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The SAT performance rate increased from 30% to 70%, and the SBT performance rate increased from 55% to 70%.

Awakening trials cut ventilator events

BY SHARON WORCESTER
Frontline Medical News

PHILADELPHIA – A protocol for coordinated daily spontaneous awakening trials and spontaneous breathing trials was associated with significant reductions in hospital length of stay and ventilator-associated events in a multicenter quality improvement collaborative nested within a prospective study of ventilator-associated events.

The protocol led to significant increases – after adjustment for age, sex, Sequential Organ Failure Assessment score, reason for intubation, comorbidity score, and unit ID – in spontaneous awakening trials (SATs), spontaneous breathing trials (SBTs), and in the percentage of SBTs done without sedation among 3,425 episodes and 22,991 days of mechanical ventilation in the collaborative units, Dr. Deverick Anderson of Duke University Medical Center, Durham, N.C., reported at an annual scientific meeting on infectious diseases.

The SAT performance rate increased from 30% to 70% during the course of the study, and the SBT performance rate increased from about 55% to nearly 70%. The performance rate of SBTs done with sedatives off – an intervention that improves the ability to be ex-

See **Awakening trials** • *page 6*

LAMA/LABA may allow withdrawal of inhaled steroids

An option in severe but stable COPD.

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Inhaled corticosteroids can be successfully withdrawn without increasing the risk of exacerbations in patients who have chronic obstructive pulmonary disease and are receiving dual bronchodilator therapy with a long-acting muscarinic antagonist and a long-acting beta$_2$-agonist, according to findings from the WISDOM study.

However, inhaled corticosteroid (ICS) withdrawal should be conducted with caution, as a small but statistically significantly greater decrease in lung function occurred in patients who withdrew completely, compared with those who did not during the 12-month, double-blind, parallel-group study, Dr. Helgo Magnussen reported at the annual meeting of the American College of Chest Physicians.

"In patients with severe but stable COPD who are receiving combination therapy with tiotropium, salmeterol and ICS, a stepwise withdrawal of ICS was noninferior to continuation of ICS with respect to the risk of moderate or severe

See **COPD** • *page 5*

CDC predicts severe flu season

BY SHARON WORCESTER
Frontline Medical News

The 2014-2015 flu season may be particularly severe, and the 2014-2015 vaccine will provide important, but limited protection, according to a health advisory from the Centers for Disease Control and Prevention that is based on early analyses of reported disease cases.

The advisory also stresses the importance of antiviral treatment in those with confirmed or suspected influenza, particularly those at risk of developing complications, including young children, adults aged 65 years and older, pregnant women, and those with chronic health conditions, such as asthma, diabetes, or heart, lung, or kidney disease.

Influenza A viruses, mainly H3N2, predominate thus far during the 2014-2015 flu season, comprising more than 91% of the specimens collected and analyzed, and only about half of those have been antigenically sim-

See **CDC** • *page 5*

INSIDE

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Indication

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

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet 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.

InterMune®
Leader in IPF

Esbriet®
pirfenidone capsules 267 mg

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Disorders

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

Postmarketing Experience

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

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

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

DRUG INTERACTIONS

CYP1A2 Inhibitors

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

Strong CYP1A Inhibitors

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

Moderate CYP1A Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

CYP1A2 Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

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

Renal Impairment

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

Smokers

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Events

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

Smokers

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

Take with Food

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

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

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

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ICS withdrawal

COPD *from page 1*

exacerbations. Despite this, if you do [withdraw ICS] – and we believe you can try to withdraw ICS – please observe the symptoms and lung function, because we found this signal [for decreased lung function]," he said.

Study subjects were 2,485 adults over age 40 years with severe or very severe COPD and a history of exacerbations.

All patients received triple therapy with the long-acting muscarinic antagonist (LAMA) tiotropium at 18 mcg four times daily, the long-acting beta$_2$-agonist (LABA) salmeterol at 50 mcg twice daily, and the ICS fluticasone at 500 mcg twice daily for a 6-week run-in period.

The patients were randomized to continue the triple therapy or to undergo ICS withdrawal over 12 weeks, with a dose reduction every 6 weeks.

ICS withdrawal met the prespecified noninferiority criterion of 1.20 for the upper limit of the 95% confidence interval, compared with continued ICS with respect to moderate or severe COPD exacerbation (hazard ratio, 1.06), but the adjusted mean reduction from baseline in the trough forced expiratory volume in 1 second (FEV_1) at week 18 was 38 mL greater in the ICS withdrawal group, said Dr. Magnussen of the Pulmonary Research Institute at Lung Clinic Grosshansdorf (Germany), Airway Research Center North.

A similar between-group difference of 43 mL was seen at week 52, Dr. Magnussen said.

He noted that this did not differ significantly from the difference seen at week 18, demonstrating that there is no further decline in lung function after complete ICS withdrawal at week 18.

Also, the decline in lung function – even at the peak decrease in function at week 18, was not associated with an increase in dyspnea.

The difference in change from baseline in the modified Medical Research Council (mMRC) dyspnea scale was nonsignificant for ICS withdrawal, compared with ICS continuation at week 18 or week 52.

The change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score was 0.55 with ICS withdrawal, compared with –0.42 with ICS at week 27, and 1.15, compared with –0.07 for withdrawal vs. continuation, respectively, at week 52. This difference, though statistically significant, was not considered clinically relevant, Dr. Magnussen said.

VITALS

Key clinical point: Dual bronchotherapy might allow some COPD patients to stop using inhaled corticosteroids.

Major finding: There was no difference with respect to COPD exacerbations (HR, 1.06) in LAMA/LABA users who discontinued and those who remained on inhaled corticosteroids.

Data source: The WISDOM study of 2,485 adults with COPD.

Disclosures: This study was funded by Boehringer Ingelheim. Dr. Magnussen reported receiving consultant fees and/or serving on a speakers bureau or advisory committee for Almirall, Boehringer Ingelheim, Chiesi, Berli-Chemi, and Novartis. His employer, the Pulmonary Research Institute, received payments for the conduct of this study.

ICS treatment is recommended along with long-acting bronchodilators in patients with frequent exacerbations of severe COPD, but the benefits of ICS use in addition to dual bronchodilator therapy have not been fully elucidated, he said.

The findings of the WISDOM study (N. Engl. J. Med. 2014;371:1285-94), suggest that ICS discontinuation is possible, Dr. Magnussen concluded.

Severe flu season predicted

CDC *from page 1*

ilar to H3N2 components included in the 2014-2015 vaccine, according to the advisory.

This doesn't bode well for the effectiveness of the vaccine, which is troubling given that H3N2-predominate seasons historically have been associated with up to twice the rate of overall and age-specific flu-related hospitalizations and deaths, CDC director Dr. Thomas R. Frieden explained during a press briefing.

Still, vaccination remains the best line of defense against infection, he said. The vaccine will protect against circulating strains that have not undergone significant antigenic drift, including the influenza B viruses, which have comprised about 9% of those collected to date. In addition, the vaccine has been found to provide some protection against the antigenically drifted H3N2 viruses.

"We continue to recommend flu vaccine as the single best way to protect yourself against the flu," he said.

Dr. Frieden also stressed the importance of antiviral use.

"Antivirals aren't a substitute for vaccinations … but they are an important second line of defense for treating the flu, and this year, treatment with antiviral drugs is especially important, particularly for people who are at high risk for serious flu complications or for people who are very sick with flu," he said.

These agents are greatly underprescribed, with fewer than one in six severely ill patients receiving antiviral treatment, he noted.

"It's very important that we do better for people who are severely ill or who could become severely ill with influenza," he said, adding that antiviral use is even more important during seasons such as this one when the circulating viruses are different from the vaccine viruses.

The two neuraminidase inhibitor antiviral medications currently approved for treating influenza – oseltamivir and zanamivir – shorten the duration of fever and illness symptoms by about a day and can reduce the risk of severe outcomes, he said.

Treatment should be provided within 2 days of symptom onset when possible, but it may also provide benefit if taken later in the course of illness.

"We strongly recommend that if doctors suspect the flu in someone who may be severely ill from the flu, they don't wait for the results of a flu test before starting antivirals," he said.

"There is no way to predict with certainly what will happen. We have four different strains of flu circulating. The B strain, the H1 strain, the well-matched H3 strain, and the poorly matched H3 strain. Only time will tell which of them, if any, will predominate for the coming weeks and months of this year's flu season."

However, already this season there have been five pediatric deaths from influenza, including three in patients with H3N2 disease, and one in a patient with influenza type B.

"We've also heard of outbreaks in schools and in nursing homes," Dr. Frieden said, adding that "getting a vaccine, even if it doesn't provide as good protection as we would hope, would be more important than ever, and remains the single most effective way to protect against the flu."

Physicians should continue to vaccinate patients, he said, noting that nearly 150 million doses have been distributed by manufacturers, and that the supply is expected to meet the demand.

The supply of antiviral medications is also expected to be adequate.

Patients should also be advised to stay home when they are sick to avoid spreading influenza, and to seek treatment promptly for flu symptoms, including fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills, and fatigue, he said.

VIEW ON THE NEWS

Dr. Daniel R. Ouellette, FCCP, comments: "Every time I take the vaccine, I get the flu. Besides, it doesn't work this year. I heard it on the news."

Sheila, a woman in her 50s with asthma, responded to my advice to be inoculated with the influenza vaccine this fall with this refrain. Refrain indeed, because my patients sing this song on a daily basis. Simply telling them that I know that the vaccine doesn't cause the flu isn't effective. Responding with an anecdote about patients who have been under my care in the ICU, who were previously healthy, and who died of influenza, works better. Following this with the statement that 'I make sure that I get vaccinated every year' seems to work the best.

And yet, there is some truth to the statement above. The CDC has informed us that not all strains of influenza will be covered by this year's version of the vaccine. Despite this, our patients will have increased protection by getting vaccinated, and we must be advocates for this measure. However, we also must be vigilant this year so that we may identify influenza cases early, and start antiviral treatment when appropriate, to limit the effects of this disease.

Ventilator-associated events

Awakening trials *from page 1*

tubated – increased from nearly 55% to more than 95%.

The mean duration of mechanical ventilation decreased by 2.4 days, mean ICU stay decreased by 3 days, and mean hospital length of stay decreased by 6.3 days, he said at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

Ventilator-associated conditions and infection-related ventilator-associated complications significantly decreased (odds ratio, 0.63 and 0.35, respectively); however, there was no decrease in possible or probable pneumonia (OR, 0.51).

Self-extubations increased (OR, 2.1, but there was no change in reintubations within 24 hours (OR, 0.96), Dr. Anderson said.

"We were able to show a decrease in our rates of VAEs [ventilator-associated events] per 100 episodes. Over the course of the entire study, we calculated a 37% decrease in the risk of VAEs," he said.

However, the number of VAEs per 1,000 days didn't change, because both the denominator and the numerator changed with the intervention. Based on the findings, it appears that ventilator episodes, rather than ventilator days, might be the best denominators, he said.

The study was done at 12 adult ICUs at seven hospitals participating in the Centers for Disease Control and Prevention's Prevention Epicenters Wake Up and Breathe Collaborative between November 2011 and May 2013.

The collaborative was designed to prevent VAEs by decreasing patients' sedative and ventilator exposures. It was developed after early 2013 when the CDC replaced its ventilator-associated pneumonia (VAP) definitions with VAE definitions, expanding surveillance to VAEs in an effort to improve the objectivity of the definitions, to improve the ease of performing surveillance, and to improve the ability to make interhospital comparisons, Dr. Anderson said, adding that VAEs include VAP, but also include pulmonary edema, atelectasis, and acute respiratory distress syndrome.

Thus, interventions aimed simply at reducing VAP may not change the rate of VAEs, he said.

Patients with VAEs stay on ventilators longer, stay in the ICU longer, are exposed to more antibiotic, and have two- to threefold increased rates of mortality, compared with those on ventilators but without VAEs, but little is known about preventing VAEs.

A larger study suggested that a third of cases were preventable, but no intervention has been tested and found to have an effect on the rate of VAEs. The Wake Up and Breathe Collaborative was tasked with answering the question of whether VAEs are preventable; the researchers thought the best opportunity for prevention was to decrease the amount of sedation that ventilated patients received, Dr. Anderson said. "More specifically – to decrease sedation through daily SATs and SBTs."

The opt-out protocol called for SATs and SBTs in all ventilated patients unless they met specific safety criteria or a physician wrote a specific opt-out order.

Though limited by the quasi-experimental open label study design, the findings are consistent with those from prior studies of such protocols.

"We felt that our multicenter prospective collaborative study was a success. … putting it all together, we conclude that VAEs are preventable when we improve compliance with evidence-based practice for our ventilated patients," he said.

Dr. Anderson reported receiving royalties from UpToDate and research support from the CDC and the National Institutes of Health/National Institute of Allergy and Infectious Diseases.

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: The results of this collaborative underscore an important point in patient-focused care, namely that participation of the patient in his or her own care is often able to accelerate a patient's recovery. It seems that with a protocol for coordinated daily spontaneous awakening trials, patients were more likely to be able to have success with a spontaneous breathing trial. A more awake state enables the patient to have a stronger cough, do a better job of clearing secretions, and take deeper breaths. In this study, these interventions resulted in a reduction in mechanical ventilator days, a reduction in ICU days, and a decrease in mean hospital length of stay. The partnership between patient, physician and care team has enhanced the care delivery and improved health in many chronic conditions. With the current focus on population health, engaging patients in improving their health will be a win for all. As care providers, we should continue to look for every opportunity to engage our patients to participate actively in their health care.

IN THIS ISSUE

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New faces: *CHEST Physician* board and sections

Editor in Chief

Dr. Vera A. De Palo, MBA, FCCP, is the new Editor in Chief of *CHEST Physician*. She is the Chief Medical Officer at Signature Healthcare in Brockton, Massachusetts. Signature Healthcare, in affiliation with Beth Israel Deaconess Medical Center of Boston, which is a not-for-profit teaching hospital that serves the greater Brockton area and its surrounding communities. Dr. De Palo is also an Associate Professor of Medicine at the Warren Alpert Medical School of Brown University, in Providence, Rhode Island. Her clinical practice experience is in pulmonary, critical care and sleep medicine.


DR. DE PALO

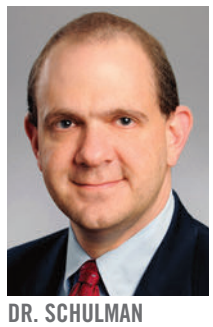
Dr. De Palo has served the American College of Chest Physicians (CHEST) in numerous leadership roles, including serving on the Board of Regents and on the Executive Committee of the Board of Regents during her term as the Chair of the Council of Governors and as a Trustee of the CHEST Foundation. Through the years, she has been a member of the Nominating Committee, the Government Relations Committee, the Chairperson of the Credentials and Membership Committees, and has served as the College's Governor for Rhode Island.

Dr. De Palo has been a member of the CHEST Foundation's Pro Bono Committee and Humanitarian Awards Review Committee. She has participated in and had leadership roles with many other national societies and local health-care groups, including the American Thoracic Society and the Society of Critical Care Medicine.

Dr. De Palo's current interests include quality and safety in health care – specifically in critical care, health care reform, and systems transformation.

Deputy Editor

Dr. David Schulman, FCCP, is the new Deputy Editor of *CHEST Physician*. He is an Associate Professor of Medicine at Emory University School of Medicine, Atlanta; he also serves as Associate Division Director for Education for Pulmonary, Allergy, and Critical Care Medicine and Director of the Pulmonary and Critical Care Medicine Fellowship Training Program.


DR. SCHULMAN

Dr. Schulman serves CHEST as Vice Chair of the ACCP Council of NetWorks and has served as member of the CHEST Scientific Program Committee for 4 years. His academic interests are in developing novel educational curricula and in identifying optimal management strategies for patients with mild sleep-disordered breathing.

New Section Editors
Critical Care Commentary


DR. MORROW

Dr. Lee E. Morrow, FCCP, is Professor of Medicine and Professor of Pharmacy at Creighton University as well as the Pulmonary & Critical Care Fellowship Program Director at the university in Omaha, Nebraska. Dr. Morrow joined the American College of Chest Physicians (CHEST) in 1999 and previously served as the ACCP Governor for Nebraska. Dr. Morrow's research interests focus on nosocomial infections and have previously been recognized by the College with two Alfred Soffer Research Awards, a Young Investigator Award, and an ACCP-ASP Geriatric Grant.

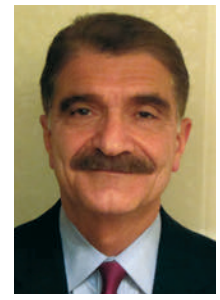
Sleep Strategies

Dr. Jeremy Weingarten, FCCP, is an Assistant Professor of Clinical Medicine at Weill-Cornell Medical College, New York, as well as the Chief of the Division of Pulmonary, Critical Care, and Sleep Medicine at New York Methodist Hospital (NYM). Dr. Weingarten also is the Medical Director of the Center for Sleep Disorders at NYM in Brooklyn, New York. He is a current member of the Sleep NetWork Steering Committee at CHEST. His clinical and research interests are in sleep medicine, pulmonary physiology, and chronic obstructive pulmonary disease.


DR. WEINGARTEN

New Editorial Board Members

Dr. Hossein Almassi, FCCP, is Professor of Cardiothoracic Surgery at the Medical College of Wisconsin in Milwaukee. He joined the American College of Chest Physicians (CHEST) in 1987 and served as the Governor for Wisconsin for two terms. He has been a member of the Critical Care Council, Scientific Presentation and Awards Committee, Scientific Program Committee, Chair of the Credentials Committee, and Vice Chair and Chair of the Cardiovascular Medicine and Surgery NetWork. His clinical and research interests are in multicenter trials in patients' outcome, atrial fibrillation, and critical care in cardiac surgery.


DR. ALMASSI

Dr. Jacques P. Fontaine, FCCP, is an Associate Professor at the University of South Florida, in Tampa. He works as a thoracic surgeon in the Departments of Thoracic and GI Oncology at the H. Lee Moffitt Cancer Center in Tampa. He is the Director of the Mesothelioma Treatment & Research Center. He has also been active in developing the robotic surgery program at the H. Lee Moffitt Cancer Center. His interests include robotic surgery, lung cancer screening, mesothelioma, thymoma, and resident education.


DR. FONTAINE

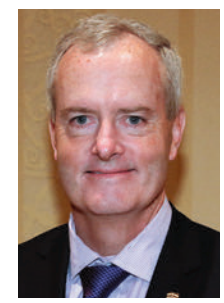
Dr. Octavian C. Ioachimescu, PhD, FCCP, is an Associate Professor of Medicine at Emory University, in Atlanta, Georgia; staff physician, Medical Director of the Sleep Medicine Center and Sleep Medicine Section Chief at the Atlanta Veterans Affairs Medical Center (VAMC), and the site director of the Emory University Sleep Medicine Fellowship. He is the incoming President of the Georgia Association of Sleep Professionals (GASP) and the Chair of the Clinical Pulmonary Medicine Steering Committee. He is passionate about medical education in pulmonary, critical care, and sleep medicine, and was recently inducted into the Emory University Academy of Medical Educators. His research interests include airway disorders, pulmonary physiology, and obstructive sleep apnea. Dr. Ioachimescu is the editor of the first online textbook of Sleep Medicine, entitled "Contemporary Sleep Medicine." He is the VAMC Sleep Medicine Center Medical Director and Sleep Section Chief.


DR. IOACHIMESCU

Dr. Jason M. Lazar, FCCP, is Professor of Medicine at the State University of New York Downstate Medical Center, New York, where he serves as the Director of Noninvasive Cardiology and Director of the Cardiovascular Training Program. He joined CHEST in 1990 and has served as Chair of the Cardiovascular NetWork and more recently as New York State Governor. Dr. Lazar's clinical interests include pulmonary hypertension in multisystem disease and multimodality imaging of cardiovascular disease. His research interests include ventriculoarterial coupling, cardiovascular manifestations of HIV and rheumatologic disorders, and assessment of micro- and macrovascular function.


DR. LAZAR

Dr. Michael E. Nelson, FCCP, works in Shawnee Mission, Kansas, where he practices pulmonary, critical care and sleep medicine. He has been a member of CHEST since 1989 and has served in many positions, which include the Governor for Kansas, the Practice Management Committee, the CHEST Regulations and Reimbursement Committee, the steering committee of the Private Practice and Practice Operations NetWorks, and the Board of Trustees of the CHEST Foundation. He is the ACCP alternate adviser to the AMA CPT editorial panel. Dr. Nelson's interests include pulmonary physiology, obstructive lung disease, and practice management.

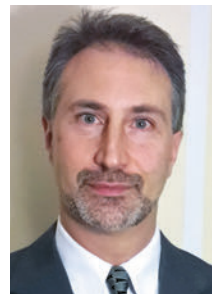

DR. NELSON

SLEEP STRATEGIES: The circadian system and its dysfunctions

BY DR. BORIS DUBROVSKY AND DR. LIZIAMMA GEORGE, FCCP

The human circadian system (from Latin "circa diem" or "about a day") internally generates daily physiologic and behavioral variations with a period slightly longer than 24 hours. Its master pacemaker is the suprachiasmatic nucleus (SCN) of the hypothalamus, whose function is based on the oscillating expression of several genes (termed the clock genes). The SCN regulates melatonin secretion, body temperature changes, and sleep rhythms via projections to other hypothalamic nuclei and the superior cervical ganglion innervating the pineal gland (*Reuss Cell Tissue Res.* 1996;285[3]:353; Vitaterna et al. *Alcohol Res Health.* 2001; 25[2]:85).

Because the normal daily rhythm is slightly longer than 24 hours, the circadian cycle is synchronized with the environment by cues called Zeitgebers (from German "time givers"). Light is the primary Zeitgeber and affects the circadian system via retinal projections to the SCN and related nuclei. Its immediate effect involves expression of several clock genes in the SCN and other neural structures resulting in melatonin regulation. The lasting effect of light is either entrainment (ongoing synchronization between the internal pacemaker and the environmental time) or phase shift (adjustment of the circadian system to a different time). The effect of light depends on the circadian time of exposure, as described by a phase-response curve (PRC). During the subjective evening and early night, light produces phase-delay, shifting the circadian rhythms to a later time relative to the external clock. During the late subjective night and early morning, light produces phase-advance, a circadian shift to an earlier time. The switch from delay to advance occurs in the middle of the night, at the core body temperature minimum. During the subjective day, light has little effect on the circadian phase (Golombek et al. *Physiol Rev.* 2010;90[3]:1063).


DR. DUBROVSKY

Among nonphotic Zeitgebers, melatonin has been studied most extensively. Melatonin production by the pineal gland, governed by the SCN, is an important output of the circadian system that helps regulate body temperature and sleep-wake cycles. Melatonin levels rise in the evening, stay relatively high throughout the night, and drop to low daytime levels in the morning. Exogenous melatonin affects the circadian system according to a PRC that is the opposite of light: in the evening it produces phase-advance, and in the morning, phase-delay (Lewy et al. *Chronobiol Int.* 1998;15[1]:71).

Circadian Rhythm Disorders

Clinically, a complaint of poor sleep may be related to one of the six circadian rhythm disorders. Four of them represent endogenous circadian dysfunctions: delayed sleep-wake phase disorder (DSWPD), advanced sleep-wake phase disorder (ASWPD), irregular sleep-wake rhythm disorder (ISWRD), and the non-24-hour sleep-wake disorder (N24SWD). Patients with DSWPD, more frequently represented by adolescents and young adults, are unable to sleep until well past midnight and have severe difficulty waking up for morning commitments. When allowed to maintain bedtime schedule consistent with the endogenous sleep propensity, eg, on vacation, patients typically fall asleep quickly, sleep continuously, and wake up spontaneously feeling refreshed.

ASWPD, more often seen in older adults, is characterized by the opposite pattern of overwhelming sleepiness in the early evening and waking up fully alert in the wee hours.

ISWRD is often associated with dementia and developmental disorders of childhood and may also be seen in disabled individuals spending most of their time reclining indoors. Patients with this disorder lack a consolidated sleep episode and instead take multiple naps at various intervals throughout the 24-hour period. N24SWD frequently afflicts patients with blindness or retinal damage and is characterized by a continuous drift of the sleep-wake cycle that results in periods of nocturnal insomnia and daytime sleepiness alternating with periods of relatively normal sleep.

Critical illness and treatment in the ICU can cause ISWRD and N24SWD due to excessive noise, continuous care schedules, and medications. The other two disorders, shift work and jet lag, are caused by a schedule that is out of synch with the person's biological clock (Fahey et al. *Psychiatr Clin N Am.* 2006;29[4]:989).

Evaluation and Management

While presentation may be different, evaluation and management tools are often similar. Clinical history targeting the sleep-wake pattern may be supplemented by the Morningness-Eveningness Questionnaire. Sleep logs, filled out daily by the patient, provide valuable information about sleep patterns before and during treatment and should be collected routinely at follow-up.

Sleep studies are not recommended for circadian rhythm disorders unless a comorbid condition is suspected. However, a 2-week actigraphic evaluation of the rest-activity cycle is useful for gaining insight into the patient's behavior and ascertaining treatment outcomes. Treatment techniques include establishing a consistent bedtime schedule, timed exposure to bright light outdoors or via a specially designed light box, and timed melatonin administration (Morgenthaler et al. *Sleep.* 2007;20[11]:1445).

For a patient with DSWPD, the best starting point is typically the patient's endogenous sleep propensity. Going to bed several hours earlier than the subjective sleep time only increases dysphoria associated with staying awake in bed; therefore, a later bedtime is initially recommended as a way to shorten the time to fall asleep.

Similarly, light should be given close to the patient's natural wake-up time, as giving it at the "normal" wake-up time several hours earlier may result in the phase-delay instead of the desired phase-advance. Melatonin administration in the evening should also be timed to the endogenous cycle and take place 3 to 4 hours prior to the subjective sleep time.

After the initial stabilization, the patient is to gradually shift the entire pattern to earlier times until the target schedule is reached. Chronotherapy is another technique used specifically for DSWPD. It entails delaying the sleep period by 2 to 3 hours every day until the target schedule is reached, followed by daily morning light exposure.

In ASWPD, behaviorally resisting sleep in the early evening and delaying bedtime to socially appropriate time is recommended. Evening light, approximately 2 hours prior to the scheduled bedtime, is also used to produce phase delay. Early morning melatonin, although theoretically helpful, has not been shown to produce improvement in ASWPD symptoms and is not recommended.

For ISWRD, a combination of strict bedtime schedule, avoidance of daytime napping, morning light exposure, and evening melatonin may be useful for sleep consolidation at nighttime.

In N24SWD, strict bedtime schedule and evening melatonin are recommended and may be especially useful in blind individuals. Morning light exposure may also be used for patients with N24SWD who show clinical response.

For shift workers, a strict bedtime schedule should be established that is dictated by their work schedule. The workplace should be brightly lit to promote alertness, but light exposure should be minimized shortly prior to the sleep period, eg, via use of sunglasses while coming home from work in the morning. The bedroom

Continued on following page

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should be dark and noise-free as much as possible. Melatonin prior to the sleep period and light at the end of the sleep period may help consolidate sleep at the scheduled time.

For jet lag, phase-advance several days prior to the eastward travel using evening melatonin and morning light is recommended, while evening light for several days following the westward travel is helpful for phase-delay. For both shift work and jet lag, hypnotic and stimulant medications may be used to induce sleep at the scheduled time and to improve alertness during the wake period.

The length of light exposure is not standardized, but approximately 1 hour is typically recommended for therapeutic effect. As bright light may trigger a manic episode and also affect retinal health in certain individuals, patients should be screened for psychiatric or ophthalmologic contraindications.

Although melatonin doses are not standardized, 1 to 3 mg is typically clinically effective. Its side effects are generally considered mild and include headaches, nausea, and daytime grogginess. It is not recommended for pregnant or nursing women.

As sleep is a circadian-driven process, evaluation and management of circadian dysfunctions are integral parts of sleep therapy.

Specific techniques, such as a carefully planned bedtime schedule, timed light exposure, and melatonin administration, can be successfully implemented to optimize the patient's sleep.

Dr. Dubrovsky is with the Center for Sleep Disorders Medicine and Research, Division of Pulmonary and Critical Care Medicine; and Dr. George is Associate Professor of Clinical Medicine, Weill Cornell Medical College, and Director of the MICU; New York Methodist Hospital, Brooklyn, New York.

EDITOR'S COMMENTS

The human timing of sleep has been studied throughout history and continues to be a fascinating subject.

Circadian rhythm sleep disorders are in fact exceedingly common, whether we are considering the delayed sleep phase disorder of adolescents attempting to rise from bed in order to get to class after going to sleep in the early hours of the morning, the advanced sleep phase disorder of the elderly in which bedtime is regularly at 8:00 PM with early predawn awakening, or the dreaded jet lag that many individuals have experienced at one time or another.

Dr. Dubrovsky and Dr. George have distilled a complex topic into a concise article.

I hope that it will be useful to many chest physicians in attaining a greater understanding of not only patients who have sleep disorders but also of our own sleep cycle and how aberrations in the sleep-wake cycle may result in diminished performance.

Dr. Jeremy Weingarten, FCCP, Section Editor

PPI, steroid ups *C. difficile* recurrence in ICU patient

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Use of proton pump inhibitors and steroids was independently associated with recurrences of *Clostridium difficile*–associated diarrhea among patients in an intensive care unit, based on a retrospective chart review reported at the annual meeting of the American College of Chest Physicians.

Recurrences were noted in 268 of 2,019 patients who were admitted to a single intensive care unit during a 6-year period and were initially treated successfully for *C. difficile*–associated diarrhea (CDAD). In a univariate analysis, recurrence was correlated with use of proton pump inhibitors (PPIs) and steroids, but not with age, male gender, or length of hospital stay. After adjustment for age, sex, length of stay, and treatment used, the relationships between recurrence and PPI and steroid use remained statistically significant ($P = .03$ and $P = .03$, respectively), said Dr. Ala Nijim of Akron (Ohio) General Medical Center.

The study comprised 798 men and 1,221 women, average age was 68 years, average hospital stay was 10 days. Severe disease was present in 233 patients, and 51 had cancer.

CDAD was defined as at least three episodes of loose stools in less than 24 hours with a positive *C. difficile* toxin assay. Recurrence was defined as a second positive stool test within 90 days following complete resolution of a previous episode of diarrhea episode and cessation of treatment comprising a 10-day period.

Data suggest that the rate of CDAD recurrence is between 10% and 25% at a cost of between $3.2 and $4.8 billion, Dr. Nijim said.

Glucocorticoids are known risk factors for acquiring CDAD, likely due to their immunosuppressive effects, and PPIs have also been suggested as risk factors for acquiring CDAD. Likewise, treatment with metronidazole for an initial episode has been linked with treatment failure and recurrence risk. In the current study, one of the largest to date to evaluate factors associated with CDAD recurrence, both PPIs and glucocorticoids were associated with recurrence risk, but no link was found between metronidazole or any CDAD treatment modality and recurrence.

Though limited by the single-center, retrospective design, the study includes a large ICU sample, and the findings suggest intensivists should watch carefully for recurrence in patients using PPIs and/or steroids.

VITALS

Key clinical point: PPIs may be inadvisable in patients with a history of CDAD.

Major finding: CDAD recurrence was significantly associated with PPI and steroid use ($P = .0331$ and $P = .0305$, respectively).

Data source: A retrospective cohort study of 2,019 ICU patients.

Disclosures: Dr. Nijim reported having no disclosures.

Acid suppression linked to more severe CAP

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Use of acid-suppressing drugs was associated with more severe presentation and longer hospital stays among patients with community-acquired pneumonia in a single-center, retrospective analysis.

Of 866 CAP patients, 54% were on acid suppression. Those patients were more likely to have positive blood cultures (12% vs. 5.5%), thrombocytopenia (22% vs. 17%), and longer lengths of stay (10.5 days vs. 9 days), Dr. Bikash Bhattarai said at the annual meeting of the American College of Chest Physicians.

Acid suppression therapy was more common in patients with comorbidities, said Dr. Bhattarai of the Interfaith Medical Center in Brooklyn, N.Y. Dr. Bhattarai had no disclosures.

Extended use of oral anticoagulants reduces VTEs

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Extended treatment with any of the novel oral anticoagulants, but with apixaban in particular, provides a net clinical benefit in patients at risk of recurrent venous thromboembolism, according to a review of three randomized trials.

Apixaban appears to provide the optimal net clinical benefit, with the lowest number needed to treat to avoid one venous thromboembolic or major bleeding event, Dr. Alpesh Amin reported at the annual meeting of the American College of Chest Physicians.

In 5,035 patients in three trials of extended treatment with novel oral anticoagulants (NOACs) for venous thromboembolism (VTE) – including the RE-SONATE trial, the EINSTEIN-EXT trial, and the AMPLIFY-EXT trial – the differences in event rates, compared with placebo, were –5.15% for dabigatran, –5.74% for rivaroxaban, –7.14% for 2.5 mg apixaban, and –7.0% for 5 mg apixaban, reported Dr. Amin of the University of California, Irvine.

The number needed to treat to avoid one VTE or major bleeding event was 21 for dabigatran, 20 for rivaroxaban, 14 for 2.5 mg apixaban, and 13 for 5 mg apixaban, Dr. Amin said.

"The good news is that the number needed to treat for all of [the oral anticoagulants] is actually less than 25," he said.

As for costs, the savings from avoiding a recurrent VTE were $2,995 with dabigatran, $3,300 for rivaroxaban, and $4,100 for both 2.5 and 5 mg apixaban.

For major bleeding events, the corresponding rates, compared with placebo, were 0.29%, 0.67%, –0.20%, and –0.36%.

There was a net clinical benefit for all patients treated with the NOACs, but in those treated with 5 mg apixaban, the rates of improvement were

Continued on following page

VITALS

Key clinical point: All of the NOACs provide a net clinical benefit for reducing VTE recurrence.

Major finding: The number needed to treat to avoid one VTE or major bleeding event was 21 for dabigatran, 20 for rivaroxaban, 14 for 2.5 mg apixaban, and 13 for 5 mg apixaban.

Data source: An analysis of data from three clinical trials, including a total of 5,035 patients.

Disclosures: Dr. Amin reported serving as a paid consultant and/or member of a speakers bureau or advisory committee for Bristol-Myers Squibb and Pfizer.

The number needed to treat for all of [the oral anticoagulants] is actually less than 25.

DR. AMIN

Adding transthoracic echo speeds CVC placement

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Ultrasound plus real-time transthoracic echocardiography sped up placements of central venous catheters and rule outs of insertion-related pneumothorax, compared with ultrasound alone in a prospective, randomized, controlled study of 60 patients in the medical intensive care unit of a single center.

Compared to conventional ultrasound placement with x-ray confirmation, ultrasound plus transthoracic echocardiography also reduced the time to approval of the line for use, Dr. Dileep Raman reported at the annual meeting of the American College of Chest Physicians.

Ultrasound plus transthoracic echocardiography reduced the use of bedside chest x-rays by 57% compared with conventional ultrasound placement wiht x-ray confirmation.

Waiting for a chest x-ray adds anywhere from 16 minutes to 2 hours to the approval of line use, according to the literature.

Ultrasound is "a cheap bedside tool that can be repeatedly used to reduce the amount of chest x-rays for line placement and insertion" and indeed reduced the need for chest x-ray to confirm central venous catheter (CVC) position – without adding to procedure time, he said.

In the study, ultrasound plus transthoracic echocardiography reduced the use of bedside chest x-rays by 57% in 30 patients, compared with conventional ultrasound placement with x-ray confirmation in 29 patients. The mean time to line use was 25 minutes in the ultrasound plus echo group and 53.6 minutes in the conventional placement group, said Dr. Raman of the Cleveland Clinic.

The mean time to complete the procedure was 24.1 minutes in the intervention group, compared with 27.7 minutes in the x-ray confirmation group, he said.

None of the study patients had pneumothoraces.

Study subjects were consecutive patients admitted to an intensive care unit at a tertiary care medical center.

Both the intervention and control groups had central venous catheters inserted under ultrasound guidance, but the intervention group underwent real-time transthoracic echocardiography to assist in catheter positioning, as well as chest ultrasonography to exclude a pneumothorax.

After this process was completed, the line was immediately cleared for use. If the catheter wasn't detected in the right atrium, the patient was switched to the control group, which was treated using conventional techniques followed by standard chest x-ray.

The study groups were well matched with respect to age, body mass index, and APACHE III score.

Obtaining a chest x-ray to confirm line placement and to exclude pneumothorax remains the standard of care in most ICUs, but Dr. Raman said he and his colleagues dispute that chest x-ray should remain the standard, as it doesn't identify the superior vena cava–right atrium junction. Also, in addition to reducing the need for chest x-ray, the ultrasound technique seems to give a better picture of line placement.

Additional studies are needed to look at safety and feasibility, because pneumothorax rates are low, and "60 patients is clearly not enough to see if we dented the pneumothorax rate," he said.

VITALS

Key clinical point: The use of ultrasound and transthoracic echocardiography for CVC placement reduces the need for chest x-ray confirmation.

Major finding: The use of bedside chest x-ray was reduced by 57% with ultrasound plus real-time transthoracic echocardiography.

Data source: A prospective, randomized, controlled study of 60 patients.

Disclosures: Dr. Raman reported having no disclosures.

Continued from previous page

highest at –7.44%, followed by –7.38% for 2.5 mg apixaban. The rates were –5.0% with rivaroxaban and –4.85% with dabigatran.

"So we see a low number needed to treat, and a significant amount of cost avoidance by using the NOACs across the board," he said, adding that apixaban may provide the best net clinical benefit for the lowest number needed to treat to avoid one VTE or major bleeding event, and is associated with the greatest medical cost avoidance.

"In terms of safety endpoints, dabigatran and rivaroxaban cost the system a little bit of money, whereas apixaban actually decreased the cost," he said.

"How these results translate into real-world outcomes will require further evaluation, and as we get more numbers out there, we will actually be looking at the real-world impact," he said.

Dr. Amin reported serving as a paid consultant and/or member of a speakers bureau or advisory committee for Bristol-Myers Squibb and Pfizer.

Initiative cut days on a urinary catheter

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – An initiative reduced the number of days on a urinary catheter and improved catheter utilization among patients in a chronic ventilator-dependent unit.

Before the intervention, 24 of 37 patients (65%) were catheterized for a mean of 4.5 days per patient. After a 2-month intervention that relied on an electronic checklist and visual reminders, 18 of 35 subsequent patients (51%) were catheterized for a mean of 3.2 days per patient).

The device utilization ratio decreased from 0.299 before to 0.212 after the intervention, Dr. Perliveh Carrera said at the annual meeting of the American College of Chest Physicians.

The catheter utilization rates on the unit were below the national average of 0.45, and the rates of catheter-associated urinary tract infections were relatively low. The unit's rates had increased in 2012 and 2013, however, prompting this effort to reduce CAUTIs by reducing utilization.

"CAUTI is the most common health care–associated infection, affecting up to 20% of patients," said Dr. Carrera of the Mayo Clinic in Rochester, Minn.

About 80% of CAUTIs are precipitated by an indwelling catheter, and up to half of catheterized patients don't have an indication for catheter placement, she said. Data suggest that 20%-50% of catheters are inappropriately placed, and catheter placement is an important modifiable risk factor for preventing UTI.

The quality initiative was implemented on a nine-bed chronic ventilator unit where adult patients had an average length of stay of about 2 weeks. The intervention involved the use of a Define, Measure, Analyze, Improve, and Control (DMAIC) framework and included a combination of multidisciplinary teamwork and tools for promoting adherence.

These tools included educational presentations to staff, posters, reminder cards on patients' doors, and promotion of an electronic checklist that required input of an appropriate indication for catheterization. A charge nurse was provided with a portable tablet to track use of the electronic checklist.

The approach was developed after an initial survey of nursing staff identified low utilization of a paper checklist and knowledge gaps about catheter utilization and infection control efforts, Dr. Carrera said.

The initiative was associated with a significant increase in electronic checklist compliance – from 33% to 79% – and with a trend toward a reduction in the number of urinary catheter days and catheter utilization.

As a quality metric, catheter days and utilization are more stable than CAUTI, which has been recognized as labile and subject to wide variation, she added.

VITALS

Key clinical point: With education and proper tools, improvements can be made in catheter utilization.

Major finding: The percentage of catheterized patients decreased from 65% to 51%, and the mean number of catheter days decreased from 4.5 to 3.2 per patient.

Data source: A comparison of pre- and postintervention outcomes among 37 and 34 patients, respectively.

Disclosures: Dr. Carrera reported having no disclosures.

PRESIDENT'S REPORT: At the intersection of education and innovation

BY DR. CURTIS N. SESSLER, FCCP

Happy New Year to all of you! I'm delighted to have the opportunity to serve you as the 77th President of the American College of Chest Physicians (CHEST) and welcome 2015 as a very promising year for you and for CHEST.


DR. SESSLER

CHEST annual meeting

My tenure in this position began at the outstanding annual CHEST meeting in Austin, Texas. By all accounts, the meeting exceeded expectations with a superb mix of high-quality continuing medical education and a great opportunity for reconnecting with friends and colleagues. The process for producing such a robust annual meeting began many months in advance and involved a committed team of member volunteers and CHEST staff. Early stages of preparation included a careful review of successes and opportunities for improvement from the previous annual meeting (your feedback counts!) and an open call for proposals for sessions from members. We feel it is important to include a comprehensive mix of topics across disciplines and clinical problems, so we solicited proposals from the leadership of our 22 NetWorks – which address diverse areas ranging from critical care to airways disorders to women's health issues. A minimum of two proposals per NetWork is accepted, virtually ensuring a broad range of topics at each annual meeting. The complex process of prioritizing and then assembling the meeting topics is a real team effort. Finally, the Program Committee remains nimble in order to address late-breaking areas of critical importance – such as the multiple excellent sessions added this year to address clinicians' needs to prepare for the Ebola crisis.

CHEST Challenge – spreading its wings

As a clinician and educator, I am particularly excited when innovation and clinical education are combined to produce knowledge dissemination and fun! Such is the case with the annual CHEST Challenge – the finals of which are held at the annual meeting. In this competition, Pulmonary/Critical Care Medicine (PCCM) fellows from different training programs compete in a Jeopardy-style event that is fast and furious. I was recently in India and was informed that spread of this innovative event to India has resulted in participation of more than 90% of all Indian PCCM fellows in CHEST Challenge India. In fact, the first Global CHEST Challenge held at the CHEST World Congress in Madrid last year saw the US champs narrowly defeat teams from India and Spain.

Board examination preparation

CHEST has been the "go-to" organization for board exam preparation for years, including the popular board review courses in Pulmonary Medicine, Critical Care, and Sleep, and more recently, Pediatric Pulmonary, along with the SEEK series of textbooks in the same four disciplines. Our innovative CHEST staff continue to find new ways to make content even more relevant and accessible, such as through our CHEST apps. Additionally, we continue to add opportunities for Maintenance of Certification (MOC) and Self-Evaluation Process (SEP) module completion.

Innovation at its finest

Our journal *CHEST* continues to evolve and innovate, having completed its rebranding and redesign and launching a new "Online Exclusives" section of online-only content. CHEST's impact factor is the highest ever, submissions continue to be high and of excellent quality, and it was the best year financially in the journal's history.

Perhaps, some of the most exciting progress in continuing medical education has been in the rapid advances in experiential learning through simulation and other techniques. CHEST has emerged as the leader among professional medical societies, becoming the first to be accredited by the Society for Simulation in Healthcare. Since its opening in the spring of 2014, the Innovation, Simulation, and Training Center at CHEST Global Headquarters in Glenview, Illinois, has been the site for numerous courses – many simulation based – with more than 1,000 total attendees. This new state-of-the-art simulation facility incorporates six training labs designed to mirror real ICU suites, with adjacent control rooms; multiple debriefing rooms; and a 3,200-square foot auditorium that seats more than 100. But the real strength of these programs revolves around the team efforts of the many

Continued on following page

CHEST around the globe: TRS pulmonary board review

BY DR. MARK J. ROSEN, MASTER FCCP
Medical Director, CHEST

In October 2014, a collaboration between CHEST and the Turkish Respiratory Society (TRS) culminated in the first CHEST-TRS Pulmonary Board Review Course in Çesme, Turkey. The program was organized by Semra Bilaçeroglu, MD, FCCP, Governor-at-Large of the CHEST Council of Global Governors. With the participation of 16 faculty from Turkey, Greece, Egypt, and the United States, the 2-day course was designed to review major clinical topics in the curriculum of the Turkish Board of Respiratory Disease. The program included lecture-based and interactive sessions on physiology, COPD, lung cancer, bronchology, infections, venous thromboembolism, pulmonary hypertension, diffuse lung diseases, and pleural disease.

The CHEST-TRS Board Review expands on a model started in Greece with a collaboration of CHEST with the Hellenic Thoracic Society (HTS) that led to CHEST-HTS board review courses in Athens in 2009 and 2012. After the success of these courses in Greece and Turkey, we intend for CHEST to collaborate with other regional and national societies to conduct board review courses in chest medicine in other countries.

CHEST-TRS Pulmonary Board Review Course Faculty, from left: Dr. Panagiotis K. Behrakis, PhD, FCCP, President of European Network of Smoking and Tobacco Prevention, Past Chair of CHEST Council of Global Governors; Dr. Mark J. Rosen, Master FCCP, Hofstra University, Hempstead, N.Y. Medical Director and Past President, CHEST; Dr. Elif Küpeli, FCCP, Baskent University, Ankara, Turkey; Dr. Semra Bilaçeroglu, FCCP, Izmir Training and Research Hospital, Izmir, Turkey, CHEST Global Governor-at-Large; Dr. Rex Yung, FCCP, Johns Hopkins University, Baltimore; and Dr. Mustafa Özhan, Ege University, Izmir, Turkey.

Continued from previous page

knowledgeable content-expert members and our technically savvy CHEST staff. In fact, a brief review of the CHEST website (chestnet.org) reveals a great cross-section of courses in the first quarter of 2015, including "Comprehensive Bronchoscopy With Endobronchial Ultrasound," "Mechanical Ventilation: Advanced Critical Care Management," "Ultrasonography: Essentials in Critical Care," "Advanced Clinical Training in Pulmonary Function Testing," and others. The hands-on learning from established experts in these and other courses has proven to be highly valuable.

I will close by thanking you for your interest and involvement with CHEST and by offering my profound thanks to the many dedicated member volunteers and the tremendous CHEST staff who continue to push the innovation envelope in order to provide superior continuing medical education, helping our patients to receive the best care possible. See you this year!

Catching up with our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to look at what's new in their lives.

This series, and its first segment, was introduced in the CHEST 2014 Daily News in Austin, featuring Dr. Dick Briggs, and will continue on a quarterly basis in the monthly issues of CHEST Physician. Be sure to watch for it.

Dick D. Briggs Jr., MD, Master FCCP
President 1984-1985

I remember my presidency 30 years ago very well. After chairing the outstanding XV World Congress of Chest Diseases in Sydney, Australia, the 51st Annual ACCP Scientific Assembly in New Orleans was absolute chaos because a hurricane was doing figure-eights all week over lower Louisiana!

Those of us who did arrive early to the meeting substituted in lectures, on panels, and in discussion groups for many faculty and registrants who

A player on the USTA National Senior Tennis Circuit, Dr. Dick D. Briggs Jr. also enjoys running his border collies and driving his Carrera 911.

simply could not get to NOLA because of closed airports, train stations, and even highways. Those present got the job done, and my presidential address (Hippocrates' Blessing or Osler's Warning: Chest 1986;89:582) was published, thanks to Dr. Al Soffer.

I am now Emeritus Professor and Emeritus Eminent Scholar Chair in Pulmonary Diseases at the University of Alabama at Birmingham. My trips to the Kirklin Clinic, which I built, are for my own health care, not to practice medicine.

While I teach a bit, attend conferences, occasionally see a live patient, and frequently present teleconferences and other programs about health care organization and delivery of COPD [chronic obstructive pulmonary disease] care to patients, I no longer devote 80-hour weeks to medicine as I did in the good old days. I do miss some of that.

Instead, I am helping to edit a book about Tinsley Harrison. Also, I run Annie B and Maggie B (my border collies), and travel a bit by air. I also fly (a bit lower) in the Carrera 911 S pictured, and spend a lot of time on tennis courts practicing or playing the USTA National Senior Tennis Circuit. 2014 has not been a great year on the courts since I took some time out to trade in my aortic valve for a new one. But I am now in great condition and back on the tour. I looked forward with great anticipation to visiting with all my friends in Austin gathering to enlighten our minds and add body weight with barbecued brisket and Lone Star ale.

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

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

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

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

Once-daily ANORO ELLIPTA

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

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

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

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

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting $Beta_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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

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

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

5.7 Cardiovascular Effects
Vilanterol, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

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

5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

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

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

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

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

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

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

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance.

GSK
Research Triangle Park, NC 27709

Revised 12/2013 ANR:1BRS

NETWORKS: Cardiovascular Medicine, Allied Health, Infections

Cardiovascular Med/Surg

The "Third Universal Definition of Myocardial Infarction" designates cardiac troponin elevation (cTnE) to be an expression of myocardial necrosis, ie, myocardial cell death, due to: (1) primary myocardial ischemia; (2) supply-demand mismatch; (3) myocardial trauma or toxic agents; and (4) multifactorial or indeterminate myocardial injury.

The mantra that all cTnE, no matter what the etiology, is always caused by myocyte necrosis, is supported by histologic studies, although it is clear in contemporary practice that there are clinical situations in which cTnE occurs without necrosis.

DR. M. FUAD JAN

This assumes clinical relevance, as the United States gets ready for the fourth-generation, highly sensitive cardiac troponin assays ([4Ghs-cTnA] upper reference limit 1 pg/mL) that can, by definition, detect troponin in over 50% of the general population with the most sensitive assays detecting troponin in almost everyone.

Until these 4Ghs-cTnA arrive, frustration over cTnE will continue to trouble physicians taking care of the hospitalized patient. This is because of the contemporary bias in favor of a positive cTn result, which allows for the possibility of not capturing the entire picture when evaluating a patient.

This mindset has to change as we begin to interpret cTnE as a continuous variable, and within a greater context, with an understanding of the interplay of factors such as age, gender, patient's vascular bed, and renal function, among others and at the same time, not dismissing it as mere "troponinemia" (hospitalist and house-staff lingo).

cTnE should be viewed like fever – not a diagnosis but a phenomenon whose etiology is protean and may represent the final common pathway of several forms of heart disease, where there is a gradation of severity and mortality, as well as varied etiology. It is the art of the practicing physician to find out what ongoing biologic event(s) the cTnE is indicating.

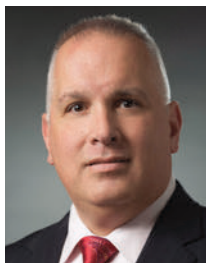
Dr. M. Fuad Jan,
Steering Committee Member; and
Dr. Suhail Allaqaband, FCCP, Chair

Allied Health

Drugs don't work in patients who don't take them – C. Everett Koop, MD

Worldwide, the burden of asthma is 22nd overall (comparable with diabetes mellitus) and COPD is 10th overall. By 2030, COPD is projected to be the third overall burden, largely attributable to nonadherence to medication or to the proper dosing regimen.

While the risk of hospitalization, morbidity, mortality, and cost of treatment is associated with medication nonadherence, up to 50% of patients believe that their prescribed medication regimens do not positively affect their health status (Horne et al. *Psychol Health*. 2002;17). Studies


MR. UNKLE

have also identified that the patient's beliefs regarding the need for controller therapy and the potential side effects of controller therapy with inhaled corticosteroids were among the most compelling reasons for medication adherence.More than 40% of study participants felt that they should not use their controller therapy when they were asymptomatic (Menckeberg et al *J Psychosom Res.* 2008;64:47).

"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed" – Hippocrates, Decorum

In an era of rapidly changing formulations for the management (and prevention of exacerbations) of COPD, a dosing regimen that supports adherence, such as once-a-day agents, warrants serious consideration. Lastly, an open, nonjudgmental discussion with the patient may yield valuable insight on their understanding of their disease and the impact of the medications prescribed and their perceptions of the prescriber.

David Unkle, APRN,
Steering Committee Member

Continued on following page

Continued from previous page

Chest Infections

Inhaled antibiotics in chest infections

The lungs are known for their large surface area, which is continuously exposed to the external environment (including droplets, gastric microaspirates, and pathogens) with minimum barrier defenses. Unlike the cutaneous surfaces wrapped in impermeable skin, and the GI tract with its peristalsis, gastric acidity, and adherent mucus, the delicate lungs' surface remains largely unprotected with anything grossly visible. Yet, despite this structural vulnerability, the lungs defend themselves successfully against most infections. Inhaled or aspirated pathogens often fail to reach peripheral airways thanks to the mucus coating and the mucociliary clearance system. Further, growth of pathogens is limited by surface immunity, alveolar macrophages, and other defense mechanisms. While the accessibility and large surface of the lungs contribute to their susceptibility to infection, these features also provide a unique opportunity for topical aerosol therapy. Indeed, antibiotics, when delivered by the respiratory route, maximize drug concentrations where microbial killing is needed and minimize systemic side effects.

As such, four products are


DR. BENCHEQROUN

approved in the United States, which include nebulized and dry powder forms of tobramycin and colistin, and nebulized aztreonam. More recently, inhaled dry powder ciprofloxacin was approved for cystic fibrosis. Injectable gentamicin, tobramycin, amikacin, ceftazidime, and amphotericin are nebulized "off-label" to manage non-CF bronchiectasis, drug-resistant nontuberculous mycobacterial infections, ventilator-associated pneumonia, aspergillosis, and posttransplant airway infections. Research has also centered on the development of newer delivery systems; easier to use, more portable, and with less administration time, they hopefully might improve adherence.

Dr. Hassan Bencheqroun, FCCP
Steering Committee Member

References

Safdar et al. *Expert Opin. Drug Saf.* 2009;8(4):435.
Brodt et al. *Eur Respir J.* 2014;44(2):382.
Quon et al. *Annals ATS.* 2014;11(3):425.

CHEST offers MOC support to members

The American Board of Internal Medicine (ABIM) rolled out new Maintenance of Certification (MOC) program requirements in January 2014 for all ABIM Board Certified physicians. In addition to publicly reporting your certification status, ABIM has also begun to report whether or not you are meeting MOC requirements.

CHEST wants to help members meet the new MOC requirements with options relevant to practice.

We offer seven assessment and improvement modules (AIM) that can earn you Medical Knowledge points in ABIM's MOC program:
CHEST: AIM Pulmonary Module 1
CHEST: AIM Pulmonary Module 2
CHEST: AIM Critical Care Module 1
CHEST: AIM Critical Care Module 2
CHEST: AIM Critical Care Module 3
CHEST: AIM Sleep Module 1
CHEST: AIM Sleep Module 2

Access chestnet.org/Education/Advanced-Clinical-Training/MOC-PIMs for information.

The ABIM recommends you review your requirements and deadlines on your customized MOC Status Report at abim.org. To be reported as meeting MOC requirements, you must:

√ Be enrolled in the MOC program (your MOC Status Report will tell you if you are already enrolled).

√ Earn MOC points.

- Earn MOC points every 2 years, by completing any MOC activity.
- Every 5 years, you must earn 100 MOC points (with a minimum of 20 in Practice Assessment and 20 in Medical Knowledge). Points earned every 2 years will also count toward your 5-year requirement.

√ Every 5 years, you must also complete the Patient Safety and Patient Voice requirements.

√ Pass an MOC exam 10 years from when it was last passed.

Remember to visit your MOC Status Report for more details on how the changes impact you.

What it takes to be a panelist for CHEST guidelines

BY REBECCA DIEKEMPER, MPH
MANAGER, GUIDELINE METHODOLOGY

Producing evidence-based guidelines that are used around the world takes a rigorous, well-established process and dedicated volunteers who are experts in pulmonology, critical care, and sleep medicine.

Volunteers dedicate countless hours to reviewing the literature, formulating recommendations, and drafting the supporting text around the recommendations.

Panelists for guidelines have the opportunity to contribute to the practice of evidence-based medicine in their field of expertise, learn how to develop an evidence-based guideline, work with other experts in their field, and be an author on a paper in a top-tier medical journal.

Find out more about the process for selecting panelists, their role on our guidelines, and the training and experience needed to serve on a guideline panel.

The Guidelines Oversight Committee (GOC) chooses a guideline topic and an Executive Committee is formed. The Executive Committee – made up of a Chair, Vice Chair, GOC Liaison, CHEST Project Manager, and CHEST Methodologist – develops the clinical questions for the guideline using the PICO format.

PICO questions define the population, intervention, comparator, and outcome that will ultimately inform the guideline recommendations.

The Executive Committee nominates individuals who have the expertise needed to address a clinical question. The nominees submit a curriculum vitae, statement of interest, and conflicts of interest disclosure form. The materials are then reviewed by the Professional Standards Committee that recommends nominees to the GOC, and the GOC then appoints the guideline panel.

CHEST guideline panelists commit to being active participants in meetings and to contributing to the development of a guideline for up to 3 years. Panelists assist with refining clinical questions and providing feedback on search strategies and study selection criteria. After a guideline methodologist conducts the searches, the panelists review the studies for inclusion.

Based on the evidence shown, panelists draft the guideline recommendations and supporting text.

CHEST guideline panelists commit to being active participants in meetings and to contributing to the development of a guideline for up to 3 years. Panelists assist with refining clinical questions and providing feedback.

All panelists participate in drafting and grading recommendations and drafting the manuscript. After a guideline is submitted to the journal *CHEST*, the panelists assist with promotional strategies.

Guideline panels comprise individuals from a variety of specialties and areas of expertise. Panelists are not chosen according to previous guideline experience but on their expertise. After selection of a guideline panel is completed, the project manager and methodologist send the panelists materials to provide an overview of the guideline development process.

Panelists attend an orientation webinar to review the guideline development process and are provided with materials on formatting recommendations and journal requirements. Panelists also learn the importance of conducting systematic reviews to inform their recommendations, which is the key to developing an evidence-based guideline.

If you are interested in participating on a CHEST guideline panel, consider attending our course, Guidelines Methodology, March 12-13, at our headquarters in Glenview, Illinois.

The course will provide participants with a skill set for developing evidence-based guidelines and consensus statements. This is a great opportunity for clinicians, interested in working on guidelines, to get a better understanding of what it takes to develop an evidence-based guideline.

Learn more at chestnet.org/live-learning.

CHEST membership evolving for relevance

CHEST is pleased to announce updates to our membership, coming this May, that will make CHEST membership more relevant to today's practicing chest medicine professionals. We're expanding our membership philosophy to ensure that every members' tomorrow is greater than today. How? Membership will soon be open to other clinicians on the chest medicine care team to reflect the growing emphasis on collaborative care. These changes are designed to allow our members to do more ...

Collaborate More

In response to emerging, team-based health-care models, CHEST is opening up membership to the entire chest medicine team, including clinicians-in-training, and making collaborative care a priority focus. We believe these changes will allow our members to be more successful at delivering high-quality, collaborative patient care.

Engage More

The new membership model will let you choose the benefits and the degree to which you want to engage with CHEST. Instead of membership levels based on your title, age, and stage of career, you'll be able to select the level you want, based on the resources and benefits you want to access. This gives you the power to decide what CHEST membership means for you.

Achieve More

We're streamlining our technology systems to make it easier to access the wealth of information and resources CHEST offers. For example, you'll have a single log-in for almost all transactions with CHEST (there's still a separate log-in for the journal, *CHEST*). With simpler navigation and a more intuitive interface, CHEST makes it easier for you to learn more, do more, and achieve more.

CHEST membership is dedicated to making your tomorrow better than today. Watch for more information at chestnet.org/tomorrow.

This month in *CHEST*: Editor's picks

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

EDITORIAL
Spread the word about *CHEST* in 2015: Rising impact factor, continuous innovations, and changes to the editorial team.
By Dr. R. S. Irwin, et al.

COMMENTARY
The association of direct thrombin inhibitor anticoagulants with cardiac thromboses.
By Dr. B. L. Davidson.

POINT AND COUNTERPOINT
Are the CHEST Guidelines global in coverage?
Yes – Dr. I. Nathanson and Dr. D. Ouellette
No – Dr. A. C. Mehta, et al.

ORIGINAL RESEARCH
Total and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged ≥18 years in the United States for 2010 and projections through 2020.
By Dr. E. S. Ford, et al.
A prospective evaluation of ventilator-associated conditions and infection-related ventilator-associated conditions.
By Dr. A. F. Boyer, et al.
Prevalence, incidence, and lifetime risk of atrial fibrillation in China: New insights into the global burden of atrial fibrillation.
By Dr. Y. Guo, et al.

Winners-All at CHEST 2014

Everyone attending CHEST 2014 was a winner and received the prize of unmatched clinical education presented by experts from around the globe. Listed below are some special events and presentations and the winners in those categories.

Abstract and Case Report Winners

CHEST 2014 was another successful meeting with presentations from the best and brightest pulmonary, critical care, and sleep physicians. Each year, we highlight and award the top abstracts and case reports presentations. CHEST 2014 abstract and case report winners are listed below.

Alfred Soffer Research Award Winners

This award was named in honor of Dr. Alfred Soffer, Master Fellow of the College, Editor in Chief of the CHEST journal from 1968 to 1993, and Executive Director for the ACCP from 1969 to 1992. The Alfred Soffer Research Award is granted to CHEST 2014 abstract presenters for their outstanding original research.

DR. CHINDAMO

DR. HARRINGTON

$500 Award Winners

Maria Chiara Chindamo, MD
Annie Harrington, MD

Young Investigator Award Winners

The Young Investigator Award is open to all CHEST abstract presenters who are enrolled in a training or fellowship program or have completed a fellowship program within 5 years prior to CHEST 2014. Semifinalists are evaluated on the basis of their written abstract and their presentation at CHEST 2014.

$500 Winners

Benjamin Mulloy, MD
Jared Radbel, MD

Top Three Poster Award Winners

Nominees for these research awards are evaluated on their written abstract and quality of their poster presentations at CHEST 2014. The Top Three Posters receive $250 each, with all other semifinalists receiving $100.

$250 Award Winners

Rupinder Kullar, MD
Robert Kyskan, MD
Safaa Wafy, MD

$100 Award Winners

Yoshiya Toyoda, MD
Jessica Barks, MD

Case Report Session Award Winners

The following case report winners presented the "Best Cases" in their respective sessions at CHEST 2014. Winners received a $100 prize.
Bronchology/Interventional Procedures Student/Resident Cases: Jason Lee, MD
Bronchology/Interventional Procedures Cases I: Shrinivas Kambali, MD
Bronchology/Interventional Procedures Cases II: Tanmay Panchabhai, MD
Cancer Student/Resident Cases: Akash Sethi, DO:
Cancer Cases I: Nina Zatikyan, MD
Cancer Cases II: Saba Hamiduzzaman, MD
Critical Care Student/Resident Cases: Pi Chun Cheng & Amith George Jacob (Dual Winners)
Critical Care Cases I: Elaine Cagnina, MD
Critical Care Cases II: Jonathan Wiesen, MD
Infectious Disease Student/Resident Cases: Haider Ali, MD
Infections Disease Cases I: Anil Singh, MBBS
Infections Disease Cases II: Walter James, DO
Interstitial Lung Disease Cases I: Kristyn Sayball, DO
Interstitial Lung Disease Cases II: Salah Fares, MD
Miscellaneous Student/Resident Cases: Amy Bellinghausen Stewart
Miscellaneous Cases I: Rajesh Zacharias, MBBS
Miscellaneous Cases II: Akshu Balwan, MBBS
Obstructive Airway Disease Cases: Margaret Zambon, MD
Pediatric Cases: Diana Chen
Pulmonary Vascular Disease Cases: Rania Abdallah, MD
Transplant Cases: Brian Cohee, MD
Juan F. Mella, MD, FCCP
Rodolfo M. Pascual, MD
Antara Mallampalli, MD, FCCP
Sandi Stewart
Carl A. Kaplan, MD, FCCP
Korambeth P. Ravikrishnan, MD, FCCP

Cleveland Clinic became the 13th team to win the popular CHEST annual event – CHEST Challenge. Members of the Cleveland Clinic's team are Dhruv Joshi, MBBS, Anupam Kumar, MBBS, and Tanmay Shashank Panchabhai, MD. They received a check for $5,000 and a team plaque.

CHEST Bingo Winners

Michael D. Wagner, MD, FCCP
Suganda Phalakornkul, MD
Olena Lineberry, MD
Daphne K. MacBruce, MD
Andrea B. Braun, MD
Karen I. Mella, RRT
Mary O. Polk, MD, FCCP
Wanda L. Greene
Krishna Murthy, MD, FCCP

CHEST Challenge

Cleveland Clinic became the 13th team to win the popular CHEST annual event – CHEST Challenge. Champions received a check for $5,000 and a team plaque. Congratulations to the winners and runners-up – New York Methodist Hospital and University of Texas Medical School at Houston.

GAMEs Winners!

Each receive an IPAD MINI!

Aspirated! Foreign body removal game Winners/winning time
Sunday: **Joshua Wald, MD** – 1 min, 6 sec
Monday: **Scott Twaddell, MBBS, FCCP** – 1 min, 25 sec
Tuesday: **Mohammed Mohammed, MD** – 34 sec

Adventures, Temple of Gloom, Sound DX, and COPD Whack-a-Doc game winners:
Colville Gibbs, MD, FCCP
Bruce Sabath, MD
Ryan Sugarman, MD

Games Augmenting Medical Education (GAMEs) Chair, William F. Kelly, MD, FCCP

Biopsy is most costly lung cancer diagnostic tool

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – Biopsies in patients ultimately not diagnosed with lung cancer accounted for 43% of the $38.3 million spent in lung cancer diagnostic costs in a Medicare analysis.

"We need to develop more precise risk stratification tools to better identify patients who require referrals for lung biopsy. This has the potential to reduce costs and improve patient outcomes," study author Tasneem Lokhandwala, Ph.D., said during a press briefing at the 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology.

To estimate the use of tests in lung cancer diagnosis and detection as well as the costs incurred, the researchers used a random 5% sample of Medicare patients.

In all, 8,979 patients, aged 65-74 years, were identified with an abnormal computed tomography scan.

The date of the patient's abnormal CT scan was defined as the index date. Patients diagnosed with any cancer, pneumonia, atelectasis, or tuberculosis in the 6-month preindex period were excluded.

VITALS

Key clinical point: Biopsy costs remain a significant proportion of the overall cost of diagnosing lung cancer.

Major finding: 43% of the $38.3 million spent in lung cancer diagnostic costs were due to biopsies for patients ultimately not diagnosed with lung cancer.

Data source: Retrospective study using a random 5% sample of 8,979 Medicare patients.

Disclosures: Dr. Lokhandwala reported employment with Xcenda. Her coauthors disclosed employment with Xcenda or GE Healthcare.

During the 12-month follow-up period, 14% of patients were diagnosed with lung cancer, with a median time to diagnosis from the abnormal chest CT of 11 days.

Diagnostic tests used were chest x-rays for 54.4%, chest CT scans for 33%, chest positron emission tomography scans for 0.5%, and lung biopsy for 19.4%, Dr. Lokhandwala, of Xcenda, Palm Harbor, Fla., reported.

The National Comprehensive Cancer Network guidelines call for low-dose chest CT followed by a PET scan to identify patients for biopsy.

The average total cost of the diagnostic work-up was $7,567 for patients diagnosed with lung cancer and $3,558 for those without a lung cancer diagnosis.

For both groups, these costs rose with the use of biopsy to $8,341 and $22,127, respectively.

Of the 1,744 patients who underwent a biopsy, 19.3% experienced a biopsy-related adverse event. An adverse event increased the average cost of a biopsy fourfold from $8,869 to $37,745, she said.

"Apart from the financial costs and the adverse events associated with tests and biopsies, there was also likely tremendous stress for those patients who ultimately were not found to have lung cancer," press briefing moderator Dr. Laurie E. Gaspar, professor and chair of radiation oncology at the University of Colorado at Denver, Aurora, said.

Dr. Gaspar agreed that the data highlight the need to better identify patients with lung cancer through the use of better imaging tests, follow-up CT or PET scans, or liquid biopsies.

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VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: 43% of spending on lung cancer diagnosis is ultimately spent on those without lung cancer. Nearly 9000 patients were included in this study and ultimately 14 % of patients were diagnosed with lung cancer. The high rate of biopsy related complications, which occurred in nearly 20% of those patients biopsied, and the severe financial costs associated with the complications, emphasize the need for better screening practices and testing before sending patients to biopsy. As the current guidelines for screening that include low dose CT scan followed by PET CT before biopsy become more mainstream, hopefully these rates of complications and cost will go down.

Oxygen therapy linked with worse outcomes in STEMI

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – Giving oxygen to patients having a heart attack may cause more harm than good, results from the AVOID study showed.

Patients who were not hypoxic and received oxygen for ST-segment elevation MI (STEMI) had larger myocardial infarct size, as measured during the first 3 days of hospitalization using cardiac enzymes.

The oxygen arm had a statistically significant 25% increase in creatine kinase, compared with the no-oxygen arm, whether measured as geometric mean peak (1,948 U/L vs. 1,543 U/L) or median peak (2,073 U/L vs. 1,727 U/L), Dr. Dion Stub, of St. Paul's Hospital, Vancouver, B.C., reported.

Cardiac troponin I levels were nonsignificantly higher with oxygen therapy (geometric mean peak, 57.4 mcg/L vs. 48 mcg/L; median peak, 65.7 mcg/L vs. 62.1 mcg/L).

When cardiac magnetic resonance imaging was applied in about a third of patients at 6 months' follow-up, the median infarct size remained significantly larger, at 20.3 g, in those given oxygen therapy, than in those who did not receive such therapy, whose median infarct size was 13.1 g, Dr. Stub said at the American Heart Association scientific sessions.

"It's important to realize that is a surrogate endpoint. That is not a mortality or outcome endpoint and the way that this was measured with biomarkers was admirable, but perhaps not today the most accurate. What is accurate was cardiac MR scanning, and the data held up at 6 months," said invited discussant Dr. Karl Kern, the Gordon A. Ewy Distinguished Endowed Chair of Cardiovascular Medicine, University of Arizona, Tucson.

Dr. Stub said that the study was not powered for clinical outcomes, but patients receiving oxygen, compared with no oxygen, also had significantly more recurrent MIs, at 5.5% and 0.9%, respectively, and major arrhythmias, at 40.4% and 31.4%, at discharge.

Oxygen therapy has been used for more than a century in the initial treatment of patients with suspected MI, although there is limited evidence suggesting such therapy is beneficial in patients without hypoxia.

A growing body of evidence, however, suggests that even 15 minutes of oxygen can reduce coronary blood flow, increase the production of oxygen-free radicals, and disturb microcirculation, all of which can contribute to reperfusion injury during MI, he said.

There was uniform agreement that there is an urgent need for an adequately powered randomized trial to evaluate the effectiveness of oxygen therapy in MI, a conclusion also reached by a recent Cochrane review of the topic (Cochrane Syst. Rev. 2013 August;8:CD007160).

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VITALS

Key clinical point: Supplemental oxygen therapy in normoxic patients with STEMI was associated with larger infarct size and more recurrent MIs and major cardiac arrhythmias.

Major finding: Median infarct size on cardiac MRI at 6 months was 203 g in those given oxygen, compared with 3.1 g in those not given oxygen (P = .04).

Data source: A randomized trial in 638 patients with STEMI.

Disclosures: AVOID was funded by the Alfred Hospital Foundation, FALCK Foundation, and Paramedics Australia. Dr. Stub and his coauthors reported having no financial disclosures.

VIEW ON THE NEWS

Dr. Jason Lazar, FCCP, comments: This prospective randomized study from Australia of 638 patients presenting with ST segment elevation myocardial infarction challenges the decades long practice of adminstering routine supplemental oxygen in such patients. Oxygen therapy was associated with larger infarct size. The study findings underscore the importance of evidence-based medicine and will undoubtedly spark additional studies to address this issue.

Spotlight on recent rise in tricuspid valve surgery

PATRICE WENDLING
Frontline Medical News

CHICAGO – The American Heart Association/American College of Cardiology (AHA/ACC) 2014 guideline on valvular heart disease reflects changing attitudes about mitral valve surgery and the need for intervention.

A class I indication for surgery remains in place for severe tricuspid regurgitation (TR) with mitral valve disease. However, what had been a class IIb indication in the 2006 guidelines for primary TR with symptoms is now a class I indication.

"Don't wait for right ventricular failure in primary TR. Plan for earlier intervention, and think of it more like we do mitral regurgitation," Dr. Patrick McCarthy said at Heart Valve Summit 2014.

The recommendation for moderate TR has also changed. The class IIb recommendation for patients with less than severe TR during mitral valve repair with pulmonary hypertension, right heart failure, or tricuspid dilation is now class IIa, indicating a lower threshold for surgery for these patients, said Dr. McCarthy, director of the Bluhm Cardiovascular Institute and chief of cardiac surgery, Northwestern University in Chicago.

Asymptomatic primary TR with right ventricle dilation or reoperations for TR with symptoms and prior left heart surgery had been a class III indication against surgery in 2006, but are now in sync with the European valvular guidelines with a class IIb indication, suggesting surgery may be considered.

The move toward earlier surgery is supported by results showing that TR only gets worse if left untreated, Dr. McCarthy said. Among patients with annular dilation greater than 70 mm as the only criterion for tricuspid valve repair (TVR), TR was shown to increase by more than 2 grades after 2 years in 2% of patients who underwent TVR during mitral valve repair (MVR) and in 48% without TVR (Ann. Thorac. Surg. 2005;79:127-32).

Another study showed that prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing MVR reduces the rate of TR progression, improves right ventricular remodeling, and improves functional outcomes on the 6-minute walk test (J. Thorac. Cardiovasc. Surg. 2012;143:632-8).

Not all data, however, have been viewed through the same lens with the "Mayo Clinic and Cleveland Clinic finding the same thing but drawing different conclusions," Dr. McCarthy observed. A Cleveland Clinic analysis involving 1,833 patients with degenerative mitral valve disease reported that MVR with concomitant TVR eliminated severe TR and improved RV function toward normal, "supporting an aggressive approach" (J. Cardiovasc Surg. 2013;146:1126-32). An 11-year review by the Mayo Clinic of 699 patients with functional TR and degenerative mitral valve leaflet prolapse found one patient required tricuspid reoperation 4.5 years after mitral repair and concluded "tricuspid valve surgery is rarely necessary for most patients undergoing repair of isolated mitral valve prolapse."

Dr. McCarthy disclosed inventing the Edwards MC3 tricuspid valve repair ring.

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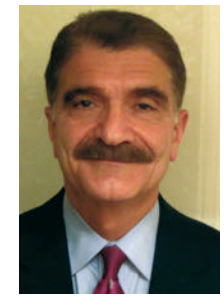
VIEW ON THE NEWS



Dr. Hossein Almassi, FCCP, comments: Historically, cardiac surgeons have been reluctant to operate on the tricuspid valve, mainly because of poor outcome and a high mortality rate. The excellent results with mitral valve repair and the emerging experience on tricuspid valve surgery have led to a welcome shift in the attitude of cardiac surgeons and cardiologists in adopting an earlier and more proactive approach in treating patients with significant tricuspid valve regurgitation, either alone or in conjunction with other valvular operations, as evidenced by changes in the 2014 AHA/ACC guidelines.

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The Central Maine Medical Family

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Leading South Florida Healthcare System Seeks Cardiac Intensivists

About the Opportunity:
Memorial Healthcare System is seeking two critical care physicians, dedicated to night shifts, to join the critical care team. Successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence-based care. Applicants must be BC/BE in critical care medicine. Previous experience in managing cardiac surgery patients is a plus, but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

- 12 hour in-house shifts (7pm-7am), no responsibilities outside of in-house shifts
- Approximately 15 shifts per month (more if desired)
- There is a highly competitive salary differential for the nocturnist position

These are full-time employed positions within the multi-specialty Memorial Physician Group. The positions offer competitive benefits, and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability is covered under sovereign immunity.

About Memorial's Cardio-Thoracic ICU
Memorial Healthcare System, a 1,900-bed multihospital system located in South Florida, is highly regarded for its exceptional patient- and family-centered care. Memorial's patient, physician and employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare. To learn more about Memorial Healthcare System visit **MHS.net.**

About South Florida
South Florida offers an outstanding quality of life rich in cultural and recreational amenities. Residents enjoy pristine beaches, top-rated golf courses, museums, world-class dining and myriad family-friendly communities. Florida also has no state income tax.

To inquire about this opportunity or learn more, visit **memorialphysician.com**

Memorial Healthcare System
Memorial Cardiac and Vascular Institute
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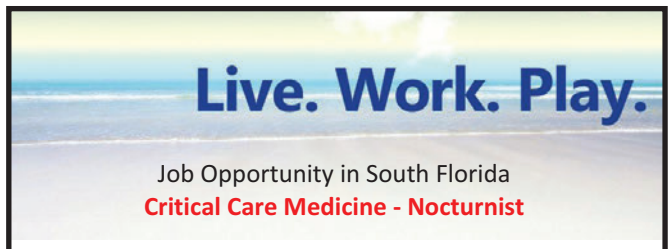

Job Opportunity in South Florida

Critical Care Medicine - Nocturnist

An MHS representative will be attending the SCCM's 2015 Critical Care Congress, visit us at booth #230

About the Opportunity:
Memorial Healthcare System's Intensivist Program has expanded. The program is currently comprised of 23 full time intensivists and five critical care ARNPs, providing 24/7 ICU coverage at multiple locations within the Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple board certifications including infectious diseases, pulmonology, surgery and neuro-critical care.

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

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

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The practice operates within Bronson Methodist Hospital which is an award winning, tertiary healthcare system serving 10 counties in southwest Michigan. With a workforce of more than 7,000, Bronson is one of the area's largest employers. We offer a full range of services from primary care to advanced critical care and have multiple service locations in Kalamazoo, Calhoun and Van Buren counties. Kalamazoo, located midway between Detroit and Chicago, is a diverse university town with highly rated public schools and affordable real estate. Offering art, symphony, theater, museums and year round festivals, there are many activities for the whole family including numerous parks, lakes, fine dining and Lake Michigan is less than an hour's drive away.

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SGR, Medicaid parity, ICD-10 left undone in 2014

BY ALICIA AULT
Frontline Medical News

The year ended on a sour note for physicians, as Congress recessed without addressing the Medicare Sustainable Growth Rate formula or acting on a number of other doctors' priorities.

Congress did not extend a pay increase for primary care physicians who serve Medicaid recipients, nor did it delay the implementation of the ICD-10 code set nor enact any legislative solutions to help physicians better grapple with meaningful use of health information technology.

Physicians held out hope until the closing days of the 113th Congress, as legislators battled over what would be put into a massive spending bill that was needed to keep the government in operation beyond Dec. 11. That $1.1 trillion bill was approved by the House just before the government was to run out of money, and by the Senate two days later.

'We're stuck with an SGR system that everyone agrees is just not good for health care and not good for patients.'

DR. HARRELL

Physicians were not able to point out much that was positive in either the spending bill or the 2014 legislative session.

"We've had a Congress that's just been much more interested in fighting with each other than with constructing meaningful legislation," Dr. R. Mack Harrell, president of the American Association of Clinical Endocrinologists, said in an interview. "For physicians that means we're stuck with an SGR system that everyone agrees is just not good for health care and not good for patients."

Many physician groups said that the failure to repeal the SGR was their biggest disappointment.

"We were cautiously optimistic that this 17th year of trying to repeal the SGR might have been the successful one," Dr. Patrick T. O'Gara, president of the American College of Cardiology, said in an interview. He said that the sticking point seemed to be that "there was no politically viable way to pay for it."

American College of Physicians President Dr. David A. Fleming noted in a statement that finding the money had hung up what otherwise was huge progress: a bill that members of the House and Senate, Republicans and Democrats had put together, and that ultimately passed the House.

The current SGR patch expires Mar. 31, 2015, giving physicians little time to convince a new Congress of the merits of replacing the formula.

Noting that there are about 37 days between when the new Congress begins in January and when a 21% pay cut goes into effect in April, American Medical Association President Robert M. Wah, said in an interview, "We're already really up against the end of the current patch."

'We're already really up against the end of the current patch,' with the 21% pay cut taking effect in April.

DR. WAH

Even so, physician groups say that they'll try to start where they left off – with the bill that had gained such widespread support 2014. "We fully expect that this bill will be considered by the new 114th Congress next year, and we will redouble our efforts to get Congress to act upon it before the current patch expires on March 31," Dr. Fleming said in the statement.

There was hope 'that this 17th year of trying to repeal the SGR might have been the successful one.'

DR. O'GARA

Dr. O'Gara said that the ACC would take a pragmatic approach. "It would likely not be successful to mount a campaign to repeal it between January and March."

Dr. Robert Wergin, president of the American Academy of Family Physicians, said that having a framework that already exists – and that was supported by most physicians – should help get the ball rolling more quickly in 2015.

Physician groups were also disappointed that the Medicaid pay parity provision – which puts reimbursement on par with Medicare for primary care services – was not extended. Dr. Wergin said going back to Medicaid pay rates amounts to essentially a 41% cut.

In a recent report, the Urban Institute estimated that fees increased an average 73% and that the federal government had spent an estimated $5.6 billion on the pay bump by June 2014.

The institute said it's not entirely clear whether the increase in fees has led to more access, or to an easing of pressures on physician practices. And it's not clear how many states might choose to continue the program without federal help. According to a Kaiser Family Foundation survey published in late October, 15 states said they will continue a pay raise in 2015; 24 states said they would not, and 12 states were undecided.

ALICIA AULT/FRONTLINE MEDICAL NEWS

Many physicians were also disappointed that legislators did not find a way to further delay ICD-10, which is scheduled to go into effect Oct. 1, 2015.

Prospects for a delay next year seem slimmer now that two key House Republicans – Rep. Fred Upton (R-Mich.) and Rep. Pete Sessions (R-Tex.) have said they won't consider a delay. But, they said in a joint statement, they also are willing to help physicians and others meet the deadline, and make sure that everything goes smoothly.

ICD-10 "is an important milestone in the future of health care technologies, and it is essential that we understand the state of preparedness at CMS," they said.

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