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Gradual smoking cessation



COURTESY OF JAMA



Varenicline for 24 weeks boosted quit rates in smokers, according to Dr. Jon O. Ebbert of the Mayo Clinic. See page 6, and watch the video at chestphysician.org.



Smoking linked to 'new' causes of death

BY MARY ANN MOON
Frontline Medical News

Smoking causes death from many diseases that until now have not been linked officially to tobacco use, including digestive disorders, liver cirrhosis, infections, renal failure, and breast and prostate cancers, according to a report published online Feb. 11 in the *New England Journal of Medicine*.

"Our results suggest that the number of persons in the United States who die each year as a result of smoking cigarettes may be substantial-

ly greater than currently estimated," said Brian D. Carter of the epidemiology research program, American Cancer Society, Atlanta, and his associates.

The 2014 Surgeon General's report estimated that smoking causes more than 480,000 deaths every year in the United States, based on mortality figures from 21 diseases that have been formally established as caused by smoking: 12 types of cancer, 6 types of cardiovascular disease, diabetes, chronic obstructive pulmonary disease, See **Smoking** • page 7

Medicare now covers CT for lung cancer screening

Benefit is limited to select beneficiaries.

BY M. ALEXANDER OTTO
Frontline Medical News

Effective immediately, Medicare will cover annual lung cancer screening with low-dose CT for certain beneficiaries, according to a Feb. 5 national coverage determination.

To qualify, beneficiaries must be 55-77 years old, have a smoking history of at least a 30 pack-years, exhibit no signs or symptoms of lung cancer, and currently smoke or have quit within 15 years. They also must have a written screening order from their provider.

Coverage includes a

counseling visit for shared decision making, so patients know beforehand the "benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive[s], and total radiation exposure," among other things, according to the decision memo from the Centers for Medicare & Medicaid Services.

Imaging centers are required to collect data on each screening and submit it to a CMS-approved registry.

"This is an important new Medicare preventive benefit since lung cancer is the third most common cancer and the leading cause of cancer

See **Medicare** • page 7

Steroid cut CAP therapy failures

BY MARY ANN MOON
Frontline Medical News

A 5-day course of methylprednisolone reduced the rate of treatment failure in adults with severe community-acquired pneumonia and a high initial inflammatory response.

"If replicated, these find-

ings would support the use of corticosteroids as adjunctive treatment in this clinical population," said Dr. Antoni Torres of Institut Clinic del Torax, Hospital Clinic, Barcelona, and his associates.

Dr. Torres and his colleagues studied the use of corticosteroids in the subgroup of patients who

present with severe disease and a proinflammatory profile characterized by a serum C-reactive protein level over 150 mg/dL – the patients most likely to benefit from anti-inflammatories and least likely to be harmed by steroid-induced superinfection.

See **Therapy failures** • page 9

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C A N A D A October 24 - 28

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chest2015.abstractcentral.com
Submission deadline: April 1

Reduce lung function decline

Delay IPF Progression with Esbriet



Indication

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

Select Important Safety Information

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

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions ($\geq 10\%$) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.



Introducing **Esbriet**[®]
(pirfenidone) capsules 267mg

Proven to delay progression in IPF²

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had $\geq 10\%$ decline in %FVC, $P < 0.001$). Treatment effect was evident at 13 weeks ($P < 0.001$) and increased through trial duration^{1,2,*†}
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)^{1,*‡}
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet¹
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide³

Learn more about Esbriet and how to access medication at Esbriet.com.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and DL_{CO} between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

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

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the $\geq 10\%$ decline category.

‡Stable was defined as no decline in lung function.

References: 1. Esbriet full Prescribing Information. InterMune, Inc. October 2014. 2. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. 3. InterMune, Inc. Data on file.

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Esbriet[®]
(pirfenidone) capsules 267mg

Start here

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 $>3 \times$ 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 $\geq 3 \times$ ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations $\geq 10 \times$ 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 $\geq 3 \times$ 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 $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in $\geq 10\%$ 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/m² 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/m² 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/m² 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

INTERMUNE®

Varenicline facilitates gradual smoking cessation

BY MARY ANN MOON
Frontline Medical News

A 24-week course of varenicline improved quit rates among smokers who preferred to gradually reduce their use of cigarettes.

In an industry-sponsored, randomized, double-blind, controlled trial, participants who were given varenicline showed higher quit rates at the end of treatment as well as 1 year later, compared with those given placebo, said Dr. Jon O. Ebbert of the Mayo Clinic, Rochester, Minn., and his associates.

Current U.S. clinical practice guidelines recommend that smokers set an immediate quit date and quit abruptly, “even though only 8% of smokers report being ready to quit within the next month.”

The findings of this study show that a more gradual, reduce-to-quit approach also can be effective, and “would be expected to be of interest to 14 million of the 42 million current smokers in this country,” the investigators noted.

The study was performed at 61 medical centers in 10 countries during a 2-year period.

The 1,510 participants would not quit abruptly, as is recommended, but were willing to reduce their smoking and make a quit attempt within the next 3 months. They were asked to reduce their smoking rate by 50% or more by week 4, to further reduce it by 75% or more by week 8, and to quit altogether by week 12.

Study participants, who smoked 10 or more cigarettes per day at

baseline, were randomly assigned to receive varenicline (760 patients) or a placebo (750 patients) for 24 weeks. All received written materials and smoking cessation counseling focused on reduction techniques, problem solving, and skills training provided during 18 clinic visits and 10 telephone sessions of 10 minutes’ duration.

The primary efficacy endpoint was the continuous abstinence rate during weeks 15-24, which was self-reported by the participants and confirmed using exhaled carbon monoxide measurements. This rate was significantly higher for the varenicline group (32.1%) than for the placebo group (6.9%). The continuous abstinence rate remained significantly higher through 1 year of follow-up for varenicline (27%) than for placebo (9.9%).

The median time to abstinence was significantly shorter with varenicline (50 days) than with placebo (85 days). Results of sensitivity analyses confirmed those of the primary analysis, the investigators said (JAMA 2015 Feb. 17;313:687-94).

The percentage of participants who reported adverse events was higher with varenicline (82.3% vs. 72.5%), and the difference was largely accounted for by increases in nausea, abnormal dreams, insomnia, constipation, vomiting, and weight gain.

Rates of serious adverse events were similar between the two study

groups, as were rates of treatment discontinuation (8.4% for varenicline and 7% for placebo). In particular, rates of suicidal ideation or behavior and depression scores were not significantly higher with varenicline. The study findings indicate that prescribing varenicline “with a recommendation to reduce the number of cigarettes smoked per day, with the eventual goal of quitting, could be a useful therapeutic option for this population of smokers,” Dr. Ebbert and his associates said.

A limitation of this study was that patients were excluded from participating if they had severe psychiatric, pulmonary, cardiovascular, or cerebrovascular disease, which hinders the generalizability of the results to a broader population of smokers.

In addition, study participants received significant counseling support that would not necessarily be available to patients in real-world clinical practice, so quit rates would be expected to be lower in actual practice.

This study was funded by Pfizer, maker of varenicline (Chantix). Pfizer also participated in the design and conduct of the study; the collection, analysis, and interpretation of the data; and manuscript preparation. Dr. Ebbert reported receiving grants from Pfizer, JHP Pharmaceuticals, and Orexigen, as well as personal fees from GlaxoSmithKline. His associates reported ties to industry sources.

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CHEST Physician

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CT screens

Medicare from page 1

deaths in the United States,” Dr. Patrick Conway, CMS chief medical officer, said in a statement. “We believe this final decision strikes an appropriate balance between providing access to this important preventive service and ensuring, to the best extent possible, that Medicare beneficiaries receive maximum benefit from a lung cancer screening program.”

The decision has been in the works for a while. In 2011, the National Cancer Institute–sponsored National Lung Screening Trial (NLST) showed that people aged 55-74 years with a history of heavy

smoking are 20% less likely to die from lung cancer if they are screened with low-dose helical CT instead of standard chest x-ray (N. Engl. J. Med. 2011;365:395-409).

Previous studies had shown that screening with standard chest x-rays does not reduce mortality from lung cancer.

Results from NLST and other studies prompted the U.S. Preventive Services Task Force in 2013 to recommend annual low-dose CT screening for adults aged 55-80 years with a 30-pack-year history; the recommendation in turn led to formal requests to CMS for coverage. In proposing coverage, the



‘This is an important new Medicare preventive benefit.’

DR. CONWAY

task force received almost 500 public comments “generally supportive of [expanding] Medicare coverage to include lung cancer screening,” it said. Low-dose CT is performed at acquisition settings to minimize radiation exposure. For lung cancer screening, CMS is requiring a volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy for standard-size patients – defined to be 5 feet 7 inches tall and approximately 155 pounds – with appropriate reductions or increases for smaller or larger patients.

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‘New’ causes of death

Smoking from page 1

and pneumonia. Mr. Carter and his associates pooled data from five large cohort studies to examine possible associations between smoking and an additional 31 cause-of-death categories. They now estimate that an additional 60,000-120,000 deaths each year can be attributed to smoking.

For their study, the investigators assessed 421,378 men and 532,651 women aged 55 years and older at baseline whose smoking status was carefully recorded and who were followed from 2000 to 2011 in the Cancer Prevention Study II Nutrition Cohort, the Nurses’ Health Study I, the Health Professionals Follow-Up Study, the Women’s Health Initiative, and the National Institutes of Health-AARP Diet and Health Study.

As expected, smokers had a two-fold to threefold higher mortality from any cause, compared with nonsmokers. Smokers also had a markedly higher risk of death than nonsmokers from all 21 causes already established as attributable to tobacco use, such as lung cancer, oral cancer, ischemic heart disease,

atherosclerosis, and stroke. But approximately 17% of smokers’ excess mortality was accounted for by several diseases that previously have not been attributable to tobacco use.

For example, the risk of death

The mortality risk from liver cirrhosis, after adjusting for alcohol consumption, was more than three times higher in smokers.

due to intestinal ischemia was approximately six times higher among smokers than among nonsmokers, a remarkably strong association that was also reported in the Million Women Study. “Smoking acutely reduces blood flow to the intestines, and evidence suggests that smoking causes risk factors that can often lead to intestinal ischemia, including atherosclerosis, platelet aggregation, and congestive heart failure,” Mr. Carter and his associates said (N. Engl. J. Med. 2015 Feb. 12 [doi:10.1056/NEJMsa140721]).

In this study, smoking also more than doubled the risk of dying from other digestive diseases. Previous studies have suggested a link between smoking and digestive disorders such as Crohn’s disease, peptic ulcers, acute pancreatitis, paralytic ileus, bowel obstruction, choletlithiasis, diverticulitis, and gastrointestinal hemorrhage. “Although these diseases are not common causes of death, they account for millions of hospitalizations each year,” the investigators noted.

The mortality risk from liver cirrhosis, after the data were adjusted to account for alcohol consumption, was more than three times higher in smokers than in nonsmokers. Even smokers who did not drink alcohol were at

significantly increased risk of cirrhosis, compared with nonsmokers.

The risk of death due to infection was 2.3 times higher in smokers than in nonsmokers. This strong association was dose dependent, as infection-related mortality rose with increasing smoking intensity. And among study participants who had quit smoking, infection-related mortality declined as the number of years since cessation increased.

The rate of death due to renal failure was twice as high among smokers as among nonsmokers.

The rate of death due to hypertensive heart disease, the only category of heart disease not already established as smoking related, was 2.4 times higher in smokers. The latter association “is relevant for assessing the public health burden of smoking, since a considerable number of deaths in the United States are attributable to hypertensive heart disease,” according to Mr. Carter and his associates.

Smoking also was strongly associated with “multiple diseases too uncommon to examine individually.” This included all rare cancers combined, rare digestive diseases, and respiratory diseases other than those already known to stem from smoking.

In women, smoking raised breast

VITALS

Key clinical point: Smoking is now thought to cause many deaths from infections; renal failure; liver cirrhosis; digestive diseases; and breast, prostate, and other cancers.

Major finding: Several diseases that previously have not been attributable to tobacco use accounted for 17% of smokers’ excess mortality.

Data source: An analysis of pooled data from five large cohort studies involving 954,029 people aged 55 years and older followed for 12 years to examine associations between smoking and 52 possible causes of death.

Disclosures: This study was supported by the American Cancer Society. Mr. Carter reported having no financial disclosures; one of his associates reported receiving grant support from Novo Nordisk.

cancer mortality, with a relative risk of 1.3. This association was strongly dose dependent. In men, smoking raised prostate cancer mortality, with a relative risk of 1.4.

This study was limited in that most of the participants were white and better educated than the general population, which may affect the applicability of the results to other populations.

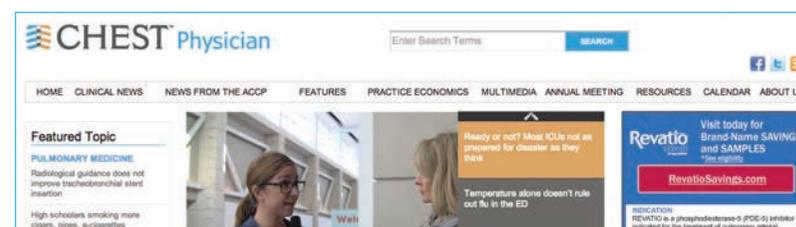
VIEW ON THE NEWS

Dr. Vera A. DePalo, MBA, FCCP, comments: We have long known of the health complications of chronic lung disease, cancer, and heart disease related to smoking. In an American Cancer Society–supported analysis of pooled data from a number of large cohort studies, not only is it clear that the burden of tobacco use has been underestimated, but a number of diseases not previously thought to be associated with tobacco use have now been linked to smoking.

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Ventilator driving pressure linked to ARDS outcome

BY MARY ANN MOON
Frontline Medical News

One variable involved with mechanical ventilation – driving pressure – may predict mortality

in adult respiratory distress syndrome. Research suggests that scaling ventilator tidal volumes (V_T) to patients' body weight will minimize ventilator-induced lung injury. But patients with ARDS have a marked decrease

in the proportion of lung available for ventilation, as is indicated by their lower respiratory-system compliance (C_{RS}), which is not related to their body weight.

"Therefore, we hypothesized that

normalizing V_T to C_{RS} and using the ratio as an index indicating the 'functional' size of the lung would provide a better predictor of outcomes in patients with ARDS than V_T alone, said Dr. Marcelo B.P. Amato of the cardiopulmonary department, University of Sao Paulo (Brazil) Heart Institute, and his associates.

This ratio, also known as the driving pressure, is easily calculated at the bedside.

The researchers explored whether driving pressure or other variables related to mechanical ventilation, including variables set by the ventilator operator, could be statistically linked to survival outcomes and therefore serve as a risk predictor.

They first devised a survival-prediction model using data from a cohort of 336 ARDS patients participating in four randomized clinical trials examining different ventilation strategies.

They then tested their findings using a validation cohort of 861 patients from a single large trial, then

Continued on following page

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VIEW ON THE NEWS

Premature to reset

We strongly urge caution against accepting the idea that clinicians should now set ventilators to limit driving pressure in patients with ARDS, even though that is an appealing concept.

The findings of Amato et al. derive from a meta-analysis, not from prospective randomized controlled trials. Their results should form the basis for a robust debate regarding the design of future trials so that, before we take action, we first ensure that limiting driving pressure will actually be beneficial.

Dr. Stephen H. Loring is in the department of anesthesia, critical care, and pain medicine at Beth Israel Deaconess Medical Center and at Harvard, both in Boston. Dr. Atul Malhotra, FCCP, is in the division of pulmonary critical care and sleep medicine at the University of California, San Diego, in La Jolla. Both Dr. Loring and Dr. Malhotra reported having no financial disclosures. They made these remarks in an editorial accompanying Dr. Amato's report (N. Engl. J. Med. 2015 Feb. 19 [doi:10.1056/NEJMe1414218]).

Continued from previous page

tested them again in a more recent validation cohort of 2,365 patients participating in four more randomized trials comparing different ventilation strategies.

Driving pressure was the only ventilation variable found to be strongly

associated with survival.

Higher driving pressures strongly predicted higher mortality: Every 1–standard deviation increase in driving pressure was related to increased mortality, with a relative risk of 1.41.

Even in patients receiving lung-protective plateau pressures and low tidal volumes, higher driv-

ing pressure was associated with increased mortality, with a relative risk of 1.36, Dr. Amato and his associates said (N. Engl. J. Med. 2015 Feb. 19 [doi:10.1056/NEJMs1410639]).

These findings can only suggest that driving pressure is a critical mediator of various ventilator strategies,

since they are derived from a post hoc observational statistical analysis and cannot establish causality, the researchers said.

Now, prospective clinical trials are needed to determine whether adjusting ventilator settings to lower driving pressure will improve survival in ARDS.

Inflammatory CAP

Therapy failures from page 1

In a randomized double-blind trial at three teaching hospitals in Spain, 120 such patients were randomly assigned to receive 5 days of either IV methylprednisolone (61 patients) at a dose of 0.5 mg/kg every 12 hours or a matching placebo (59 patients), in addition to antibiotics.

The most common cause of pneumonia in both study groups was *Streptococcus pneumoniae*, and the most frequent empiric antimicrobial treatment was a combination of ceftriaxone, levofloxacin, and azithromycin. As expected, CRP and IL-10 levels decreased more in patients who received the corticosteroid than in those who received placebo.

The primary endpoint was treatment failure, both within 72 hours (early) and at 72-120 hours (late) after initiation of therapy. This rate was significantly lower in patients who received methylprednisolone (8 patients, or 13%) than in those who received placebo (18, or 31%). This reduction was largely attributed to the prevention of radiographic progression and late septic shock.

However, there were no significant differences in the secondary outcomes of time to clinical stabilization, length of ICU stay, length of hospitalization, and in-hospital mortality, the investigators said (JAMA 2015 Feb. 17 [doi:10.1001/jama.2015.88]).

It is likely that the most feared adverse effect of corticosteroid therapy – immunosuppression leading to superinfection – wasn't an issue in this study because of the short course of treatment and the relatively low dose of methylprednisolone used.

These findings are important because any efficacious adjunctive treatment may help reduce the high mortality associated with severe community-acquired pneumonia. It is estimated that despite effective antibiotic treatment, 12%-36% of patients admitted to an ICU with this disease will die within a short period, Dr. Torres and his associates noted.

A larger study is underway to confirm the results.

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Sorting out optimal TB testing can be tricky

BY DOUG BRUNK
Frontline Medical News

LAS VEGAS – In the clinical opinion of Dr. Andi L. Shane, tuberculin skin testing and interferon gamma release assay diagnostics and surveillance for *Mycobacterium tuberculosis* infection are game changers in the ongoing effort to reduce TB infections.

“From 1982 to 2013, we’ve had a very nice decline in TB cases. However, we still have quite a bit of work to do,” Dr. Shane said at an update sponsored by the American Academy of Pediatrics California District 9.

Case rates are high in California, Nevada, Texas, Florida, New York, Washington, New Jersey, and the District of Columbia. Those under 5 years old and those aged 15-24 years

to control the infection; no systemic manifestations of infection are present. Identifying the difference between latent tuberculosis infection (LTBI) and actual tuberculosis disease is one of the most challenging

aspects to explain to families. The reason is that children or adults who have LTBI are not infectious, whereas someone who has pulmonary or laryngeal TB is considered to be an infectious risk to other individuals.

Dr. Shane went on to discuss limitations of the TST. For one, the test may be placed incorrectly, resulting in an inflammatory response or no response, “and there is reader variability,” she said. “The reading needs

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Health care providers



need to be ever vigilant of those “red snappers” when seeing pediatric patients so this article is timely in regards to the

ins and outs of interferon gamma release assay (IGRA) testing.

are more likely to be affected.

“It’s really important to identify TB as soon as possible, especially in children,” said Dr. Shane of the department of pediatrics, division of infectious diseases, Emory University, Atlanta. “An interferon gamma release assay (IGRA) or a tuberculin skin test (TST) may be used in situations where assessment for MTB [*M. tuberculosis*] exposure is indicated. IGRA is preferred in persons who received BCG vaccine and who have low rates of test completion, while TST is preferred for testing of children younger than age 5.”

TB in people younger than age 15 years is a marker for transmission of TB, usually from an adult. “So when we identify a case of TB in children, that requires a contact investigation,” she said. “We’re more concerned with children under the age of 5 with TB because they are more likely to have disseminated disease.”

Latent TB means that the patient has been exposed to the disease but that his or her body has been able

Approximately 50% of individuals with narcolepsy are undiagnosed.¹

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EXCESSIVE DAYTIME
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Narcolepsy symptoms may be lurking beneath the surface.

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to occur 48-72 hours after placement of the test. So, if you place it on a Thursday, that means you really are not going to read it at the optimal time unless the child comes to you on a weekend or the test is read by somebody else.”

As an alternative, two IGRAs have been developed that measure how

the immune system reacts to MTB. One is QuantiFERON, which is widely used in the United States; the other is the T-SPOT.TB test, which is widely used in Europe. A positive result on either test indicates that there has been interaction with MTB bacteria but it does not differentiate between LTBI and active TB disease.

“A negative IGRA tells you there is no reaction to the test and MTB is not likely, while an indeterminate result is when you’re unable to interpret the result due to low positive [mitogen] or increased negative control [nil] compared to TB response,” Dr. Shane said. “This usually indicates that there’s some problem with

the assay itself. It can also indicate that the individual may not have an immune system that can respond to and produce interferon gamma.”

Assessment of IGRA accuracy is challenged by the lack of a standard for the diagnosis of LTBI and active TB. “We just don’t have a lot of good data from resource-endowed settings,” Dr. Shane explained. “We have good data from areas where TB is prevalent.” According to the Centers for Disease Control and Prevention



IGRA is preferred in those given BCG vaccine and with low rates of test completion; TST is preferred in children under 5.

DR. SHANE

and the AAP, IGRAs are probably reliable in children over the age of 5 years, but a TST is still recommended in children under the age of 5.

The IGRAs’ specificity is much higher than TSTs, Dr. Shane said. “However, in some cases a TST might be more sensitive for detecting more remote MTB infections than an IGRA, but IGRAs may be better at detecting a recent infection. Like the TST, an IGRA also shows that if you’re infected with TB you have 5-10% chance of developing active TB in your lifetime.”

As a significant amount of blood is required to perform an IGRA, that might not always be optimal in a young child, she said. “Low CD4 counts and other immunodeficiencies have also been associated with false-negative TST and indeterminate/false-negative IGRA results.”

For contact investigations, IGRAs offer increased specificity, are completed during a single visit, and their response is not boosted if an additional evaluation is needed 8-10 weeks after exposure. If the TST or IGRA is positive, additional diagnostic efforts are needed “to differentiate between LTBI and active MTB,” said Dr. Shane, who recommended the Curry International Tuberculosis Center as a resource for clinicians (www.currytbcenter.ucsf.edu/).

If the TST or IGRA is negative, “it’s not sufficient to exclude MTB infection. If you have a discordant TST and IGRA result, consider history and epidemiologic risk factors. Treat with clinical suspicion or risk of a poor outcome (those younger than age 5 and those infected with HIV).”

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To identify the symptoms of narcolepsy, **LOOK DEEPER**

C **Cataplexy:** A sudden, temporary loss of muscle tone triggered by strong emotions^{1,2}

H **Hypnagogic Hallucinations:** Vivid dream-like experiences that occur during the transitions between wake and sleep^{1,2}

E **Excessive Daytime Sleepiness:** The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep²

S **Sleep Paralysis:** The temporary inability to move or speak while falling asleep or waking up²

S **Sleep Disruption:** The interruption of sleep by frequent awakenings^{1,2}

C.H.E.S.S. is a useful mnemonic for recalling the 5 symptoms of narcolepsy,³ although not all patients experience all symptoms.² Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy.² All patients with narcolepsy have excessive daytime sleepiness.² The presence of cataplexy is pathognomonic for narcolepsy.²

Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder^{2,3}

Narcolepsy is a chronic, life-disrupting neurologic disorder in which the brain is unable to regulate sleep-wake cycles normally, resulting in sleep-wake state instability.¹⁻⁴

Narcolepsy Is Underdiagnosed

It is estimated that approximately 50% or more of individuals with narcolepsy remain undiagnosed.¹ Initial onset of symptoms typically occurs between the ages of 15-25,² although an accurate diagnosis can take more than 10 years.¹

Narcolepsy Symptoms Can Be Difficult to Recognize

Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.^{1,2} The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.^{1,2,5} Individual symptoms should be evaluated carefully to determine whether they are due to narcolepsy or another condition. Looking deeper at the symptoms can help healthcare professionals establish a differential diagnosis.

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SLEEP STRATEGIES: Multilevel surgical approach to OSAS

BY DR. BORIS CHERNOBILSKY

Despite significant technologic, diagnostic, and therapeutic advancements, obstructive sleep apnea syndrome (OSAS) remains difficult to treat. The surgical “gold standard” for the treatment of severe OSAS remains tracheotomy. While completely bypassing all sites of upper airway obstruction, this treatment entails a significant alteration in lifestyle, may not be palatable to patients, and has cultural implications. The noninvasive “gold standard” has been positive airway pressure (PAP). When properly titrated and fitted, PAP is curative of OSAS provided the patient is compliant with therapy. Unfortunately, studies demonstrate noncompliance rates in the 40% to 54% range, which significantly drop to 84% at 1 year of use (Terri et al. *Proc Am Thoracic Soc.* 2008;5[2]: 173).



DR. CHERNOBILSKY

Alternate treatments have been proposed. These include mandibular advancement devices (MAD) and upper airway surgery. Surgery has been proposed as both adjunctive treatment to PAP and as a potential curative alternative, which does not require “maintenance” on the part of the patient but requires long-term follow-up and observation, especially in the event of symptom recurrence or major fluctuations in body mass index (BMI).

Surgery has fallen in and out of favor in the last 3 decades due to mixed observational and experimental data, particularly the difficulty in constructing good clinical surgical series, as well as the morbidity often associated with these procedures. The challenge of surgical treatment is patient selection, as well as proper surgical procedure selection for each patient. OSAS is a complex disease process composed of both fixed and fluctuating variables. In brief, it is a complex interplay of static factors such as craniofacial anatomy, cephalometrics and nasal anatomy with soft tissue fluctuations dependent on weight, age (tonsil and adenoid size, palatal length), syndromes (macroglossia, palatal function), and varying distribution of fat in the three tongue fat pads and visceral vs peripheral body fat distribution. Couple this with conditions that af-

fect muscle tone, cardiopulmonary function, “tracheal tug,” and even normal nightly variations in tone with the onset of REM and physiologic transitions that occur from one sleep stage to another, one begins to understand that the patient with OSAS requires an individualized multidisciplinary approach.

Proper understanding of the patient’s physiology and anatomy is crucial to success with treatment. The physical examination starts with inspection of the face: does the patient appear syndromic, have significant hemifacial microsomia, major maxillary or mandibular hypoplasia (or both)? These factors can lead to significant difficulty in fitting a PAP mask or MAD. Options for correction include maxillary-mandibular advancement (MMA) or isolated mandibular advancement / reconstruction. MMA is an oromaxillofacial procedure that shifts the entire maxilla and mandible forward; the soft palate, base of the tongue, and, to an extent, the larynx move forward, resulting in multilevel correction. It has the added benefit of potentially improving a patient’s occlusion and cosmetic appearance, as the chin and cheek bones advance to a more favorable position. While this is a major procedure for the patient, success rates have been reported upwards of 90% (Lei et al. *Sleep Breath.* 2000;4:137).

The nasal exam is crucial. While we start off as obligate nose breathers in infancy, this preference never goes away. Studies demonstrate that PAP requirements between nasal and oronasal masks are equivalent, but patient preference weighs heavily toward nasal masks where leak is significantly reduced (Bakker et al. *Sleep Breath.* 2012;16[3]:709).

The exam should start with the external nose looking for dorsal deviations (congenital or traumatic), a significant ptotic tip, or lateral nasal wall collapse. Repair of the nasal valve or even functional rhinoplasty are the procedures of choice for these problems.

The internal nasal exam consists of evaluation for turbinate hypertrophy, significant nasal septal deviation, widening of the middle turbinates from concha bullosa, the presence of mucosal edema from allergy or infection, extensive crusting from nasal dryness or septal perforation, significant nasal polyposis or even a nasal tumor. Initiation of PAP therapy is very often a “one-shot deal” and patients who were otherwise moti-

vated to use PAP failed because their nasal obstruction was not diagnosed. Ideally, the exam should include nasal endoscopy.

Intranasal surgical techniques include septoplasty, turbinate reduction, polypectomy, and functional endoscopic sinus surgery. While AHI is usually not significantly affected by nasal surgery, there are major im-

The challenge of surgical treatment is patient selection, as well as proper surgical procedure selection for each patient.

provements in quality of life scores and PAP compliance (Poirier, et al. *Laryngoscope.* 2014;124[1]:317). Rare patients, especially those with complete obstruction, can be cured in mild to moderate cases. In most, it is an important adjunct to the treatment of the patient with OSAS.

The exam should then proceed to the oral cavity and oropharynx. Careful note should be taken of the dentition and occlusion class, arching of the hard palate (especially in children), tongue size (Friedman or Mallampati class), length of soft palate, and uvula and tonsil size. In children and young adults, adenotonsillectomy or tonsillectomy alone can be curative as a first line therapy. Compliance issues with PAP are especially problematic in these populations. High arched palates in children can be managed with rapid maxillary expansion which can significantly broaden both the nasal and oral airway. MMA for retro / micrognathia was discussed previously.

The patient should next have a flexible laryngoscopic exam, usually a continuation of the nasal endoscopy. The nasopharynx is inspected for adenoid hypertrophy, polyps, cysts, and tumors. The palate is inspected from above. The exam proceeds to the level of the pharynx and hypopharynx with attention paid to the pharyngeal and lingual tonsils and the base of tongue position. Finally, the larynx is inspected for position of the epiglottis, laryngeal masses, vocal fold immobility, laryngomalacia, and arytenoid redundancy and prolapse with inspiration. A drug-induced sleep endoscopy (DISE) should be performed at a later date to assess these same structures dynamically in a state mimicking sleep to help guide appropriate surgical

technique. DISE was reviewed in a previous issue and will not be discussed in detail.

Nasopharyngeal lesions are treated with surgical excision. The velopharynx is usually addressed with uvulopalatopharyngoplasty which often, but not always, includes the tonsils. Various techniques have been developed to address circumferential vs anteroposterior (AP) collapse of the palate and uvula. Present practices favor soft tissue / muscle rearrangement over soft tissue ablation. One such technique preferred by the author is expansion sphincter pharyngoplasty. Lingual tonsillectomy addresses large lingual tonsils, if present.

Many operations exist to address the tongue base, and consensus as to best practice is yet to be reached. Generally, two broad categories exist: suspensory or ablative. Suspension can be accomplished with sutures along the base of tongue, hyoid fixation to the anterior mandible or thyroid cartilage, and genioglossus advancement. A novel technology recently FDA-approved shows immense promise. Upper-airway stimulation uses electrodes on the hypoglossal nerve to protrude the tongue, timing it with each respiration through an intercostal muscle sensor lead (Strollo Jr et al. STAR Trial Group. *N Engl J Med.* 2014;370[2]:139).

Ablation can be accomplished by reducing the base of tongue through the delivery of energy, such as use of radiofrequency or excising tissue through techniques like midline glossectomy. This can be accomplished both directly and with robot-assisted techniques using the daVinci system transorally (TORS).

Laryngeal techniques include epiglottopexy or epiglottectomy in cases where the epiglottis retroflexes and obstructs the airway on inspiration. Laryngeal lesions are generally addressed with excision. Vocal fold paralysis in the midline can be addressed with cordotomy or arytenoidectomy. Prolapsing redundant tissue can be tightened using a laser. Laryngomalacia can be addressed surgically, as well.

Finally, the neck should be examined. Masses, tracheal deviation, evidence of prior tracheotomy, hyoid position, circumference, and lymphadenopathy should all be noted. Masses, especially goiters, can compress the internal jugular veins leading to laryngeal and pharyngeal

Sleep strategies continued on page 13

Upper airway stimulation an OSA option

BY DOUG BRUNK
Frontline Medical News

CORONADO, CALIF. – Some patients with treatment-refractory obstructive sleep apnea may be candidates for upper airway stimulation, though those with complete concentric palatal collapse may not respond, according to Dr. Marion Boyd Gillespie.

“There’s been sound research showing that patients with obstructive sleep apnea have reduced neural tone,” Dr. Gillespie, who directs the snoring clinics at the Medical University of South Carolina, Charleston, said at the Triological Society’s Combined Sections Meeting. “During these apneic events, there’s a reduction in the neural tone of the genioglossus muscle, which is

the main dilator of the upper airway. With upper airway stimulation, we’re trying to account for that loss of neural tone by providing more neural impulse to these muscle groups that perform the dilator functions.”

In 2014, the Food and Drug Administration cleared an upper airway stimulation system manufactured by Inspire Medical Systems, a pacemaker-like device that’s implanted in the subclavicular space. The system fea-

tures a stimulator lead that attaches to the right hypoglossal nerve and a sensing lead that goes between the external and internal intercostal muscles to detect breathing, said

Continued on following page

Sleep strategies *continued from page 12*

edema. Surgical removal of the mass is the treatment of choice.

In summary, OSAS is a complex disease that often requires multiple therapeutic modalities. Proper patient selection and a thorough physical exam are crucial to proper treatment choice. Surgery can be both adjunctive and curative. Patients often have multiple levels of airway obstruction that can be treated simultaneously or staged. Careful follow-up and involvement of a multidisciplinary care team will result in the highest success rates for these patients with complex disease.

Dr. Chernobilsky is Director of Sleep and Airway Surgery, Mount Sinai Beth Israel, Assistant Professor of Otolaryngology-Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, New York.

Editor’s comments

Although positive airway pressure is the gold standard treatment for obstructive sleep apnea, poor compliance with this modality provides the impetus for alternative treatments that are both effective and acceptable to patients. Upper airway surgery is a viable alternative for select patients, either as a primary treatment modality or as adjunctive therapy. In this installment of sleep strategies, Dr. Boris Chernobilsky discusses and clarifies, from a surgical perspective, the surgical techniques available, as well as the systematic approach, in the evaluation of the patient with sleep apnea.

Dr. Jeremy A. Weingarten, FCCP

*When you need to
increase bronchodilation for
your patients with COPD...*



Continued from previous page

Dr. Gillespie, professor of otolaryngology–head and neck surgery at the university. “The sensing lead detects the respiratory wave, and the stimulatory lead starts stimulation at the end of expiration, because that’s when the airway is in its most

collapsible state. It continues about two-thirds of the way through the inspiratory cycle to keep the airway open.”

Titration of the device is very similar to continuous positive airway pressure, he continued. Once implanted, the patient “will go back to the sleep lab where a tech who’s



There’s been sound research showing that patients with OSA have reduced neural tone.

DR. GILLESPIE

trained in the device will ramp up stimulation until observed apneas and hypopneas are adequately reduced. You would think that isolated stimulation of the hypoglossal nerve would only open up the airway at the level of the tongue. However, our initial investigation showed that there is dilation at the velopharynx

Indication

Striverdi® Respimat® (olodaterol) Inhalation Spray is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations: STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD and is not indicated to treat asthma.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life threatening condition, or used as rescue therapy for acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting beta₂ agonist.

STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂ agonists as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted.

NEW

A Once-Daily LABA Maintenance Therapy for COPD

STRIVERDI® RESPIMAT® GETS RESULTS

24-Hour Bronchodilation With Effects Seen Within 5 Minutes of the First Dose¹

- Significant 24-hour response at 24 weeks when added to background therapy in a 48-week study¹
 - With the exception of other LABAs, all pulmonary medications were allowed as concomitant therapy (24% tiotropium, 25% ipratropium, 45% inhaled corticosteroids, and 16% xanthines)
- Mean increase in FEV₁ of 110 mL at 5 minutes after the first dose compared to placebo (range: 100 to 120 mL)¹
- 34% reduction in use of rescue medication at week 48 (1.2 puffs/day vs background therapy)²
 - Comparable results achieved in similarly designed trials
- **STRIVERDI RESPIMAT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms**

FEV₁, forced expiratory volume in 1 second.



as well,” Dr. Gillespie said. By moving the tongue out of the posterior airway, “you’re moving the dorsum of the tongue away from the velopharynx. You’re also getting active traction on the palatoglossal fold,” he added.

Results of the initial trial of the system in 126 patients with a mean

Before surgery, 72% of patients had severe, annoying snoring; after surgery, 15% had severe, annoying snoring.

body mass index of 28.4 kg/m² were published last year (N. Engl. J. Med. 2014;370:139-49). At 12 months of follow-up, patients experienced a 68% overall reduction in

their apnea-hypopnea index (AHI) score, from a preoperative mean of 29 to a postoperative mean of 9. In addition, patients had a 70% overall reduction in their oxygen desatu-

ration index (ODI). The researchers also observed normalization of patient-based outcomes, with improvement in the Functional Outcomes of Sleep Questionnaire score and reduction of the Epworth Sleepiness Scale score to a level of 10 on average. “We also saw a re-

Continued on following page



To learn more about
STRIVERDI RESPIMAT,
visit www.STRIVERDI.com

Please see Brief Summary of full Prescribing Information, including **boxed WARNING** for STRIVERDI RESPIMAT on adjacent page.

STRIVERDI[®]
RESPIMAT[®]
(olodaterol)
INHALATION SPRAY



STRIVERDI RESPIMAT can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms, and should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. If cardiovascular symptoms occur, STRIVERDI RESPIMAT may need to be discontinued.

STRIVERDI RESPIMAT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Be alert to hypokalemia and hyperglycemia.

Immediate hypersensitivity reactions, including angioedema, may occur. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

The most commonly reported adverse reactions (≥2% incidence and more than placebo) with STRIVERDI RESPIMAT (and placebo) were nasopharyngitis, 11.3% (7.7%); upper respiratory tract infection, 8.2% (7.5%); bronchitis, 4.7% (3.6%); urinary tract infection, 2.5% (1.0%); cough, 4.2% (4.0%); dizziness, 2.3% (2.1%); rash, 2.2% (1.1%); diarrhea, 2.9% (2.5%); back pain, 3.5% (2.7%); and arthralgia 2.1% (0.8%).

STRIVERDI RESPIMAT should be used with extreme caution in patients treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated.

STRIVERDI RESPIMAT should be used with caution in patients treated with additional adrenergic drugs, non-potassium-sparing diuretics, and beta-blockers.

STRIVERDI RESPIMAT is for oral inhalation only.

Please see full Prescribing Information, including **boxed WARNING**, Medication Guide, and Instructions for Use.

References:

1. STRIVERDI RESPIMAT prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. 2. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

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Continued from previous page

duction of snoring,” said Dr. Gillespie, who was a member of the research team. “Snoring went from 72% of patients having severe, annoying snoring to the point where a bed partner leaves the room, to 15% postoperatively.” Even so, 96%

of patients who had a previous history of uvulopalatopharyngoplasty (UPPP) or laser-assisted uvulopalatoplasty (LAUP) still had tongue-based collapse after 12 months of follow-up. “But we found that their response to this therapy was just as good as people who had never had a UPPP or LAUP,” Dr. Gillespie said

at the meeting, jointly sponsored by the Triological Society and the American College of Surgeons. “So it seems like patients who have failed UPPP are still good candidates for upper airway stimulation therapy.”

Dr. Gillespie noted that selection criteria for the trial were limited to

patients with a BMI of less than 32 kg/m² and to those who did not have complete circumferential collapse at the level of the soft palate on preoperative drug-induced endoscopy. These criteria were based on an earlier pilot study that showed that patients with complete circumferential collapse at the level of the soft palate did not respond to upper airway stimulation (J. Clin. Sleep Med. 2013;9:433-8).

Dr. Gillespie is a consultant for and has received research support from Inspire Medical Systems, Olympus, and Surgical Specialties. He is also a consultant for Medtronic.

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VIEW ON THE NEWS

Dr. David A. Schulman, FCCP, comments: The data presented by Dr. Gillespie add to the growing body of literature showing the benefits of stimulation of the upper airway muscles during sleep in a selected subgroup of obstructive sleep apnea (OSA) patients, demonstrating improvements in both physiologic and functional parameters. Given the well-described issues with continuous positive airway pressure (CPAP) adherence and the lesser



efficacy of currently available CPAP alternatives, patients with obstructive sleep apnea and their providers have long awaited access to hypoglossal nerve stimulators to add to the armamentarium of options for management of the disorder. While early data continue to show promise for this treatment, a number of physiologic and anatomic characteristics serve as relative contraindications, limiting the generalizability of study results to some patient populations (such as those with body mass index greater than 32 kg/m² or those with concentric collapse of the soft palate). While upper airway stimulation is not likely to be the first-line OSA treatment for the majority of patients, it is an important step forward for those unwilling or unable to use CPAP.

STRIVERDI® RESPIMAT® (olodaterol) Inhalation Spray FOR ORAL INHALATION BRIEF SUMMARY OF PRESCRIBING INFORMATION Please see package insert for full Prescribing Information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications, Warnings and Precautions].

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STRIVERDI RESPIMAT is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. **Important Limitations of Use:** STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STRIVERDI RESPIMAT in asthma have not been established.

CONTRAINDICATIONS: All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

WARNINGS AND PRECAUTIONS: Asthma-Related Death [see Boxed Warning]: Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists 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 long-acting beta₂-adrenergic agonists. A 28-week, placebo-controlled US study comparing the safety of another long-acting beta₂-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta₂-adrenergic agonists, including STRIVERDI RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STRIVERDI RESPIMAT has been conducted. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications]. **Deterioration of Disease and Acute Episodes:** STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STRIVERDI RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STRIVERDI RESPIMAT in this setting is inappropriate. STRIVERDI RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STRIVERDI RESPIMAT 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 beta₂-agonist. When beginning STRIVERDI RESPIMAT, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing STRIVERDI RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled beta₂-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 STRIVERDI RESPIMAT no longer controls symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-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 dosage of STRIVERDI RESPIMAT beyond the recommended dose is not appropriate in this situation. **Excessive Use of STRIVERDI RESPIMAT and Use with Long-Acting Beta₂-Agonists:** As with other inhaled drugs containing beta₂-adrenergic agonists, STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. **Paradoxical Bronchospasm:** As with other inhaled beta₂-agonists, STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted. **Cardiovascular Effects:** STRIVERDI RESPIMAT, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STRIVERDI RESPIMAT may need to be discontinued. In addition, beta₂-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Long acting beta₂-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. **Co-existing Conditions:** STRIVERDI RESPIMAT, like other sympathomimetic amines, should be used with caution in patients

with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia: Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment [see Drug Interactions], which may increase the susceptibility for cardiac arrhythmias. Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of STRIVERDI RESPIMAT with the rates similar to those for placebo controls. STRIVERDI RESPIMAT has not been investigated in patients whose diabetes mellitus is not well controlled. **Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including angioedema, may occur after administration of STRIVERDI RESPIMAT. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

ADVERSE REACTIONS: Long-acting beta₂-adrenergic agonists, such as STRIVERDI RESPIMAT, increase the risk of asthma-related death. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Boxed Warning and Warnings and Precautions]. Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: 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 STRIVERDI RESPIMAT clinical development program included seven dose-ranging trials and eight confirmatory trials. Four of the confirmatory trials were 6-week cross-over trials and four were 48-week parallel group trials. Adverse reactions observed in the dose-ranging trials and four 6-week cross-over trials were consistent with those observed in the 48-week parallel group trials, which formed the primary safety database. The primary safety database consisted of pooled data from the four 48-week double-blind, active and placebo-controlled, parallel group confirmatory clinical trials. These trials included 3104 adult COPD patients (77% males and 23% females) 40 years of age and older. Of these patients, 876 and 883 patients were treated with STRIVERDI RESPIMAT 5 mcg and 10 mcg once-daily, respectively. The STRIVERDI RESPIMAT groups were composed of mostly Caucasians (66%) with a mean age of 64 years and a mean percent predicted FEV₁ at baseline of 44% for both the 5 mcg and 10 mcg treatment groups. Control arms for comparison included placebo in all four trials plus formoterol 12 mcg in two trials. In these four clinical trials, seventy-two percent (72%) of patients exposed to any dose of STRIVERDI RESPIMAT reported an adverse reaction compared to 71% in the placebo group. The proportion of patients who discontinued due to an adverse reaction was 7.2% for STRIVERDI RESPIMAT treated patients compared to 8.8% for placebo treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation, pneumonia, and atrial fibrillation. Table 1 shows all adverse drug reactions reported by at least 2% of patients (and higher than placebo) who received STRIVERDI RESPIMAT 5 mcg during the 48-week trials.

Table 1: Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to STRIVERDI RESPIMAT 5 mcg: Pooled data from the four 48-week, double-blind, active- and placebo-controlled clinical trials in COPD patients 40 years of age and older

Treatment	STRIVERDI 5 mcg once-daily	Placebo
Body system (adverse drug reaction)	n=876 n (%)	n=885 n (%)
Infections and infestations		
Nasopharyngitis	99 (11.3)	68 (7.7)
Upper Respiratory Tract Infection	72 (8.2)	66 (7.5)
Bronchitis	41 (4.7)	32 (3.6)
Urinary Tract Infection	22 (2.5)	9 (1.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	37 (4.2)	35 (4.0)
Nervous system disorders		
Dizziness	20 (2.3)	19 (2.1)
Skin and subcutaneous tissue disorders		
Rash*	19 (2.2)	10 (1.1)
Gastrointestinal disorders		
Diarrhea	25 (2.9)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back Pain	31 (3.5)	24 (2.7)
Arthralgia	18 (2.1)	7 (0.8)

* Rash includes a grouping of similar terms.

Additional adverse reactions that occurred in greater than 2% (and higher than placebo) of patients exposed to STRIVERDI RESPIMAT 10 mcg were pneumonia, constipation, and pyrexia. Lung cancers were reported in 6 (0.7%), 3 (0.3%), and 2 (0.2%) patients who received STRIVERDI RESPIMAT 10 mcg, 5 mcg, and placebo, respectively.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of STRIVERDI RESPIMAT may be potentiated [see Warnings and Precautions]. **Xanthine Derivatives, Steroids, or Diuretics:** Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of STRIVERDI RESPIMAT [see Warnings and Precautions].

Non-Potassium Sparing Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs:** STRIVERDI RESPIMAT, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and STRIVERDI RESPIMAT may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. **Inhibitors of Cytochrome P450 and P-gp Efflux Transporter:** In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of maximum plasma concentrations and AUC was observed. STRIVERDI RESPIMAT was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with STRIVERDI RESPIMAT in pregnant women. STRIVERDI RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. STRIVERDI RESPIMAT was not teratogenic in rats at inhalation doses approximately 2,731 times the maximum recommended human daily inhalation dose (MRHDID) on an AUC basis (at a rat maternal inhalation dose of 1,054 mcg/kg/day). Placental transfer of STRIVERDI RESPIMAT was observed in pregnant rats. STRIVERDI RESPIMAT has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7,130 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 2,489 mcg/kg/day). STRIVERDI RESPIMAT exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at an inhalation dose approximately 1,353 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 974 mcg/kg/day).

Labor and Delivery: There are no adequate and well-controlled human studies that have investigated the effects of STRIVERDI RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STRIVERDI RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. **Nursing Mothers:** Olodaterol, the active component of STRIVERDI RESPIMAT, and/or its metabolites are excreted into the milk of lactating rats. Excretion of olodaterol and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of STRIVERDI RESPIMAT on nursing infants. Caution should be exercised when STRIVERDI RESPIMAT is administered to nursing women. **Pediatric Use:** STRIVERDI RESPIMAT is not indicated for use in children. The safety and effectiveness of STRIVERDI RESPIMAT in the pediatric population have not been established. **Geriatric Use:** Based on available data, no adjustment of STRIVERDI RESPIMAT dosage in geriatric patients is necessary. Of the 876 patients who received STRIVERDI RESPIMAT at the recommended dose of 5 mcg once-daily in the clinical studies from the pooled 1-year database, 485 were less than or equal to 65 years of age and 391 (44.6%) were greater than 65 years of age. No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Hepatic Impairment:** Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed. **Renal Impairment:** Subjects with severe renal impairment showed no clinically relevant changes in C_{max} or AUC compared to their healthy controls.

OVERDOSAGE: The expected signs and symptoms with overdose of STRIVERDI RESPIMAT are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of STRIVERDI RESPIMAT. Treatment of overdose consists of discontinuation of STRIVERDI RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdose of STRIVERDI RESPIMAT. Cardiac monitoring is recommended in cases of overdose.

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Panel backs antifungal for invasive aspergillosis

BY ELIZABETH MECHCATIE
Frontline Medical News

SILVER SPRING, MD. – A novel treatment for invasive aspergillosis and invasive mucormycosis gained the support of a Food and Drug Administration advisory panel, although members were ambivalent about the mucormycosis indication, based on the small study size.

The FDA's Anti-Infective Drugs Advisory Committee voted 11-0 that there was "substantial evidence" that isavuconazonium, an antifungal pro-

drug, was safe and effective for the treatment of invasive aspergillosis. A phase III study compared isavuconazonium to voriconazole, the standard of care, in more than 500 patients.

The panel voted 8-2, with one abstention, that there was substantial evidence isavuconazonium is safe and effective for treating patients with invasive mucormycosis, with panelists citing concerns about a study size of only 37 patients and historical controls. If approved for mucormycosis, the panel said that the manufacturer, Astellas, should be required to con-

duct a phase IV trial further evaluating treatment in this population.

Isavuconazonium is a prodrug of isavuconazole, a triazole antifungal, and would be available as an oral capsule and as a powder formulation reconstituted for intravenous administration through an in-line filter.

For aspergillosis, "I do believe that this drug provides a reasonable alternative ... without additional toxicities," said panelist Dr. Paige Waterman of the Global Emerging Infections Surveillance and Response System at the Walter Reed Army Medical Center, Silver Spring, Md. Labeling should make clear that the drug should not be used in people under age 18 years or in pregnant women, and that a filter should be used with IV administration. Also, labeling should state a risk of hepatotoxicity, which appears in the labeling of other drugs in the same class.

Because isavuconazonium has been associated with a shortened QT interval, Dr. Waterman said that screening ECGs should be recommended. There should be extra caution when prescribing the drug to those of Asian descent, since drug concentrations were higher in those patients.

For treatment of invasive mucormycosis, those voting in favor of approval cited the significance of the condition and the reasonable efficacy results. Panelists also noted that more clinical data are clearly needed and that the lack of data directly comparing isavuconazonium to amphotericin B – the only FDA-approved drug for this indication – was problematic.

Isavuconazonium "really does fill an unmet need; I have high hopes that it is at least as good as amphotericin. But I do think we need more data to confirm that," said Dr. Michael Neely, chair of antimicrobial stewardship at Children's Hospital, Los Angeles, who voted for this indication.

If approved, isavuconazonium would provide an alternative to voriconazole for treating aspergillosis. Further, the IV formulation of isavuconazonium does not contain cyclodextrin, which is present in the IV formulation of voriconazole and limits its use in patients with moderate to severe renal dysfunction, according to Astellas. Safety concerns include QT-segment shortening and particulate formation in the IV formulation, according to the FDA.

The randomized, double-blind, international, noninferiority study compared treatment with isavucona-

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: Serious fungal infections are being increasingly recognized in patients who are immunocompromised or criti-



cally ill, but effective treatments with an acceptable side-effect profile have been sparse. Just a few years ago, the mainstay

of treatment was amphotericin, an agent whose use has been associated with a variety of complications. However, novel agents have been developed that hold promise. The recent development of isavuconazonium, a prodrug of isavuconazole, may lead to further augmentation of the clinician's armamentarium in fighting these illnesses.

zationium to voriconazole in 516 adults with invasive aspergillosis. In the randomized study, 11% of patients were in the United States and Canada, 20% had had an allogeneic bone marrow transplant, and 70% had an uncontrolled malignancy (*Infect. Drug Resist.* 2013;6:16374). The primary effectiveness endpoint, all-cause mortality through day 42, was

19% in those on isavuconazonium, compared with 20% in those on voriconazole. There were fewer events in those on isavuconazonium requiring discontinuation of the drug (14% vs. 23%). Decreases in the QT segment occurred in 7.5% of those on isavuconazonium, compared with 4.5% of those on voriconazole, but were not associated with events.

The prospective, open-label, single-arm study evaluated isavuconazonium in 37 patients with proven or probable mucormycosis infections; 59% had a hematologic malignancy, and about 40% were neutropenic at baseline. All-cause mortality at day 42 was 38%, which was similar to the mortality rate for amphotericin in the literature, according to Astellas.

Besides voriconazole, drugs approved for aspergillosis include amphotericin, itraconazole, and caspofungin. Astellas will market isavuconazonium as Cresemba if approved.

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Reviewers from the FDA's Division of Anti-Infective Products listen to testimony at the advisory committee meeting.

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ABIM responds to criticism, makes changes to MOC

BY ALICIA GALLEGOS
Frontline Medical News

In a frank announcement, the American Board of Internal Medicine has apologized to doctors for a Maintenance of Certification program that “clearly got it wrong,” and pledged to make the program more consistent with internists’ practice and values.

Among the immediate changes: updates to its internal medicine exam; suspension of the practice assessment, patient voice, and patient safety requirements for at least 2 years; and MOC enrollment fees set at or below the 2014 levels through at least 2017.

Dr. David A. Fleming, president of the American College of Physicians (ACP), called the move monumental and historic.

“This turnaround has occurred in the face of mounting pressure and discontent expressed by a growing number of U.S. internists concerned about the MOC process,” Dr. Fleming said in an interview. “With the new changes in MOC, internists are still being held accountable and responsible for maintaining profes-

sional competence, but by removing the practice assessment and patient [safety] requirements that are not well supported by evidence, we go a long way in taking the pressure off very busy physicians who already feel burdened by many layers of regulatory and administrative reporting that many view as burdensome and a barrier to our first duty – caring for patients.”

In a statement, ABIM President and CEO Richard J. Baron said it was clear that aspects of the program were not meeting physicians’ needs.

“We got it wrong and sincerely apologize,” Dr. Baron said in the statement. “We are sorry. ABIM is changing the way it does its work so that it is guided by, and integrated fully with, the medical community that created it. The goal is to co-create an MOC program that reflects the medical community’s shared values about the practice of medicine today and provides a professionally created and publicly recognizable framework for keeping up in our discipline.”

As part of the newly announced changes, ABIM will make its internal

medicine exam more reflective of physician practice, with changes to be incorporated in fall 2015, according to the announcement. The decision to suspend the practice assessment, patient voice, and patient safety requirements means internists who have not completed activities in these areas



‘If you got something wrong, you apologize for it’ and you commit to trying to get it right.

DR. BARON

will not have their certification status changed. Diplomates who are currently uncertified but who have satisfied all requirements for MOC except for the practice assessment requirement will be issued a new certificate this year. Within the next 6 months, ABIM will also change the language used to publicly report a diplomate’s MOC status on its website from “meeting MOC requirements” to “participating in MOC.”

By the end of 2015, ABIM said it

will ensure new and more flexible ways for internists to demonstrate self-assessment of medical knowledge by recognizing most forms of Accreditation Council for Continuing Medical Education–approved continuing medical education. An online FAQ provides more information on the changes.

ABIM initially revamped its certification policies beginning in January 2014, shortening the time physicians had to earn MOC points and publishing online whether doctors were meeting requirements. The actions meant that every 2 years physicians certified by ABIM had to earn at least some points by completing some of the educational activities approved for MOC credit, and at the 5-year mark, earn 100 points. Previously, physicians were given 10 years to earn 100 points. Physicians were also listed publicly as either “certified, meeting maintenance of certification requirements” or “certified, not meeting MOC requirements.”

The changes were met with almost immediate backlash. Doctors expressed frustration that the requirements were burdensome, expensive,

Continued on following page

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October start favored for ICD-10

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – The transition to the ICD-10 coding set should take place as planned on Oct. 1, witnesses testified at a hearing of the House Energy and Commerce Committee's Subcommittee on Health.

The message was welcome to committee leadership, who invited testimony almost solely from experts who support that position.

Subcommittee members from both sides of the aisle expressed a desire to not delay the implementation any further, though some at

the Feb. 11 hearing questioned whether the Centers for Medicare & Medicaid Services was ready for the transition.

Subcommittee member Rep. Michael Burgess (R-Tex.), an

ob.gyn., said he had no questions about the readiness of Medicare contractors and insurance companies for the transition, but "all roads eventually lead to the Centers for Medicare & Medicaid Services.

And if you will pardon me, that does appear to be a weak link in the chain because from HealthCare.gov to the Sunshine Act reporting website, when CMS flips a switch, something breaks."

Continued from previous page

and irrelevant. By January 2015, a Web-based petition against the program garnered more than 19,000 signatures and has drawn thousands of comments in protest of the new requirements. A second petition had nearly 6,000 signatures with doctors taking a "pledge of noncompliance" with the requirements.

A January perspective piece in the New England Journal of Medicine expressed that the MOC program is essentially a money-generating activity for the ABIM and that the organization has lost contact with the realities of day-to-day clinical practice.

In an interview, Dr. Baron said such feedback drove ABIM to make the changes. He acknowledged that it would take time to build back trust within the community.

"Part of why we're taking the steps we're taking is that it's critical to have trust with the community," Dr. Baron said. "Part of how you do that is if you got something wrong, you apologize for it, you acknowledge you got it wrong, and you commit to making changes and try to get it right."

Dr. Baron noted that ABIM will be working with medical societies and directly with diplomates to seek input regarding the MOC program through meetings, webinars, forums, online communications channels, surveys, and other mediums.

"I fervently hope that we will come together as a community to figure out how to build a program that embodies and actualizes the values that internists have," he said in the interview. "We're going to need a lot of community participation to make that work and I hope that people will step up."

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment.

In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury.

Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Gastrointestinal Disorders

Diarrhea

Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. In most patients, the event was of mild to moderate intensity and occurred

within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients.

Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV.

Nausea and Vomiting

Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients.

Please see additional Important Safety Information on next page and accompanying brief summary.

While no representative from the CMS testified, a report from the Government Accountability Office suggested that the agency is positioned to make the transition to ICD-10 by the Oct. 1 deadline, although continued testing is warranted. That report was commissioned by the Senate Finance Committee,

which also expressed support for an Oct. 1 start date for ICD-10.

Kristi Matus, chief financial and administrative officer for Athenahealth, testified to the general readiness of the health IT community to make the switch to ICD-10. The government should either “maintain the current date for ICD-10 imple-

mentation or cancel it once and for all. Pull the trigger or pull the plug,” Ms. Matus said.

Dr. William J. Terry Sr., a urologist from Mobile, Ala., testified on behalf of the American Urological Association and expressed concern that not all physicians are ready.

He suggested that a transition

period might allow physicians and other providers to run ICD-9 and ICD-10 simultaneously to ensure that physicians do not inadvertently lose any payments because of coding errors that might occur as they learn the new system.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV.

Embryofetal Toxicity

OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

Arterial Thromboembolic Events

Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding

Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation

Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in $\geq 5\%$ of patients treated with OFEV and more commonly than in patients treated with placebo included diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs 6%), liver enzyme elevation (14% vs 3%), vomiting (12% vs 3%), decreased appetite (11% vs 5%), weight decreased (10% vs 3%), headache (8% vs 5%), and hypertension (5% vs 4%).
- The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant

(0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients.

DRUG INTERACTIONS

P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers

Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

Anticoagulants

Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

Nursing Mothers

- Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic Impairment

- Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment (Child Pugh A). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended.

Smokers

- Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

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Please see accompanying brief summary on next page.



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GOP lawmakers offer ACA alternative plus tort reform

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Three Republican lawmakers are proposing an alternative to the Affordable Care Act

that would undo the individual and employer mandates, cap medical liability damages, and offer a slimmed-down set of consumer insurance protections.

Sen. Orrin Hatch (R-Utah), chair

of the Senate Finance Committee; Rep. Fred Upton (R-Mich.), chair of the House Energy and Commerce Committee; and Sen. Richard Burr (R-N.C.), a Senate Finance Committee member, proposed

the Patient Choice, Affordability, Responsibility, and Empowerment (CARE) Act to repeal and replace the health law.

“Our nation’s health care system was broken before Obamacare, and

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests prior to initiating treatment with OFEV [see Warnings and Precautions]. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. **Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV [see Warnings and Precautions and Adverse Reactions]. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) [see Warnings and Precautions and Adverse Reactions]. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment [see Use in Specific Populations]. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN [see Use in Specific Populations]. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders: Diarrhea:** Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the

reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV (nintedanib). **Nausea and Vomiting:** Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV [see Use in Specific Populations]. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations [see Warnings and Precautions]; Gastrointestinal Disorders [see Warnings and Precautions]; Embryofetal Toxicity [see Warnings and Precautions]; Arterial Thromboembolic Events [see Warnings and Precautions]; Risk of Bleeding [see Warnings and Precautions]; Gastrointestinal Perforation [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 OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to

89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV (nintedanib), more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain ^a	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation ^b	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension ^c	5%	4%

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

^b Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

^c Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 inhibitors and inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust

the President's health care debacle has only made things worse," Sen. Burr said in a statement. "The Patient CARE Act repeals Obamacare and addresses the fundamental cost drivers that Obamacare failed to address. We can lower costs and expand access to quality coverage and care by empowering individuals and their

families to make their own health care decisions."

The Patient CARE Act outlines some federal medical liability reforms, including a cap on non-economic damages and limits on attorneys' fees. It also seeks to encourage new models for resolving disputes on the state level, such as ex-

pert panels to evaluate injury claims and administrative health courts.

The proposal offers a more limited range of consumer insurance protections than does the ACA, including:

- Adopting an age rating ratio of 5-1 for premiums, which would limit plans from charging older individuals any more than five times what

anticoagulation treatment as necessary [see *Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category D.* [see *Warnings and Precautions*]: OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed

between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see *Warnings and Precautions*]. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (*Patient Information*). **Liver Enzyme and Bilirubin Elevations:** Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites 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*]. **Gastrointestinal Disorders:** Inform patients that gastrointestinal disorders such as diarrhea, nausea,

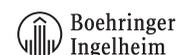
and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see *Warnings and Precautions and Adverse Reactions*]. **Pregnancy:** Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV [see *Warnings and Precautions and Use in Specific Populations*]. **Arterial Thromboembolic Events:** Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see *Warnings and Precautions*]. **Risk of Bleeding:** Bleeding events have been reported. Advise patients to report unusual bleeding [see *Warnings and Precautions*]. **Gastrointestinal Perforation:** Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see *Warnings and Precautions*]. **Nursing Mothers:** Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing [see *Use in Specific Populations*]. **Smokers:** Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. **Administration:** Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see *Dosage and Administration*].

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VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: With a new Congress controlled by Republicans, and given the prior attempts to overturn the Patient Protection and Affordable Care Act (a.k.a. "Obamacare"), it is not surprising that early in this legislative session an alternative plan has been proposed. One could ar-



gue some of the points of the proposal but not the accuracy of the statement made by one of the bill's authors that "our nation's

health care system was broken before Obamacare." While this bill does address some issues of importance to physicians, it is certainly disappointing that this bill does not address the Sustainable Growth Rate formula (SGR). This looming threat of a 20% or more cut in physician reimbursement will do more harm to patient access and care than any other aspect addressed in this bill. Unfortunately, physicians rarely advocate at the federal level for themselves or their patients. Perhaps, with the introduction of this bill, it is the time to start.

a younger person pays. Under the ACA, the age rating ratio is 3-1.

- Banning the use of lifetime dollar limits on health coverage.

- Allowing states to opt out of the ACA's dependent coverage provision, which lets young adults stay on their parents' health plans up to age 26.
- Providing guaranteed renewability, with plans able to cancel coverage only



SEN. HATCH

in cases of fraud, misrepresentation, or failure to pay premiums.

- Banning denials of coverage based on preexisting medical conditions as long as the individual has been continuously covered for 18 months. The proposal includes a one-time open enrollment for people currently uninsured.

PRESIDENT'S REPORT: Collaborating to achieve great things

BY DR. CURTIS N. SESSLER,
FCCP

One of the most satisfying roles of a leader is to see the hard work of dedicated individuals pay off with a successful event or product. I find this particularly gratifying when the work is the result of collaboration among key groups who bring different perspectives and, by virtue of combining forces, make a greater impact on important issues.

Recently, I had the honor of being one of several representatives of our organization to the annual business meeting of the Forum of International Respiratory Societies (FIRS), in Cape Town, South Africa. CHEST is one of seven founding professional societies that represent all regions of the world – from the Pan African Thoracic Society (PATS) to the Asia Pacific Society of Respiriology (APSR) and the European Respiratory Society (ERS) – all “united for lung health.” Established in 2001, the Forum is dedicated to controlling respiratory disease worldwide and promotes advocacy in matters of respiratory health. CHEST leaders have played prominent roles in FIRS

activities that help influence international health policy and contribute to better care of patients worldwide. For example, CHEST Past President Darcy Marciniuk chaired and was lead author of the recent sentinel FIRS document, *Respiratory Diseases in the World: Realities of Today – Opportunities for Tomorrow*, which draws attention to the magnitude and



DR. SESSLER

opportunities for improving management of the five main global respiratory diseases: COPD, asthma, TB, respiratory infections, and lung cancer. Among its list of activities to promote lung health, FIRS develops position statements that influence key organizations like the World Health Organization and United Nations in important areas, with recent examples of statements on e-cigarettes and on Ebola virus disease. Additionally, FIRS and member organizations actively support greater awareness of important respiratory

problems internationally through promotion of events like “World No Tobacco Day” and “World Asthma Day.” Watch for CHEST sponsorship of “World Lung Cancer Day.” Clearly, this group of professional societies that spans the globe has a louder voice to call attention to respiratory illness and improve health than that of a single organization.

CHEST is dedicated to improving the care of our critically ill patients and through the Critical Care Societies Collaborative (CCSC) has contributed to the advancement of intensive care medicine on many fronts. Founded in 2000, the CCSC – composed of the four major American professional and scientific critical care societies (American Association of Critical-Care Nurses (AACN), American Thoracic Society (ATS), Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (CHEST)) – represents greater than 150,000 critical care professionals and has addressed a myriad of important topics. Noteworthy efforts by the CCSC include publishing statements on critical care research, critical care training and competency, ICU tele-medicine, and ICU workforce shortage, as well as directly addressing research needs with key leaders within the National Institutes of Health and other federal funding agencies and collaborating with the CDC on issues related to nosocomial pneumonia.

The CCSC recently contributed to the “Choosing Wisely” campaign – which is dedicated to addressing common but overutilized tests and treatments, aiming to eliminate low-value but expensive care. With four professional societies, CCSC represented the largest collaborative group to contribute to the Choosing Wisely series and the first to include a professional nursing society (AACN) – accurately reflecting the multiprofessional nature of ICU care.

One of the current CCSC projects focuses on the challenging nature of work in the ICU setting and its impact on care providers. In fact, in a recent survey, intensivists had the highest rate of burnout among all specialties. I have the honor of chairing our multiprofessional CCSC work group tasked with examining the frequency, causes, and consequences of burnout syndrome among ICU health-care workers. Our intentions are to raise awareness among administrators and policymakers of ICU Burnout Syndrome and to help establish the frame-

work for potential solutions to this pervasive and critical problem.

The power of collaboration of CHEST with other professional societies extends to another core mission of our organization, that of synthesizing the medical literature and developing well-reasoned recommendations for clinicians through publication of evidence-based clinical practice guidelines. A recent noteworthy example is the comprehensive set of recommendations for the Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease developed in collaboration with the Canadian Thoracic Society (CTS) and published in *CHEST* (*Chest*. Oct 2014. Online First). Similarly, CHEST recently collaborated with the ATS to publish a combined CHEST and ATS

The Forum of International Respiratory Societies develops position statements that influence key organizations . . . recent examples include statements on e-cigarettes, and on Ebola virus disease.

policy statement on high-quality lung cancer screening, also published in *CHEST* (*Chest*. 2015;147[2]:295). In addition to providing practical information necessary for high quality lung cancer screening for practitioners and institutions, this important evidence-based document was highly influential in guiding CMS to make recent changes in coverage.

Finally, collaboration can assume the form of guidance and assistance in development of new programs. In 2013, leaders and experts in graduate medical education from CHEST, in collaboration with leaders from the Chinese Thoracic Society (CTS), developed and initiated a plan to create the first formal Pulmonary and Critical Care Medicine (PCCM) fellowship training programs in China. Leaders from major teaching hospitals in China were recruited, curricula developed, and the first class of PCCM fellows enrolled. The challenges and the magnitude of the task require dedication and true collaboration that include genuine appreciation for differences in culture, in expectations, and ongoing mutual respect. It is exciting to anticipate the results of this collaboration with the graduation of the first class of PCCM fellows coinciding with CHEST World Congress 2016 in Shanghai.



“I am honored to have received a CHEST Foundation grant! It’s enabling me to collect data that will be used in my K23 application and supporting my transition from fellow to junior faculty.”

Alison Lee, MD



Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars in a field of expertise.

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Call for Abstracts

Submission Deadline: April 1
Submit an abstract of your original investigative work for presentation at the meeting. Accepted abstracts will be published in an online supplement to *CHEST*. Three types of abstracts will be considered:

- Slide presentations
- Poster presentations
- Poster discussions

Learn more and submit at chestmeeting.chestnet.org.

Call for Case Reports

Submission Deadline: April 1
Submit case reports for presentation during special sessions. Accepted case reports (excluding clinical case puzzlers) will be published in an online supplement to *CHEST*. Four types of case reports will be considered:

- Affiliate case reports
- Medical student/resident case reports
- Global case reports
- Clinical case puzzlers

Learn more and submit at chestmeeting.chestnet.org.

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Call for Moderators

Moderators are needed on-site during the meeting. Responsibilities include reviewing the abstracts and case reports prior to the meeting, then facilitating discussion, questions, and answers within your assigned session(s). All slide sessions and most poster sessions will have two moderators. Moderators will be recognized in the CHEST 2015 program and will

receive a reduced registration rate to the meeting. Travel reimbursement will not be offered. Learn more at chestmeeting.chestnet.org.

The CHEST Foundation 2015 Grants Program

Application Deadline: April 30
The CHEST Foundation tradition of recognizing and rewarding health-care professionals for scholarly projects and research continues. Grants for both leaders in chest medicine and young investigators are available, including:

- CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency - \$25,000 1-year grant
- CHEST Foundation Research Grant in Women's Lung Health - \$10,000 1-year grant
- CHEST Foundation Research Grant in Pulmonary Fibrosis - \$30,000 1-year grant
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease - \$50,000 1-year grant
- CHEST Diversity Committee Minority Investigator Research Grant - \$25,000 1-year grant

- Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP - up to \$15,000 1-year grant
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension - \$50,000 1-year grant
- Eli Lilly and Company Distinguished Scholar in Critical Care Medicine - \$150,000 for 3 years

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Play CHEST Challenge

Game Ends: May 30
CHEST affiliate members, play CHEST Challenge to test your knowledge of pulmonary, critical care, and sleep medicine while competing for prizes. The three top-scoring programs will compete in the CHEST Challenge Championship at CHEST Annual Meeting 2015. All championship players will receive:

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- Complimentary hotel
- Cash prizes

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Innovation, Simulation, and Training Center



CHEST 2015 Education Calendar



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April 30-May 1

Critical Care Echocardiography
May 28-30

Advanced Critical Care Echocardiography
May 28-30

Celebration of Pediatric Pulmonology
June 12-13

Comprehensive Pleural Procedures
June 19-20

Difficult Airway Management
July 16-18

Mechanical Ventilation: Advanced Critical Care Management
July 30-August 1

Pulmonary Procedures for the Intensivist
August 7-8

Ultrasonography: Essentials in Critical Care
September 10-12

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 24-26

Focused Thoracic and Vascular Ultrasound
November 12-13

Critical Care Echocardiography
November 14-15

Ultrasonography: Essentials in Critical Care
December 3-5

CHEST Board Review
Gaylord National Resort and Convention Center
Washington, DC

Critical Care Medicine
August 21-24

Sleep Medicine
August 22-24

Pulmonary Medicine
August 26-30

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Meet ABIM's Pulmonary Disease Board

BY DR. SERPIL C. ERZURUM
Chair, ABIM Pulmonary Disease Board

As you have likely heard, the American Board of Internal Medicine (ABIM) has recently introduced a number of changes to its Maintenance of Certification (MOC) program, but what you may not know is that its governance structure has also undergone some important changes, including the formation of new specialty boards.

In the past, the specialty boards or test writing committees were charged with developing new exam questions, and due to the amount of time and effort involved in this process, they had little time to weigh in on specialty-specific issues related to certification and MOC.

One of the major criticisms of the MOC program is that certain requirements do not have options relevant to specific specialties or that on-the-ground physicians were not engaged in the process. In direct response to that criticism, ABIM established these specialty boards so they could:

- Define, refine, and set standards for certification and MOC in the discipline;
- Perform oversight/review of performance assessments in the discipline; and to
- Build partnerships with societies and other organizational stakeholders.

The secure examination will continue to be developed by a separate, dedicated group of physicians but will now be referred to as exam committees, ie, Pulmonary Disease Board Exam Committee.

As the Chair of the ABIM's Pulmonary Disease Board, I am excited to take this opportunity to introduce the role of this newly formed specialty board, as well as introduce its members.

The ABIM Pulmonary Disease

Board, along with nine other specialty boards, held their inaugural meetings this fall. Each of the specialty boards consist of practicing ABIM Board-Certified physicians, an intraprofessional team member, and a patient representative.

Members of the ABIM Pulmonary Disease Board include:

Dr. Serpil C. Erzurum, Chair, Cleveland, OH

I am board-certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, practice Pulmonary Medicine at the Cleveland Clinic and serve as the Alfred Lerner Chair of the Department of Pathobiology in the Lerner Research Institute.

Dr. Kevin M. Chan, FCCP, Ann Arbor, MI

Dr. Chan, who is board-certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, is Fellowship Program Director for the Division of Pulmonary and Critical Care Medicine, and Medical Director of Lung Transplantation at the University of Michigan.

Dr. John Allen Cooper, Birmingham, AL

Dr. Cooper, who is board-certified in Internal Medicine and Pulmonary Disease, is Professor of Medicine at the University of Alabama Medical School, and Chief of the Pulmonary Section at the Birmingham Veteran's Administration Medical Center.

Dean R. Hess, PhD, RRT, FCCP, Boston, MA

Dr. Hess, our intraprofessional member, is Assistant Director of Respiratory Care, Massachusetts General Hospital, and Associate Professor of Anesthesia, Harvard Medical School.



(From Left to Right) Dr. Chan, Dr. Hess, Dr. Tanoue, Dr. Cooper, Dr. Erzurum, Mrs. Lambert, Dr. Nelson, and Dr. Siu

Tomye Lambert, MBA, MDIV, Hoover, AL

Mrs. Lambert, our patient representative, is a leader in the caregiver community who focuses on patient-doctor communication and collaboration and was primary caregiver for 28 years to her daughter who suffered with cystic fibrosis. Mrs. Lambert earned her MDIV at Beeson Divinity School, Samford University, and her Executive MBA from the University of Alabama.

Dr. Michael E. Nelson, FCCP, Shawnee Mission, KS

Dr. Nelson, who is board-certified in Internal Medicine, Sleep Medicine, Pulmonary Disease, and Critical Care Medicine, is a practicing physician in Shawnee Mission, Kansas, and Medical Director of the Sleep Laboratory of the Shawnee Mission Medical Center.

Dr. Stanton T. Siu, Oakland, CA

Dr. Siu, who is board-certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, is Chief of Pulmonary Medicine and Director of Graduate and Undergraduate Medical Education for Kaiser Permanente East Bay in Northern California, and Full Clinical Professor

at the University of California San Francisco.

Dr. Lynn T. Tanoue, FCCP, New Haven, CT

Dr. Tanoue, who is board-certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, is Professor of Medicine and Clinical Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine, and Vice-Chair for Clinical Affairs in the Department of Internal Medicine at Yale School of Medicine. As a long-time member and current Chair of ABIM's Pulmonary Disease Board Exam Committee, Dr. Tanoue works closely with me in planning and carrying out the work of the Pulmonary Disease Board.

I am honored to lead such a diverse group of professionals from across the spectrum of pulmonary disease and look forward to sharing updates with you as we embark on our work of ensuring the relevancy of MOC to pulmonary disease physicians across the country.

Further information about ABIM's new governance structure may be found via the ABIM website: www.abim.org/about/governance.

This Month in CHEST: Editor's Picks

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

Platelet Count Mediates the Contribution of a Genetic Variant in *LRRC16A* to ARDS Risk. By Dr. Y. Wei et al.

Impact of COPD on the Mortality and Treatment of Patients Hospitalized With Acute Decompensated Heart Failure: The Worcester Heart Failure Study. By Dr. K. A. Fisher et al.

The Prognostic Value of Undetectable Highly Sensitive Cardiac Troponin I in Patients With Acute Pulmonary Embolism. By Dr. E. U. Hakemi et al.



Treatment of Alveolar-Pleural Fistula With Endobronchial Application of Synthetic Hydrogel. By Dr. H. J. Mehta et al.

COMMENTARY

Evolution in Reimbursement for Sleep Studies and Sleep Centers. By Dr. J. M. Parish et al.

EVIDENCE-BASED MEDICINE

Tools for Assessing Outcomes in Studies of Chronic Cough: CHEST Guideline and Expert Panel Report. By Dr. L-P Boulet et al.

NAMDRC Roundtable on ‘Respiratory Compromise’

BY DR. DENNIS E. DOHERTY,
FCCP
NAMDRC President

PHIL PORTE
NAMDRC Executive Director

NAMDRC brought together representatives of key medical societies, including CHEST, ATS, AARC, SCCM, AACN, SHM (hospitalists), PPAHS (patient safety), and ACEP (emergency physicians) to address respiratory compromise, that cascade of events that moves from respiratory insufficiency to respiratory failure to respiratory arrest. Recognizing that respiratory compromise occurs in various settings, the conference, Feb 26-27 in Orlando, Florida, focused on the hospital setting.

In addition to society representatives, the NAMDRC leadership, in consultation with recognized experts, also invited key opinion leaders to participate, including physicians, respiratory therapists, and nurses.

There were several challenges facing the participants, perhaps paramount was to define the concept of “respiratory compromise.” Some have signaled, “I know it when I see

it,” but the expectation was to formulate a specific clinical definition of the respiratory deterioration, and devise a recognition pathway that can easily be used in the hospital setting to identify patients earlier in the course of this cascade.



DR. DOHERTY



MR. PORTE

How to identify high risk patients is critical to the discussion, because it is generally believed that this is where resources need to be focused, both from a personnel and monitoring perspective. Can consensus be drawn to determine which patient characteristics can reliably classify that patient into a high risk for respiratory compromise, and, if so, those characteristics should be delineated. The corollary challenge is to identify the low risk patients so that inap-

propriate resources are not focused where efforts might not be necessary.

Individual hospital policies are integral to this issue, as the relative value of rapid response teams appears to vary greatly. Add to the equation a recent *Wall Street Journal* article (<http://online.wsj.com/search/term.html?KEYWORDS=Heart%20attack>) that highlighted the success of managing heart attacks outside the hospital but the notable challenges of managing those events when they occur within the inpatient population.

Another key challenge facing roundtable participants was to focus their discussions on what clinical parameters should be monitored and which, if any, should be put on the back burner. There was a relatively wide variation of views regarding what should be monitored, what thresholds are problematic and indicative of a declining patient, and what actions need to be taken, and how swiftly, to abate the downward cascade of respiratory compromise. A related challenge facing participants was, “should the industry be moving toward refinement of their monitoring technologies to give physicians and the health-care team

more valuable and more timely information? Are we monitoring the right parameters, or are we monitoring what the technology allows us to monitor? Are there gaps that can be addressed?”

It is likely that not only will the proceedings be documented for submission for publication, but this may very well lead to other conferences that focus on respiratory compromise in other settings. Both the skilled nursing facility and long-term acute care hospital settings provide care for a spectrum of pulmonary/ventilator patients, and the characteristics of their potential cascade of deterioration may or may not be the same as in an acute care hospital. The challenges are similar, but solutions may be different – a subject for further discussion.

This conference was just one example of NAMDRC’s approach to a range of pulmonary-related clinical issues. While NAMDRC’s broad mission is to “improve access to quality care for patients with respiratory disease by removing regulatory and legislative barriers to appropriate treatment,” the roundtable does fit **Respiratory Compromise** *continued on page 30*

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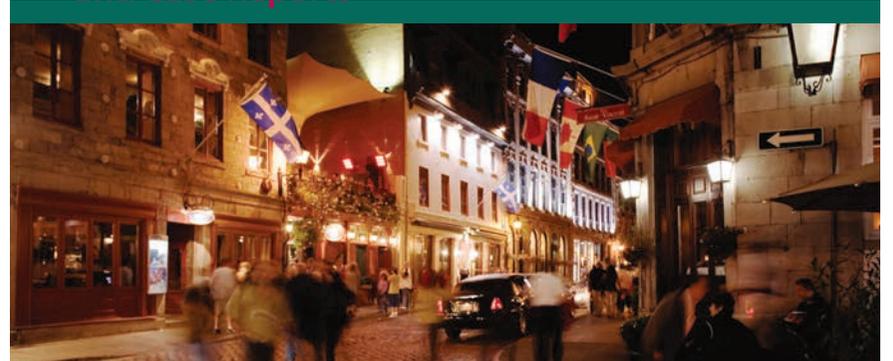
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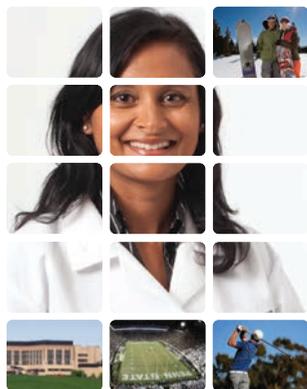
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Job Opportunity in South Florida
Critical Care Medicine - Nocturnist

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.

The available positions are full-time employed positions with competitive benefits and compensation package, sovereign immunity, paid CME and state-of-the-art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds, etc).

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.

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

OHIO CRITICAL CARE MEDICINE - DAYTON, OH

Excellent opportunity for BC/BE CCM physician to join growing 36+ physicians' private practice CCM/ID/Hospitalist/Endocrine group. Dayton is located in south-western, OH. The metropolitan area of 800,000 offers many cultural, sports and recreational activities, excellent public and private school systems and affordable housing. Competitive salary and outstanding benefit package. Not a J-1 Visa opportunity.

Send CV or call:

Becky Kronauge
Practice Administrator
33 West Rahn Rd
Dayton, OH 45429
PH:(937)433-8990 ext.124
FAX:(937) 433-8691
Email: rkronauge@sdacc.com
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For Deadlines and More Information,

Contact: John Baltazar
Tel: (917) 488-1528
Email: jbaltazar@americanmedicalcomm.com

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PROFESSIONAL OPPORTUNITIES



**PENNSYLVANIA
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EVANGELICAL COMMUNITY HOSPITAL is recruiting a full time **Critical Care** and **Pulmonology/Critical Care Physician** focusing on pulmonary care and covering critical care patients. Entertain hiring a EM/Critical Care Physician, Intensivist or Pulmonologist for outpatient procedural services, in-patient pulmonary medicine and/or intensivist services. Critical Care Physician to work in ICU with other Intensivists 7 on 7 off. Critical component works with 2 full time Intensivists in 12-bed ICU; collaboration with experienced Hospitalist group (hospital-employed). Must be BE/BC in field of specialty with Fellowship training. New grads welcome!

Contact: Dennis Burns
Physician Recruitment
570-522-2739
dennis.burns@evanhospital.com



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1-800-869-4201 or Lori.Matthews@coxhealth.com




Inpatient Pulmonary/Critical Care Position in Maine:

Join a vibrant Inpatient Pulmonary and Critical Care group of five in beautiful Maine! Central Maine Medical Center (CMMC) is seeking a BC/BE Pulmonary/Critical Care Physician to help provide pulmonary and critical care services to medical, surgical, trauma, and cardiac patients.

CMMC is a 250 bed, full service regional referral center with busy trauma, cardiothoracic, interventional radiology, vascular, and neurosurgical programs. We have a state-of-the art 19 bed ICU and a separate 16 bed cardiothoracic unit.

Competitive salary and benefits including CME, paid vacation, student loan repayment, 403b match, and relocation fees. Work schedule revolves around a 6 day on and 6 day off philosophy, with no longer than 12 hour shifts per day. There is no outpatient clinic work.

Residents and visitors enjoy an extraordinary lifestyle that revolves around top school systems, ski resorts, lake and ocean water sports, theatre, and world-class dining.

Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org. Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

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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





Fort Collins, Colorado

Colorado Health Medical Group is seeking a Pulmonologist/Critical Care trained physician. Sleep Medicine training desirable but not required. Will rotate in two hospitals and our Loveland based clinic. Call is 1:11 nights and 1:5-6 weekends. Physician will be doing general Pulm/CC procedures and read sleep studies from outlying facilities.

If interested, email your CV to Briann.Leone@uchealth.org



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



CHEST PREP – Disease-State Education for Industry

BY LISA STANICK, MBA
Director, PREP Operations

Did you know the American College of Chest Physicians (CHEST) has provided disease-state-specific education for pharmaceutical and medical device representatives for over 12 years?

The CHEST Professional Representative Education Program, or PREP, is an unbranded disease-state clinical immersion program. The PREP Team works with pharmaceutical and medical device companies to understand their learning objectives and the educational needs of their representatives. A customized program to address those specific needs is then developed.

Each program uses different learning methods – problem-based case studies, patient testimony, simulation, and faculty-led workshops – to create a dynamic learning environment that increases interaction and develops deeper comprehension. The PREP

curriculum is based on evidence-based clinical practice guidelines and consensus statements. Each program is created by clinical thought leaders and delivered by expert faculty, typically drawn from our CHEST membership. PREP courses are held at leading hospitals and academic medical centers throughout the country, as well as at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois.

Participants who complete the course objectives, including the post-course knowledge assessment, are awarded a Certificate of Completion valid for a 3-year period. More importantly, they gain the most current, in-depth clinical information needed to engage with health-care professionals knowledgeably, confidently, and meaningfully. This translates to better-educated representatives who interact with you as you make clinical decisions that enhance patient outcomes.

CHEST has trained over 4,000 sales representatives over the past 2 years. Not only has CHEST conducted PREP programs for disease states such as atrial

fibrillation, venous thromboembolism, and COPD, PREP programs are also available for women's health, oncology, and interventional radiology through strategic agreements with the American Congress of Obstetricians and Gynecologists (ACOG), the American Society of Clinical Oncology (ASCO), and the Society of Interventional Radiology (SIR). The PREP Team recently conducted a Prostate Cancer PREP course at Huntsman Cancer Institute in Salt Lake City, Utah. This course is the first of four to be conducted over the next months at academic medical centers around the country. Over 100 sales representatives will participate in this PREP, which was developed and is being conducted through CHEST's agreement with ASCO.

The PREP Team continues to expand its offerings. If you would like to develop curriculum content or participate as faculty for a PREP course or to receive more information about how your hospital or medical center can become a course site, please contact me at lstanick@chestnet.org or 224/521-9518.

NAMDRC

Respiratory Compromise from page 27

into the mission because of growing concerns that we are facing challenges that are solvable if we take the initiative to address solutions to these

challenges. Another broad challenge facing NAMDRC is its belief that the growing area of home mechanical ventilation is being shaped by archaic and outdated legislation and regulation. In a discussion with Marilyn Tavenner, CMS Administrator (and critical care nurse by training) last

August, she conceded that the laws and regulations have not kept pace with innovations as basic as noninvasive mechanical ventilation. The idea that mechanical ventilation involves intubation or tracheostomy is universally recognized as archaic. As archaic is the concept that, by definition,

ending mechanical ventilation leads to imminent death. Amending the existing laws and regulations in this area may become a high priority for NAMDRC over the next few years.

For membership information, visit the NAMDRC website at www.namdr.org or call 703/752-4359.

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PROFESSIONAL OPPORTUNITIES



Overton Brooks VA Medical Center in Shreveport, LA is seeking full-time BE/BC staff physicians in the following areas:

Pulmonary/Sleep Medicine or Sleep Medicine Position

Applicant must be BC/BE in Pulmonary and Sleep Medicine OR Sleep Medicine alone. Position involves teaching students, residents and Pulmonary & Sleep fellows. Duties include hospital consultations, clinic responsibilities, and proficiency in pulmonary and/or sleep diagnostic procedures. Experience in EBUS and Ultrasonography would be desirable if trained in Pulmonary.

Key requirements: BC in Internal Medicine and BE/BC in Pulmonary and/or Sleep Medicine, US citizenship, proficiency in English, full & current unrestricted licensure. Applicant must also qualify for an appointment with LSU Health Center, Shreveport.

Pulmonary/Critical Care or Critical Care Position

Applicant must be BC/BE physician in either Pulmonary/Critical Care or Critical Care alone teaching students, residents and Pulmonary & Critical Care fellows while at the VA. Duties include hospital consultations, clinic responsibilities, and proficiency in pulmonary and critical care procedures as appropriate. Experience in EBUS and Ultrasonography would be desirable if trained in Pulmonary. Experience in ultrasonography would be desirable. Experience in extracorporeal modalities a plus.

Key requirements: BC in Internal Medicine and BE/BC in Pulmonary/Critical Care or Critical Care Medicine, US citizenship, proficiency in English, full & current unrestricted licensure. Applicant must qualify for an academic appointment with LSU Health Center, Shreveport

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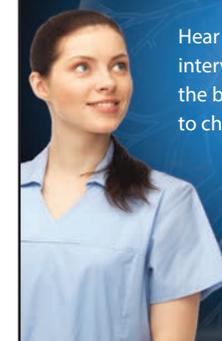
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NETWORKS: Outbreak research, social media, lung transplant, OSA

Disaster Response

Chasing the tail of Ebola's epi curve: Outbreak research

In 2014, the American College of Chest Physician's Task Force on Mass Critical Care published its second supplement on Care of the Critically Ill and Injured During Pandemics and Disasters (Christian et al. *Chest*. 2014;146:8S).

The initial aim was for this supplement to be evidence-based; however, due to the paucity of high quality evidence in the field of outbreak response and disaster management, ultimately, consensus-based guidelines were developed.

Today, as the world has faced its largest outbreak of Ebola costing upwards of tens of thousands of lives, once again, we find ourselves in a situation where just when research



DR. CHRISTIAN

efforts are ramping up, the tail of the epidemiologic curve for the outbreak is rapidly falling off. While this is excellent news for those living in the affected countries, it unfortunately means that similar to efforts during SARS and H1N1, the potential to advance our clinical management and treatment options through research is likely to fall short of both the potential and need to do so.

Conducting research during disasters and outbreaks is fraught with challenges ranging from the sudden and, arguably, unpredictable nature of these events, through to the time required for ethics approval (Cook et al. *Crit Care Med*. 2010;38:e138) and execution of the studies. Despite these challenges, we must not accept failure and work to ensure the research is an essential component of the public health emergency response (Lurie et al. *N Engl J Med*. 2013;368[13]:1251).

A promising effort is now underway through a collaboration between the International Federation of Acute Care Trialists [InFACT] (*Lancet*. 2010;375[9708]:11) and the International Severe Acute Respiratory and Emerging Infection Consortium [ISARIC] (<https://isaric.tghn.org/>) to put in place a "sleeper study" to be tested annually on severe acute respiratory infections but will otherwise lie in wait ready to spring into action at the onset of the

next emerging infection. This holds promise for potentially enabling a true rapid research response.

Dr. Mike Christian, MSc (Public Health), FCCP
NetWork Vice-Chair
Chief Safety Officer
Niagara Health System
Critical Care & Infectious Diseases
Attending Physician
Corporate Services

Practice Operations

Why Your Practice Should Be Involved in Social Media

Social media has been taking on an increasingly important role in medicine. Patients use social media to learn and share information, while medical establishments use it to help build their brands. Yet we, as individual practitioners, have been slow to adapt to the expanding role of social media in our profession.

There are three key reasons why we need to be more involved in using social media tools.

First, more patients are getting health-care information through it. Connections that are made through social media tend to be more valued than other sources. Practitioners know all too well that medical advice obtained through social media may be as highly regarded as their own advice to their patients. This provides an important opportunity. Using social media, we can provide useful information and contradict false information. For example, using your practice's Facebook page, you could provide information about sleep apnea or dispel vaccine myths.



DR. RAMACHANDRAN

Second, patients use social media to choose health-care providers. One in six patients now post online reviews about their health-care encounters. Inviting patients to give you positive reviews now can help counteract negative reviews later. In addition, registering at rating sites can elevate your Google profile and allows you to educate prospective patients about the services you offer. Third, social media is where our patients are. It's time we were there, too.

Dr. Pradeep Ramachandran,
Steering Committee Member
Social Media Co-Editor, CHEST

Transplant

What is the skinny on weight in adult lung transplant?

More than two-thirds of American adults are overweight (body mass index [BMI] 25 mg/kg² or greater) (Ogden et al. *JAMA*. 2014; 311[8]:806).

Trends in patients presenting for initial lung transplant evaluations are only slightly better, with 55% of candidates categorized as overweight (Chandrasekaran et al. *J Heart Lung Transplant*. Nov 17, 2014; epub ahead of print).

This raises the question--does increased weight confer increased risk in lung transplantation?

Kanasky and colleagues first described a possible mortality risk posed by excess weight in lung transplant candidates in 2002 (*Chest*. 2002;121[2]:401).

Subsequently, obesity was also associated with an increased risk of primary graft dysfunction (Lederer et al. *Am J Respir Crit Care Med*. 2011;184[9]:1055).

Recently, Singer and colleagues demonstrated that class II or III obesity (BMI greater than 35 kg/m²) was associated with an increased risk of death in lung transplant, but class I obesity (BMI between 30 and 34.9 kg/m²) was not (*Am J Respir Crit Care Med*. 2014;190 [9]:1012).

Last month, the International Society for Heart and Lung Transplant published updated lung transplant candidate selection guidelines that now list obesity class II or III as absolute contraindications to lung transplantation (Weill et al. *J Heart Lung Transplant*. 2015; 34[1]:1). Obesity class I remains a relative contraindication.

Interestingly, Chandrasekaran and colleagues showed that weight loss in the overweight and class I obesity group was associated with improved mortality, suggesting ongoing weight loss should be encouraged.

The clinical bottom line: all overweight lung transplant candidates should be encouraged to lose weight. Those with a BMI greater than 35 should be deferred from transplant listing until weight loss is achieved.

Dr. Cassie Kennedy, FCCP
Steering Committee Member



DR. KENNEDY

Women's Health

How prevalent is sleep apnea in women? It's how you slice and dice it.

More than 90% of women with OSA are reportedly undiagnosed (Young et al. *Sleep*. 1997;20[9]:705). There are, of course, many factors that contribute to this.

One less apparent reason is how we define and measure sleep apnea. More and more, there is an attempt to phenotype sleep apnea; an aim to be able to use the multitude of data gathered from overnight polysomnography to better prognosticate cardiovascular, mental, and other health outcomes. For example, there is evidence to suggest respiratory event-related arousals (RERAs) worsen fatigue and depression and result in greater use of hypnotics, antidepressants, and stimulants (Guilleminault et al. *J Psychiat Res*. 2006;40[3]:273).

A greater proportion of women than men are likely to have RERAs than frank apneas. As a result, the inclusion of RERAs into the hypopnea definition in the 2012 American Academy of Sleep Medicine scoring guidelines may lead to a greater proportion of women being diagnosed with OSA, as well as with more severe OSA.

A study from the Wisconsin Sleep Cohort demonstrated that AHI in REM sleep (but not in NREM sleep) confers a dose-dependent risk of hypertension (Mokhlesi et al. *Am J Respir Crit Care Med*. 2014;190[1]:1158). The clinical implication is that women, particularly younger premenopausal women who are more prone to REM-related OSA (O'Connor et al. *Am J Respir Crit Care Med*. 2000;161[5]:1465), may not be adequately treated since current standards qualify treatment based on total AHI, which is often driven by NREM AHI.

Meanwhile, we are moving more toward home sleep testing where arousals and sleep stages are often not measured. When the way we measure disease is moving dichotomously from our attempts to more precisely define and characterize OSA, we are challenged to consider how this impacts the diagnosis of sleep apnea in women.

Dr. Christine Won
Steering Committee Member



DR. WON

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