veterans With Presumed Empirical Diagnosis and Treatment of COPD.
By Dr. B. F. Collins et al.

Poetry in medical journals? You bet!

A recent issue of *The New Yorker* featured an article by Alastair Gee titled, "Ode on a Stethoscope," and provided background on a current trend in medical publishing – the inclusion of poetry in medical journals. Our own flagship journal, *CHEST*, has included a poetry section entitled "Pectoriloquy" since 2008, and is mentioned prominently in the article, as is *CHEST*'s poetry editor, Dr. Michael Zack. Access the article online (newyorker.com/tech/elements/ode-stethoscope?mbid=rss), and be sure to catch the poems published each month in *CHEST* at http://journal.publications.chestnet.org.

Continued from page 35

an cumulative net fluid balance in the albumin-given group. A post-hoc analysis of patients with septic shock showed significant improvement in 90-day mortality; however, since this was a post hoc analysis, further studies are needed to determine whether albumin has a potential benefit in patients with septic shock.

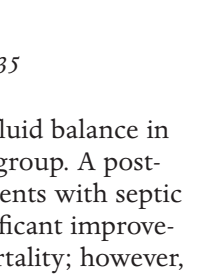
Dr. Maximiliano Tamae Kakazu
Steering Committee Member

Diffuse Lung Disease

New treatments for IPF: a word of caution

Following the announcement of the results of the ASCEND (*N Engl J Med.* 2014;370[22]:2083) and INPULSIS (*N Engl J Med.* 2014;370[22]:2071) clinical trials, the U.S. FDA-approved pirfenidone and nintedanib for use in idiopathic pulmonary fibrosis (IPF). Both trials enrolled a population with relatively mild disease, and the diagnosis was determined through a rigorous central review process.

Never before has diagnostic accuracy in IPF been so important, but translating processes established in academic centers and within the confines of a clinical trial may prove difficult for a busy community practitioner with limited access to experts in thoracic radiology or lung pathology.



DR. DE ANDRADE

Physicians must become familiar with the efficacy and safety data for each drug, as they will be managing their patients' expectations. Neither pirfenidone nor nintedanib are the cure for IPF. The main finding of both trials was a lower rate of decline in percentage forced vital capacity, which may be a difficult concept for some patients, particularly those with mild and stable disease. The safety profile of both drugs is acceptable but the commonly occurring GI side effects may cause negative impact in the quality of life of many.

Let's also keep in mind that IPF remains a progressive and unpredictable disease. The use of pirfenidone and nintedanib should not delay referrals to lung transplant programs and strategies such as pulmonary rehabilitation, and oxygen therapy should continue to be part of our arsenal. In summary: ensure proper and accurate diagnosis, become familiar with the potential benefits and limitations of each drug, educate your patients, and remember that there is still much work to be done!

Dr. Joao Alberto M. de Andrade, FCCP
Chair

So far, flu vaccine has been only 23% effective

BY DOUG BRUNK

Frontline Medical News

So far this flu season, more than two-thirds of influenza A (H3N2) viruses differ from the components of the 2014-2015 influenza vaccine. In addition, the overall estimated effectiveness of the 2014-2015 influenza vaccine for preventing laboratory-confirmed influenza infection is only 23%.

Those are key findings from an analysis of 2,321 children and adults who presented to one of five study sites in the United States with acute respiratory illness between Nov. 10, 2014, and Jan. 2, 2015.

"Although influenza vaccines are the best tool for prevention of influenza currently available, more effective vaccines are needed," wrote Brendan Flannery, Ph.D., of the Center for for Disease Control and Prevention's National Center for Immunization

and Respiratory Disease, and his associates (MMWR 2015;64:10-15). "Antiviral medications are an important adjunct in the treatment and control of influenza for the 2014-2015 season and should be used as recommended, regardless of patient vaccination status."

Targeted groups for antiviral treatment include any patient with suspected or confirmed influenza who is hospitalized, has severe or progressive illness, or is at high risk for complications from influenza, even if the illness seems mild.

"Persons at high risk include young children (especially those younger than age 2), pregnant women, persons with chronic medical conditions like asthma, diabetes, or heart disease, and adults aged 65 years and older," the researchers wrote. "Ideally, antiviral treatment should be initiated within 48 hours of symptom onset, when treatment is most effective."

Though spot shortages of Tamiflu and other antiviral drugs have been reported, the CDC investigators noted that it may be necessary to contact more than one pharmacy to fill a prescription.

Updates on the supply of antiviral drugs can be found at www.cdc.gov/flu/antivirals/supply.htm.

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Novel drug reduced hereditary angioedema attacks

BY BRUCE JANCIN
Frontline Medical News

AMSTERDAM – A targeted oral medication for the prevention of potentially life-threatening episodes of hereditary angioedema produced a clinically meaningful reduction in attack frequency in a double-blind, placebo-controlled phase II study.

"What these patients want is oral prophylaxis, and we've got proof of concept with this trial," said Dr. Marcus Maurer, who presented the results of OPuS-1 (Oral Prophylaxis for Hereditary Angioedema) trial at the annual congress of the European Academy of Dermatology and Venereology.

The investigational agent BCX4161 is a potent oral inhibitor of plasma kallikrein, which plays a key role in hereditary angioedema (HAE) by inducing vasodilation, edema, and non-vascular smooth muscle contraction.

OPuS-1 was a double-blind, randomized crossover study in which 24 patients with severe HAE were assigned to 4 weeks of BCX4161 at 400 mg or placebo three times daily, then switched to 4 weeks of the other regimen after a washout period. Participants averaged 42 years of age with a mean 32-year duration of HAE. At enrollment, they averaged 1.5 attacks per week, and they had a mean of 1.2 emergency department visits for HAE during the previous year. Twenty of the 24 patients had a history of one or more laryngeal attacks, the most serious manifestation of HAE, which eventually results in death by strangulation in roughly 30% of affected individuals, Dr. Maurer, professor of dermatology and allergy at Charité University Hospital in Berlin, said.

The primary outcome was the adjudicated attack rate, which was 1.27 attacks per week with placebo and a significantly lower 0.82 per week with BCX4161. Attack durations averaged 20-23 hours. Three patients were attack free on BCX4161; none was attack free during the placebo phase. OPuS-2, a larger 12-week trial, is planned. The OPuS trials are sponsored by BioCryst Pharmaceuticals. Dr. Maurer is a consultant to the company.

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observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

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

Effect on Growth

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

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

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

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma

Patients 12 years and older

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

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV$_1$ at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

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

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

* All treatments were administered as two inhalations twice daily.

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

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

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV$_1$ at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

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

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

* All treatments were administered as two inhalations twice daily.

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

Postmarketing Experience

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

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

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

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

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

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

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

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

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

Hospitalization for pneumonia raises CVD risk

BY MARY ANN MOON
Frontline Medical News

Among older adults, hospitalization for pneumonia raises the short-term (1-month) and long-term (10-year) risk of cardiovascular disease events to a degree comparable to those of smoking, diabetes, and hypertension, according to a report published online in JAMA.

"Our findings suggest that hospitalization for pneumonia should be considered an independent cardiovascular risk factor" and "should prompt clinical trials to test targeted strategies"' to prevent the disease in this patient population, said Dr. Vicente F. Corrales-Medina of the University of Ottawa and the Ottawa Hospital Research Institute.

The risk of cardiovascular disease (CVD) events within 30 days of severe infections, mainly those involving the respiratory tract, is well established, but the more lasting effects are uncertain.

In what the researchers described as "the first study to document the temporal variation in the long-term risk of CVD ... using rigorous methods to adjust for many potential confounders," they analyzed data from two multicenter population-based cohorts that were followed for 21 years.

The 591 participants in the Cardiovascular Health Study were 65 years of age or older and had been hospitalized for pneumonia. When researchers compared their outcomes to 1,182 matched controls without pneumonia, they found that in the pneumonia group the rate of CVD events was 4-fold higher at 30 days, dropped to 2-fold higher throughout the rest of the first year, and leveled out at 1.5-fold higher for the remainder of the decade.

In the pneumonia group, the rate of CVD events was 4-fold higher at 30 days and leveled out at 1.5-fold higher for the remainder of the decade.

Researchers verified the risk pattern in a cohort of 680 pneumonia patients aged 45-64 years and 1,360 matched controls in the Atherosclerosis Risk in Communities study.

The increased risk conferred by hospitalization for pneumonia persisted after the data were adjusted for demographic traits, preexisting CVD risk factors, and measures of patient frailty; it also was robust to numerous sensitivity analyses, the researchers said (JAMA 2015 Jan. 20 [doi:10.1001/jama.2014.18229]).

Moreover, the magnitude of risk conferred by hospitalization for pneumonia "was similar or higher, compared with the risk of CVD associated with traditional risk factors such as smoking, diabetes, and hypertension," the researcher wrote.

The Ottawa Hospital, the Ottawa Hospital Research Institute, and the Canadian National Institute of General Medical Sciences funded the study. Dr. Corrales-Medina reported having no financial disclosures.

Pulmonary edema common after convulsive seizure

BY SUSAN LONDON
Frontline Medical News

SEATTLE – Nearly a third of patients who experience a generalized convulsive seizure develop pulmonary edema, suggests a small cohort study reported at the annual meeting of the American Epilepsy Society.

The longer the seizure lasts, the higher the probability of pulmonary edema.

"There are a few theories about how pulmonary edema can develop" in this context, noted first author Dr. Jeffrey Kennedy of the UC Davis Health System in Sacramento. Neurogenic mechanisms, hypoxemia, and prolonged negative intrathoracic pressure have all been implicated.

As far as the clinical implications, "postictal pulmonary edema may play a role in the mechanisms of SUDEP (sudden unexpected death in epilepsy)," he proposed at the meeting.

"I think (pulmonary edema) just identifies patients who are at higher risk" for poor outcomes, he speculated. "In the EMU [epilepsy monitoring unit], when it comes to letting patients have more seizures, it does make us conservative as far as restarting medications and maybe trying to start giving them some benzodiazepines to try to shut things down."

One session attendee commented, "Some of my patients' relatives are very alarmed when the patient suffers severe cyanosis after a seizure. The first thing that our emergency staff will do when they arrive will be to clasp an oxygen mask over them. So our patients ask us, 'Please, will we provide them with oxygen?' I have a sneaking suspicion from your data that they may be justified in that."

Another study done by the UC Davis group looked at a variety of peri-ictal interventions and found simple nursing practices worked about as well as oxygen, according to Dr. Kennedy (Epilepsia 2013;54:377-82). "It seems like just doing something – stimulating the patient, turning them on their side – is enough, rather than just administering oxygen."

In an interview, session comoderator Dr. Amy Crepeau, a neurologist at the Mayo Clinic Arizona in Phoenix, said the observed incidence of pulmonary edema raises important questions: "Is this something we need to be more conscientious about and really intervene more closely? Should we be shortening the duration of time before we stop seizures and not letting them go as long? It seems as though they have done that at UC Davis – kind of limited the number of seizures that they allow patients to have in the epilepsy monitoring unit."

"This study comes back to this issue of who's at risk for SUDEP, what are the causes for SUDEP, and what are

DR. CREPEAU

the interventions we can use to try to prevent that or lessen the risk for it," Dr. Crepeau added. "We are looking forward to seeing whether these patients have any increased risk of SUDEP that associates with the pulmonary edema."

Dr. Kennedy and his colleagues studied 24 consecutive adult patients, mean age 32 years, who experienced generalized convulsive seizures while undergoing monitoring in the UC Davis EMU, where all patients with such seizures receive a chest x-ray soon afterward as a safety measure.

Overall, 29% of the patients had pulmonary edema, with or without focal infiltrates, on their chest x-ray, and another 17% were found to have focal infiltrates only.

The mean time elapsed between the seizure and the chest x-ray acquisition was 225 minutes in the patients with abnormal findings and 196 minutes in the patients with normal findings, a nonsignificant difference, reported Dr. Kennedy, who disclosed that he had no relevant conflicts of interest.

The seizure duration was more than twice as long among patients with chest x-ray abnormalities as among counterparts without these abnormalities (250 vs. 101 seconds; $P = .002$), and the probability of abnormalities increased with seizure duration.

The groups with and without chest x-rays abnormalities did not differ with respect to a variety of demographic and cardiorespiratory and other clinical factors.

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OSA 'advantage' for ventilated pneumonia patients

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Obstructive sleep apnea appeared to provide protection against in-hospital mortality and nonroutine discharge among mechanically ventilated patients with pneumonia who were included in the National Inpatient Sample from 2009 to 2011.

Patients included in the analysis were 20,652 adults with a mean age of 65 years who were hospitalized with a primary diagnosis of pneumonia requiring invasive mechanical ventilation, representing nearly 107,000 such discharges nationally.

About 8% of the patients had obstructive sleep apnea (OSA), and 11% were obese. Overall mortality was 31%, and the overall rate of nonroutine discharge, defined as discharge to a skilled nursing facility or to home with home health care, was 84%, Dr. Charlisa Gibson reported at the annual meeting of the American College of Chest Physicians.

Though limited by its retrospective nature and possible underreporting of OSA, this study demonstrates that OSA in patients with pneumonia requiring invasive mechanical ventilation confers a survival benefit, she said.

Those with OSA had a significantly higher rate of tracheostomy (9.2% vs. 8.3%), a lower rate of in-hospital mortality (19% vs. 31%), and a lower rate of nonroutine discharge (77% vs. 84%), compared with non-OSA patients. Length of stay was about 14 days in both groups, said Dr. Gibson, of Mount Sinai St. Luke's-Roosevelt Hospital, New York.

Those in the non-OSA group had higher rates of shock and septicemia. After adjustment for age, sex, obesity, comorbidities, and disease severity, OSA was a significant predictor of decreased in-hospital mortality (odds ratio, 0.74) and nonroutine discharge (odds ratio, 0.73), Dr. Gibson said.

"In pretty much all of the conditions of interest we looked at, we consistently saw that mortality was lower in the OSA group, whether they were obese or not … and whether or not they were deemed to have a low, moderate, or severe [Charlson Comorbidity Index]," she said.

OSA is an important and likely underdiagnosed comorbidity in hospitalized patients, and pneumonia remains a significant infectious cause of morbidity and mortality in hospitalized patients, she said. OSA affects about 5%-24% of the general population, but the percentage of hospitalized patients with OSA is uncertain. About 20% of hospitalized patients with pneumonia end up in the intensive care unit for supportive treatment with mechanical ventilation.

"Once they are vented, there are data to suggest that early tracheostomy may shorten time on mechanical ventilation and hospital length of stay, but whether or not there's an actual impact on mortality is controversial," she said.

While prospective randomized controlled studies are needed to better identify risk factors for mortality in these patients, Dr. Gibson said there are several possible explanations for the findings of a protective effect of OSA in hospitalized patients with acute respiratory failure due to pneumonia.

First, non-OSA patients had more septicemia and shock, which suggests they may have had multisystem organ failure and required treatments like renal replacement therapy that independently increased their risk of mortality.

Also, the increased incidence of tracheostomy in the OSA patients may indicate that clinicians were more aggressive in treating patients with OSA, and that those patients may have benefited from earlier tracheostomy, she said.

There is some evidence to suggest that OSA patients have additional coronary collateral circulation, which means that they may have less severe cardiac injury because of this adaptation, and thus may have a lower risk of experiencing a fatal heart attack, compared with non-OSA patients, she explained.

The "obesity paradox" might also work in OSA patients' favor, she said.

There is some evidence that obese patients have increased metabolic reserve that results in lower complication rates, compared with normal weight patients.

"However, we do recommend that regardless of what the reason is, when these patients do come to the unit we should be aggressive and treat them with invasive mechanical ventilation if needed," she said.

VITALS

Key clinical point: Pneumonia patients with OSA who require mechanical ventilation have a survival advantage, but should still be treated aggressively.

Major finding: OSA was a significant predictor of in-hospital mortality and nonroutine discharge (odds ratios, 0.74 and 0.73).

Data source: A retrospective analysis of data from 20,652 patients in the National Inpatient Sample.

Disclosures: Dr. Gibson reported having no disclosures.

Kidney function declines faster with high risk of OSA

BY SHARON WORCESTER
Frontline Medical News

PHILADELPHIA – Patients with type 2 diabetes, chronic kidney disease, and a high risk of obstructive sleep apnea have more rapid loss of kidney function than do similar patients with a low risk of sleep apnea, findings from a retrospective cohort study suggest.

Of 56 patients with diabetic nephropathy who underwent screening for obstructive sleep apnea, 34 (61%) were at high risk. Compared with 22 patients with a low-risk score, the high-risk patients had a significantly greater loss of estimated glomerular filtration rate over time (median loss of –3.4 vs. 1.5 mL/min per 1.73 m^2 per year for the high- vs. low-risk patients, respectively), Dr. Roberto Pisoni reported in a poster at the annual meeting of the American Society of Nephrology.

This finding was despite comparable blood pressure for the high- and low-risk groups (systolic: 141.7 and 143.7 mm Hg; diastolic: 72.0 and 72.4 mm Hg, respectively), proteinuria upon admission to a chronic kidney disease clinic (urinary protein/creatinine ratio, 1.9 and 1.6 g/g, respectively), and time spent in clinic (1.9 vs. 2.1 years, respectively), said Dr. Pisoni, who is with the Medical University of South Carolina, Charleston.

Of 56 patients with diabetic nephropathy who underwent screening for obstructive sleep apnea, 34 (61%) were at high risk.

Patients in the high- and low-risk groups also had similar baseline gender, body mass index, use of renin-angiotensin-aldosterone system blockers, eGFR, and co-morbidities, he noted.

Data used for this study were from the University of Alabama at Birmingham Chronic Kidney Disease Database.

Patients had completed the Berlin questionnaire to assess for sleep apnea during a 9-month study period.

Obstructive sleep apnea is common in patients with type 2 diabetes and is also associated with glomerular hyperfiltration and proteinuria in patients with normal renal function, which raised the question of whether it might be related to chronic kidney disease progression, Dr. Pisoni explained.

He noted that the association between obstructive sleep apnea and diabetic nephropathy has not been fully investigated.

The study demonstrated that the "simple approach" of assessing obstructive sleep apnea risk identifies patients who are also at increased risk of CKD progression, he said.

The findings of this study require replication in a prospective cohort.

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