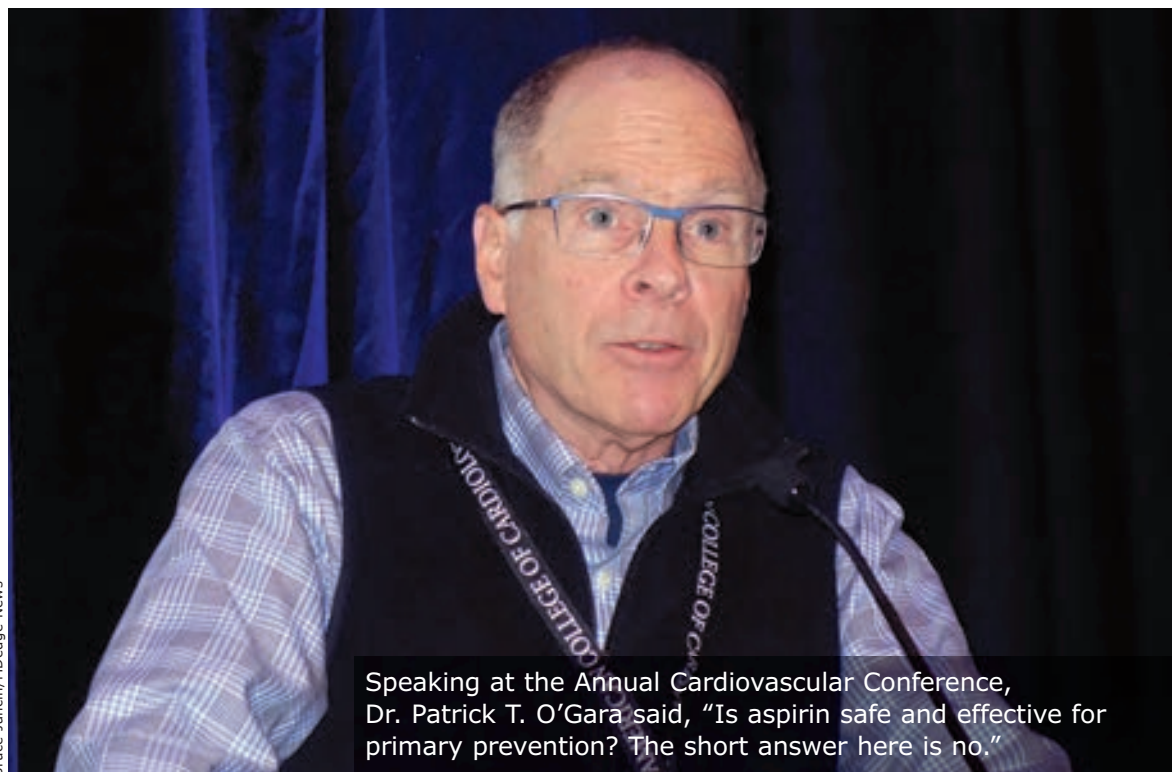




# CHEST<sup>®</sup> Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Speaking at the Annual Cardiovascular Conference, Dr. Patrick T. O'Gara said, "Is aspirin safe and effective for primary prevention? The short answer here is no."

## Aspirin for primary cardiovascular prevention: RIP

BY BRUCE JANCIN

MDedge News

SNOWMASS, COLO. – The decades-long belief that aspirin is beneficial for primary prevention of cardiovascular events was utterly dashed by three major randomized clinical trials during the space of a few short weeks in autumn 2018.

"Is aspirin safe and effective for primary prevention? The short answer here is no," Patrick T. O'Gara, MD, declared at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.

"Think of all those decades of aspirin therapy in the hopes of making ourselves healthier," added Dr. O'Gara, professor of medicine at Harvard

Medical School, Boston, and a past president of the American College of Cardiology.

He cited the results of three placebo-controlled randomized trials totaling more than 47,000 patients without known cardiovascular disease: ARRIVE, published in late September 2018, followed in October by ASPREE and ASCEND.

• **ARRIVE.** This double-blind study conducted in seven countries included 12,546 patients deemed at moderate cardiovascular risk, with an estimated 10-year cardiovascular event risk of 17%. Eligibility was restricted to men aged 55 and up and women aged 60 or older. After a median follow-up of 5 years, there was no difference between patients assigned to enteric-coated

ASPIRIN // continued on page 6

## E-cig use undoes gains of tobacco control in youth

BY HEIDI SPLETE

MDedge News

A significant increase during 2017-2018 in e-cigarette use among U.S. youths has erased recent progress in reducing overall tobacco product use in this age group, a study from the Centers for Disease Control and Prevention has found.

Nearly 5 million middle school and high school students in the United States, approximately 27% of high school students and 7% of middle school students, used tobacco products, including e-cigarettes, in 2018, according to study findings.

E-cigarettes are driving the trend. About 4 million high school students in the United States reported using any tobacco product in the last 30 days, and 3 million of them reported using e-cigarettes, according to a Vital Signs document published by the CDC on Feb. 11 in its Morbidity and Mortality Weekly Report.

In addition, many high school students who use e-cigarettes use them often; 28% reported using the products at least 20 times in the past 28 days, up from 20% in 2017.

"Any use of any tobacco product is unsafe for teens," Anne Schuchat, MD, principal deputy

E-CIGARETTES // continued on page 4

### INSIDE HIGHLIGHT



#### NEWS FROM CHEST

#### SLEEP STRATEGIES

Phrenic nerve stimulation for treatment of central sleep apnea

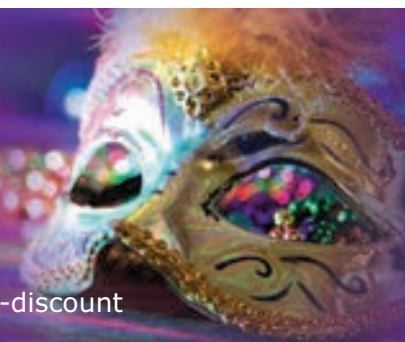
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CHEST<sup>®</sup>  
Annual Meeting  
2019

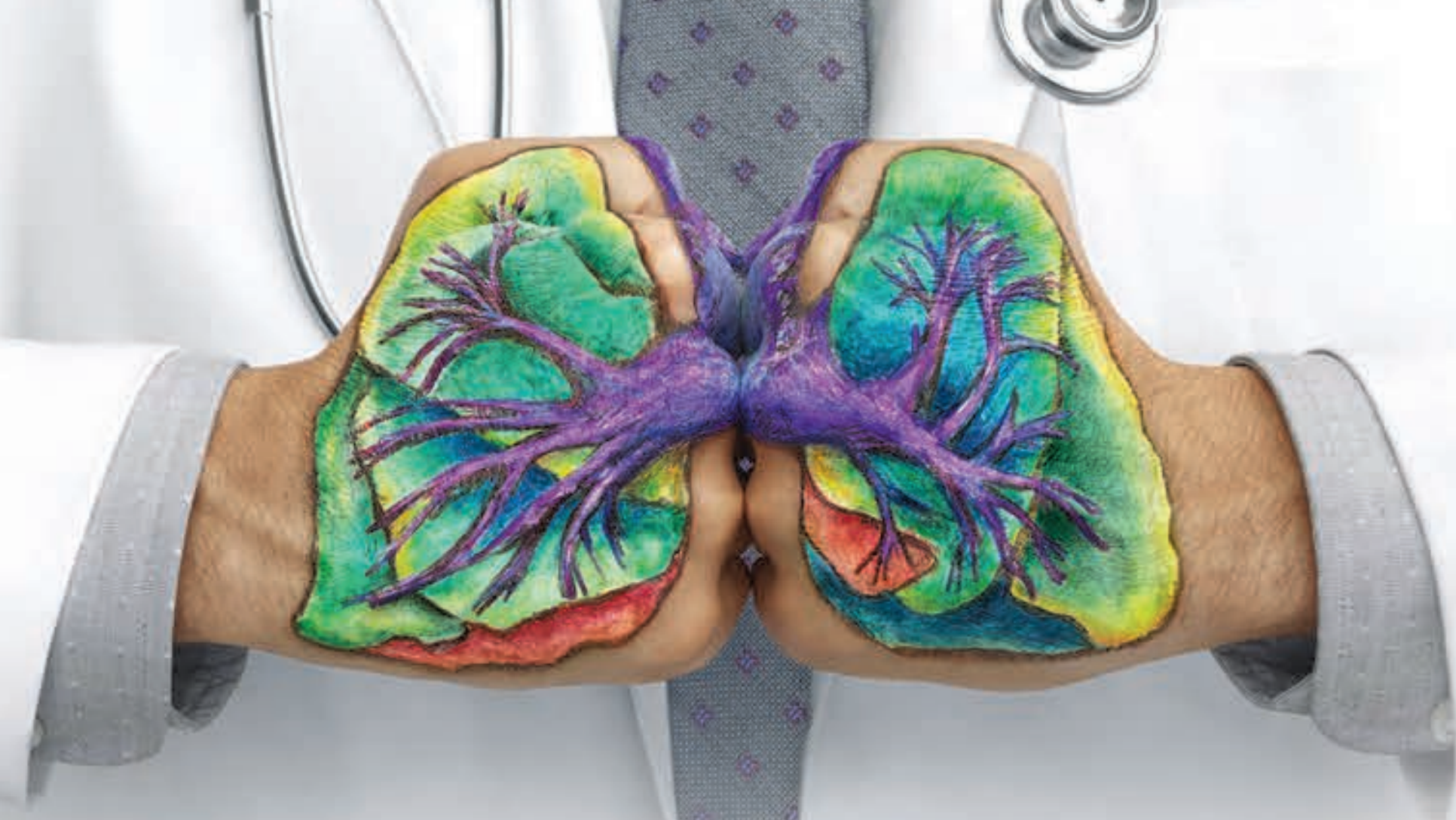
October 19-23  
New Orleans, LA



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## Indication

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

## Select Important Safety Information

**Elevated liver enzymes:** Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of  $\geq 3 \times$  ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels 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 placebo patients (1%). Patients should avoid or minimize exposure to sunlight and sunlamps, regularly use sunscreen (SPF 50 or higher), wear clothing that protects against sun exposure, and avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

**Gastrointestinal (GI) disorders:** Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, compared with 1.0% of placebo patients. The most common ( $>2\%$ ) GI events leading

to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary.

**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, GERD, sinusitis, insomnia, weight decreased, and arthralgia.

### Drug Interactions:

**CYP1A2 inhibitors:** Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

**CYP1A2 inducers:** Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

### Specific Populations:

**Mild to moderate hepatic impairment:** Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

**Severe hepatic impairment:** Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

# Genentech

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# WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.<sup>1-3</sup>

## STUDIED IN A RANGE OF PATIENTS



Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications<sup>4</sup>

## DEMONSTRATED EFFICACY



In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF<sup>1-4\*</sup>

## ESTABLISHED SAFETY AND TOLERABILITY



The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials<sup>1†</sup>

## COMMITTED TO PATIENTS



Genentech offers a breadth of patient support and assistance services to help your patients with IPF<sup>‡</sup>

## WORLDWIDE PATIENT EXPERIENCE



More than 37,000 patients have taken pirfenidone worldwide<sup>4§</sup>

Mild ( $CL_{cr}$  50-80 mL/min), moderate ( $CL_{cr}$  30-50 mL/min), or severe ( $CL_{cr}$  <30 mL/min) renal impairment: Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

**End-stage renal disease requiring dialysis:** Esbriet is not recommended. Esbriet has not been studied in this patient population.

**Smokers:** Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment 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](http://www.fda.gov/medwatch) or to Genentech at 1-888-835-2555.**

**Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.**

**References:** 1. Esbriet Prescribing Information. Genentech, Inc. October 2017. 2. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med*. 2014;371(12):1172]. *N Engl J Med*. 2014;370(22):2083-2092. 3. Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760-1769. 4. Data on file. Genentech, Inc. 2016.

**Learn more about Esbriet and how to access medication at [EsbrietHCP.com](http://EsbrietHCP.com)**

IPF=idiopathic pulmonary fibrosis.

\*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).<sup>1</sup> In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%-90% and percent predicted diffusing capacity of lung for carbon monoxide (%DL<sub>co</sub>) between 30%-90%. The primary endpoint was change in %FVC from baseline at 52 weeks.<sup>2</sup> In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL<sub>co</sub> ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL<sub>co</sub> ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.<sup>3</sup> Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.<sup>1,2</sup> Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).<sup>1,3,4</sup> **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.**<sup>1,3</sup>

<sup>†</sup>In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).<sup>1</sup>

<sup>‡</sup>Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

<sup>§</sup>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.<sup>1</sup>

**Esbriet**  
(pirfenidone) tablets 267 mg  
801 mg



director of the CDC, said in a tele-conference to present the findings. Nicotine is highly addictive and can harm brain development in youth, including capacity for learning, memory, and attention, she said. The rise in e-cigarette use corresponds with the rise in marketing

and availability of e-cigarette devices such as JUUL, which dispense nicotine via liquid refill pods available in flavors including strawberry and cotton candy, said Brian King, MPH, PhD, deputy director for research translation at the CDC’s Office on Smoking and Health.

“The advertising will lead a horse to water, the flavors will make them drink, and the nicotine will keep them coming back for more,” said Dr. King. Approximately 27.1% of high school students and 7.2% of middle school students used a tobacco product in 2018, a significant in-

crease from 2017 data and with a major increase in e-cigarette use. No change was noted in the use of other tobacco products, including cigarettes, from 2017 to 2018, according to the report. However, conventional cigarettes remained the most common companion product to e-cigarettes for



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.

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

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

5.2 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].

5.3 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].

6 ADVERSE REACTIONS

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

- Liver Enzyme Elevations [see Warnings and Precautions (5.1)]
- Photosensitivity Reaction or Rash [see Warnings and Precautions (5.2)]
- Gastrointestinal Disorders [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

ESBRIET® (pirfenidone)

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

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

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

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

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain <sup>1</sup>	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%
<sup>1</sup> 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%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval 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

7 DRUG INTERACTIONS

7.1 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 CYP1A2 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

youth who use two or more tobacco products (two in five high school students and one in three middle school students in 2018). From a demographic standpoint, e-cigarette use was highest among males, whites, and high school students.

Tobacco use in teens is trending in the direction of wiping out the progress made in recent years to re-

duce exposure to youths. The report noted, “The prevalence of e-cigarette use by U.S. high school students had peaked in 2015 before declining by 29% during 2015-2016 (from 16% to 11.3%); this decline was the first ever recorded for e-cigarette use among youths in the National Youth Tobacco Survey since monitoring began, and it was subsequently sustained

during 2016-2017). However, current e-cigarette use increased by 77.8% among high school students and 48.5% among middle school students during 2017-2018, erasing the progress in reducing e-cigarette use, as well as any tobacco product use, that had occurred in prior years.”

The CDC and the Food and Drug Administration are taking action to

curb the rise in e-cigarette use in youth in particular by seeking regulations to make the products less accessible, raising prices, and banning most flavorings, said Dr. Schuchat.

“We have targeted companies engaged in kid friendly marketing,” said Mitch Zeller, JD, director of the Center for Tobacco Products for the FDA.

In a statement published simultaneously with the Vital Signs study, FDA Commissioner Scott Gottlieb, MD, emphasized the link between e-cigarette use in teens and the potential for future tobacco use. “The kids using e-cigarettes are children who rejected conventional cigarettes, but don’t see the same stigma associated with the use of e-cigarettes. But now, having become exposed to nicotine through e-cigs, they will be more likely to smoke.” Dr. Gottlieb declared, “I will not allow a generation of children to become addicted to nicotine through e-cigarettes. We must stop the trends of youth e-cigarette use from continuing to build and will take whatever action is necessary to ensure these kids don’t become future smokers.” He reviewed steps taken in the past year by the FDA to counter tobacco use in teens but he warned of future actions that may need to be taken: “If these youth use trends continue, we’ll be forced to consider regulatory steps that could constrain or even foreclose the opportunities for currently addicted adult smokers to have the same level of access to these products that they now enjoy. I recognize that such a move could come with significant impacts to adult smokers.”

Parents, teachers, community leaders, and health care providers are on the front lines and can make a difference in protecting youth and curbing nicotine use, Dr. King said.

Although there are no currently approved medications to treat nicotine addiction in youth, research suggests that behavioral counseling, as well as reinforcement of the danger of nicotine from parents and other people of influence, can help, Dr. King said.

The Vital Signs report is based on data from the 2011-2018 National Youth Tobacco Survey, which assesses current use of cigarettes, cigars, smokeless tobacco, e-cigarettes, hookahs, pipe tobacco, and bidis among a nationally representative sample of middle and high school students in the United States. The findings were analyzed by the CDC, FDA, and the National Cancer Institute.

chestphysiciannews@chestnet.org

**SOURCE:** Gentzke AS et al. MMWR. 2019 Feb 11. doi: 10.15585/mmwr.mm6806e1.

ESBRIET® (pirfenidone)	ESBRIET® (pirfenidone)
<p>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].</p> <p>Moderate CYP1A2 Inhibitors</p> <p>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.</p> <p>Concomitant CYP1A2 and other CYP Inhibitors</p> <p>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.</p> <p><b>7.2 CYP1A2 Inducers</b></p> <p>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].</p> <p><b>8 USE IN SPECIFIC POPULATIONS</b></p> <p><b>8.1 Pregnancy</b></p> <p><u>Risk Summary</u></p> <p>The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see Data].</p> <p>In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.</p> <p><u>Data</u></p> <p><u>Animal Data</u></p> <p>Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m<sup>2</sup> basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m<sup>2</sup> basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m<sup>2</sup> basis at a maternal oral dose of 1000 mg/kg/day).</p> <p><b>8.2 Lactation</b></p> <p><u>Risk Summary</u></p> <p>No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.</p> <p><u>Data</u></p> <p><u>Animal Data</u></p> <p>A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.</p>	<p><b>8.4 Pediatric Use</b></p> <p>Safety and effectiveness of ESBRIET in pediatric patients have not been established.</p> <p><b>8.5 Geriatric Use</b></p> <p>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.</p> <p><b>8.6 Hepatic Impairment</b></p> <p>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 2.3 in full Prescribing Information].</p> <p>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].</p> <p><b>8.7 Renal Impairment</b></p> <p>ESBRIET should be used with caution in patients with mild (CL<sub>cr</sub> 50–80 mL/min), moderate (CL<sub>cr</sub> 30–50 mL/min), or severe (CL<sub>cr</sub> 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.</p> <p><b>8.8 Smokers</b></p> <p>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.</p> <p><b>10 OVERDOSAGE</b></p> <p>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.</p> <p>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.</p> <p><b>17 PATIENT COUNSELING INFORMATION</b></p> <p>Advise the patient to read the FDA-approved patient labeling (Patient Information).</p> <p><u>Liver Enzyme Elevations</u></p> <p>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 (5.1)].</p> <p><u>Photosensitivity Reaction or Rash</u></p> <p>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 (5.2)].</p> <p><u>Gastrointestinal Events</u></p> <p>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 (5.3)].</p> <p><u>Smokers</u></p> <p>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].</p> <p><u>Take with Food</u></p> <p>Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.</p> <p>Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way, South San Francisco, CA 94080-4990</p> <p><b>Genentech</b> A Member of the Roche Group</p> <p>ESBRIET® is a registered U.S. trademark of Genentech, Inc. © 2017 Genentech, Inc. All rights reserved. ESB/100115/0470(2) 2/17</p>



aspirin at 100 mg/day versus placebo in the incidence of major adverse cardiovascular events, with a hazard ratio of 0.96. However, GI bleeding events were 2.1-fold more common in the aspirin group (Lancet. 2018 Sep 22;392[10152]:1036-46).

• **ASPREE.** This double-blind trial, conducted in Australia and the United States, included 19,114 community-dwelling participants aged 70 years or older, or 65 years or older for Hispanics and blacks in the United States. After a median 4.7 years of follow-up, there was no difference in major adverse cardiovascular events between subjects random-

ized to 100 mg/day of enteric-coated aspirin and those on placebo. So, as in ARRIVE, no benefit. However, the rate of major hemorrhage was 38% greater in the aspirin group (N Engl J Med. 2018 Oct 18;379[16]:1509-18).

Moreover, the rate of all-cause mortality was 14% greater in the aspirin group, a statistically significant difference, compared with controls. Drilling down, the investigators showed that the major contributor to this excess mortality in the aspirin group was their 31% greater rate of cancer-related death (N Engl J Med. 2018 Oct 18;379[16]:1519-28).

“Remember, we used to think that taking aspirin reduced the incidence of GI cancer, and, in particular, colon adenocarcinoma? Well, here’s a very startling observation in 19,114 healthy elderly patients showing an increase in cancer-associated death with the use of aspirin,” commented Dr. O’Gara.

• **ASCEND.** This study randomized 15,480 subjects with diabetes but no known cardiovascular disease to 100 mg/day of aspirin or placebo and followed them for a mean of 7.4 years. There was a significant 12% relative risk reduction in the composite endpoint of serious vascular events in the aspirin group; however, the aspirin-treated patients also had a 29% greater rate of major bleeding events (N Engl J Med. 2018 Oct 18;379[16]:1529-39).

“So in dealing with our diabetic patients, we could perhaps say there is a small reduction in the risk of cardiovascular outcomes that is overwhelmed by more than a factor of two with regard to an increase in the risk of bleeding,” the cardiologist observed.

How did physicians get the aspirin story for primary prevention so wrong for so long? Dr. O’Gara pointed to the Physicians’ Health Study, conducted mainly back in the 1970s, as one of the benchmark studies that led to the widespread use of aspirin in this way.

“I think the aspirin story has now been put into sharp focus just within the course of the last 6 months and should force all of us to reassess

what it is that we advise patients,” he concluded.

Dr. O’Gara’s presentation was the talk of the meeting, as many attendees hadn’t yet caught up with the latest aspirin data.

During an Q&A session, Robert A. Vogel, MD, a preventive cardiology authority at the University of Colorado, Denver, was asked, given the new emphasis placed upon coronary artery calcium as a supplemental risk assessment tool in the latest guidelines, at what magnitude of coronary artery calcium score in a patient with no history of coronary disease he would give aspirin for secondary prevention.

“I know I don’t know the answer to that question,” Dr. Vogel replied. “I no longer reflexively give aspirin to, say, a 60-year-old with a calcium score of 200. I will give a statin. Statins in my book are so effective and safe that my threshold for giving a statin in a 60-year-old is virtually nothing. But with a calcium score of 2,000 or 5,000, I worry just like you worry.”

He noted that the primary prevention patients in the three recent major trials were mostly 60-70 years of age or older. It’s safe to assume that by that point in life many of them had silent atherosclerosis and would have had a non-zero coronary artery calcium score, had they been tested. And yet, aspirin didn’t provide any net benefit in those groups, unlike the drug’s rock-solid proven value in patients who have actually experienced a cardiovascular event.

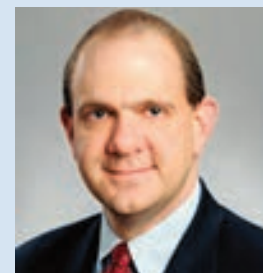
Dr. O’Gara reported receiving funding from the National Heart, Lung and Blood Institute, from the National Institute of Dental and Craniofacial Research, from Medtronic in conjunction with the ongoing pivotal APOLLO transcatheter mitral valve replacement trial, and from Edwards Lifesciences for the ongoing EARLY TAVR trial.

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*“I no longer reflexively give aspirin to, say, a 60-year-old with a calcium score of 200. I will give a statin.”*

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# Shifting drugs from Part B to Part D: Costly to patients

BY GREGORY TWACHTMAN

MDedge News

**A** shift in Medicare drug coverage from Part B to Part D might save the government some money but could end up costing some patients in the long run.

Analysis of the 75 brand-name drugs with the highest Part B expenditures (\$21.6 billion annually at 2018 prices) indicated that the government could save between \$17.6 billion and \$20.1 billion after rebates by switching coverage to Part D, Thomas J. Hwang of Harvard Medical School, Boston, and his associates said.

The potential for greater overall savings, however, “was constrained by the fact that 33 (44%) of the studied brand-name drugs were in protected classes, which HHS has reported precludes meaningful price negotiation by Part D plans,” they wrote.

The proposal also could have a “material impact” on patient out-of-pocket costs, although the impact would vary based on the drug as well as patients’ insurance coverage in addition to Medicare (JAMA Int Med. 2019. doi: 10.1001/jamainternmed.2018.6417).

For example, moving drug coverage to Part D would lower out-of-pocket costs for the majority of the 75 drugs for patients with Medigap supplemental insurance, but out-of-pocket costs could go up for almost 40% of products. Patients who would benefit most from the shift would be those



DYNAMIC GRAPHICS/THINKSTOCK

who qualify for the low-income subsidy, which can eliminate coinsurance requirements.

“By contrast, for patients with Medigap insurance, out-of-pocket costs in Part D were estimated to exceed the annual premium costs for supplemental insurance [approximately 47-56 of the 75 drugs],” Mr. Hwang and his colleagues added. “Out-of-pocket costs would be increased under the proposed policy for beneficiaries with Medigap but without Part D coverage.”

The analysis was limited by the inability to predict the proposed transition’s impact on insurance premiums or drug utilization. Patients who

## VIEW ON THE NEWS

### Transition must be carefully evaluated

**P**olicy analysts need to be careful and do their due diligence to ensure all consequences of the policy options are fully understood, especially as pharmaceuticals account for greater costs in the Medicare program. Future policy analyses must, like Mr. Hwang and his associates did, account for changes to Medicare costs as well as beneficiary costs to understand the overall effects of policy changes.

*Francis Crosson, MD, chairman of the Medicare Payment Advisory Commission, and Jon Christianson, PhD, vice chairman of MedPAC, made these comments in an accompanying editorial (JAMA Int Med. doi: 10.1001/jamainternmed.2018.6146).*

were dually eligible for Medicare and Medicaid were excluded.

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**SOURCE:** Hwang TJ et al. JAMA Int Med. 2019. doi: 10.1001/jamainternmed.2018.6417.

# ONC aims to help physicians, patients with information sharing in proposed rule

BY GREGORY TWACHTMAN

MDedge News

**T**he Office of the National Coordinator of Health Information Technology is looking to adopt standardized application programming interfaces (APIs) in an effort to boost interoperability of health data.

The Department of Health & Human Services office posted a proposed rule Feb. 11 that would, according to an agency press release, “help allow individuals to securely and easily access structured and unstructured EHI [electronic health information] formats using smartphones and other mobile devices.”

“We think our rule is going to help reduce burden and improve care,” Michael Lipinski, director of the Regulatory Affairs Division in the ONC Office of Policy, said in an interview. “It is going to do that through technology. With the APIs, you should be able to get to your information easier and have it readily available. Whether that is from another health care provider or using

other health care products through the API to improve care, you will have that ability between the certified API and the information blocking policies to use third party developers and their products.”

The proposed rule also included a requirement that EHRs certified by ONC be able to easily export information contained within the EHR and make the format used to extract and export the data contained within the EHR publicly available.

“Another third-party developer can build to that and offer competing services to pull that information out,” Mr. Lipinski said. “That would obviously help if you were choosing to switch [EHRs] if you didn’t like the features you were getting from your EHR.”

The standardizing of APIs to help the delivery of data will go hand in hand with information-blocking aspects of the proposed rule, which defines the few exceptions where an activity would not be considered information blocking, such as when engaging in practices will prevent

patient harm; engaging in consistent, nondiscriminatory practices to protect patient privacy; and implementing practices to promote the security of health information.

Mr. Lipinski said these changes will help prevent providers from hiding behind HIPAA rules as the excuse to not share patient information, which will help with care coordination.

“From a provider’s perspective, this should help them get more access to information, more access in a structured way and then easily get and share that information.”

Ultimately, Mr. Lipinski said, the goal is “to increase competition and lower cost while still improving the quality of care for patients.”

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# Evaluate projects, not people, to address gender bias in research funding

BY SARA FREEMAN

MDedge News

LONDON – Female investigators are less likely to secure research funding than male investigators, not because their proposed project is of lesser scientific merit, but simply because they are women, according to research published in *The Lancet*.

Women had a 30% lower chance of success in getting funding for a project than did their male counterparts when the caliber of the principal investigator was considered as an explicit part of the grant application process, with an 8.8% probability of getting funded versus 12.7%, respectively. If the application was considered solely on a project basis, however, the gender bias was less (12.1% vs. 12.9%).

The overall success of grant applications was 15.8% in the analysis, which considered almost 24,000 grant applications from more than 7,000 principal investigators submitted to the Canadian Institutes of Health Research (CIHR) between 2011 and 2016.

“I see our study as basically one good thwack in a long game of whack-a-mole,” lead study author Holly O. Witteman, PhD, said during an event to launch a special edition of *The Lancet* focusing on advancing women in science, medicine, and global health.

Dr. Witteman’s research is one of three original articles included in the thematic issue that brings together female authors and commentators to look at gender equity and what needs to be done to address imbalances. The issue is the result of a call for papers that led to more than 300 submissions from more than 40 countries and, according to an editorial from *The Lancet*, highlights that gender equity in medicine “is not only a matter of justice and rights, it is crucial for producing the best research and providing the best care to patients.”

That there are discrepancies in research funding awarded to female and male investigators has been known for years, Dr. Witteman, associate professor of family and emergency medicine at Laval University, Quebec City, said at the London press conference. To learn how and why, a “quasiexperimental” approach was used to find out what factors might be influencing the gender gap.

“Women are scored lower for competence compared to men with the same publication record,” she said. It’s not that they publish less or do easier research, or that the quality is lower, they are just viewed less favorably overall throughout their careers. Even when you control for confounding factors, “they still don’t advance as quickly,” she said.

“It had been documented for a while that, overall, women tend to get less grant funding and

there hasn’t been any evidence to show either way if maybe women’s grant applications weren’t as good,” Dr. Witteman explained.

In 2014, the CIHR changed the way it funded research projects, creating a “natural experiment.” Two new grant application programs were put in place which largely differed by whether or not an explicit review of the principal investigator and



**Dr. Holly O. Witteman:** “It had been documented for awhile that, overall, women tend to get less grant funding and there hasn’t been any evidence to show either way if maybe women’s grant applications weren’t as good.”

their ability to conduct the research was included.

Adjusting for age and type of research, Dr. Witteman and her coauthors found that there was little difference in the success of women in securing research funding when their grant applications were judged solely on a scientific basis; however, when the focus was placed on the principal investigator, women were disadvantaged.

Dr. Witteman said that “this provides robust evidence in support of the idea that women write equally good grant applications but aren’t evaluated as being equally good scientists.”

So how to redress the balance? Dr. Witteman suggested that one way was for funders to collect robust evidence on the success of grant applications and be transparent who is getting funded and how much funding is being awarded. Institutions should invest in and support young investigators, distributing power and flattening traditionally male-led hierarchies. Salaries should be aligned and research support evened out, she said.

Investigators themselves also have a role to play to do the best possible work and try to change the system. “Advocate for others,” she said. That included advocating for others in groups that you may not be part of – which can be easier in some respects than advocating for a group that you are in.

“Funders should evaluate projects, not people,” Jennifer L. Raymond, PhD, and Miriam B. Goodman, PhD, both professors at Stanford (Calif.) University wrote in a comment in *The Lancet* special issue. They suggested that people-based funding had been gaining popularity but that funders would be better off funding by project to achieve scientific and clinical goals.

“Assess the investigator only after double-blind review of the proposed research is complete,” they suggested. “Reduce the assessment of the investigator to a binary judgment of whether or not the investigator has the expertise and resources needed to do the proposed research.”

During a panel discussion at *The Lancet* event, Cassidy R. Sugimoto, PhD, associate professor of informatics at Indiana University in Bloomington and a program director for the Science and Innovation Policy Program at the National Science Foundation (NSF) observed that data on gender equality in research funding were already being collected and will be used to determine how best to adjust funding policies.

“Looking from the 1980s to the present, women make up shy of 20% of the funds given by the National Science Foundation,” Dr. Sugimoto said. “That’s improved over time, and it’s at 28% currently, which is less than their authorship.”

Tammy Clifford, PhD, vice president of research programs at the CIHR

observed that data collection was “a critically important step, but of course that’s not the only step,” she said. “We need to look at and analyze the data regularly, and then when you see things that are not on track, you make changes.”

One of the changes the CIHR has made is to train people who are reviewing grant applications on factors that may unconsciously affect their decisions. “There are things to be done, and I don’t think we are quite there yet, but we are committed to continually looking at those data, to making the changes that are required.”

Representing the Wellcome Trust, Ed Whiting, director of policy and chief of staff, said that the funding of projects led by female investigators was moving in the right direction. He noted that there was still a lower rate of applications from women for senior award levels, but that the panels that decide upon the funding were moving toward equal gender representation. The aim was to get to a 50/50 female-to-male ratio on the panels by 2020, he said; it was at 46/52 in 2018.

Dr. Witteman and all other commentators had no financial disclosures.

**SOURCE:** Witteman HO et al. *Lancet*. 2019. doi: 10.1016/S0140-6736(18)32611-4.



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# ALA report: Federal and state actions to limit tobacco use fall short

BY THERESE BORDEN

MDedge News

**T**obacco use is currently at an all-time low thanks to public and private efforts, but more aggressive action from federal, state, and local governments is needed to protect the public, according to a review of tobacco control trends in the United States.

The American Lung Association (ALA) released “State of Tobacco Control” 2019, its 17th annual state-by-state analysis and list of recommended policy priorities to limit tobacco use. Although the report notes some positive steps taken by the federal and state governments, shortfalls in policy and legislation also are highlighted. The report states, “We know how and are ready to save more lives, but we need our elected officials to do much more. To many, solving America’s tobacco crisis might seem like a complex puzzle with no solution. And yet we have known for years what pieces are needed to reduce the disease and death caused by tobacco use.”

In this report, the federal government and each state are graded on a scale, A through F, for policy actions and laws to limit tobacco use. The grading methodology is based on a detailed point system cataloging the implementation and strength of specific actions and policies to limit tobacco use.

## Areas of impact

The report focused on six areas of public policy that affect exposure to and use of tobacco:

- **Smoke-free air:** Protecting the public from secondhand smoke should be a priority for policymakers, according to the report, but 22 states have no smoke-free workplace laws in place. Laws restricting e-cigarettes in workplaces and public buildings have lagged behind tobacco laws in many states.
- **Tobacco prevention funding:** Dedicated funds to prevent tobacco addiction before it starts is a key element of a public health attack on tobacco use, but no U.S. state currently spends what the Centers for Disease Control and Prevention has recommended. Twenty years ago, the Master Settlement Agreement between the tobacco industry and 46 states and the District of Columbia

guaranteed ongoing payments to the states to be used for tobacco prevention and control. Although those funds have been collected in the states to the tune of \$27 billion since 1998, overall only 2.4% of those funds have been spent for this purpose, and the rest has been budgeted for other purposes.

- **Tobacco taxes:** Sales taxes on tobacco products have been highly effective in preventing young people from taking up tobacco use, but those taxation rates have remained unchanged in 2018 in all but the District of Columbia and Oklahoma.
- **Tobacco 21:** “Increasing the legal age of sale for tobacco products to 21 would decrease tobacco use by 12% and could prevent 223,000 deaths among those born between 2000 and 2019,” the report noted, citing a 2015 report by the Institute of Medicine. So far, the this restriction has been legislated in six states, the District of Columbia, and numerous local governments. The ALA considers increasing the age for tobacco sales to 21 to be a public health priority.
- **Helping smokers quit:** The report notes that current law requires that Medicaid expansion health plans and private insurance plans cover comprehensive smoking-cessation treatment. However, not all states have the expanded Medicaid program, and many of those with Medicaid expansion don’t offer coverage of all Food and Drug Administration–approved cessation treatments. Despite laws requiring smoking cessation coverage, many private insurance plans still do not include this coverage. The ALA recommends enforcement of the current law with regard to tobacco-cessation insurance coverage.
- **FDA regulation of tobacco products:** The FDA has announced plans to make a major effort to reduce tobacco use in young people, decrease nicotine in cigarettes, and restrict flavored tobacco products. But these plans fall short of the aggressive action needed to curb the tobacco “epidemic,” according to the report. Delayed action and timid policy have “resulted in tobacco companies becoming more emboldened to devise new and egregious ways to addict youth and sustain addiction among current

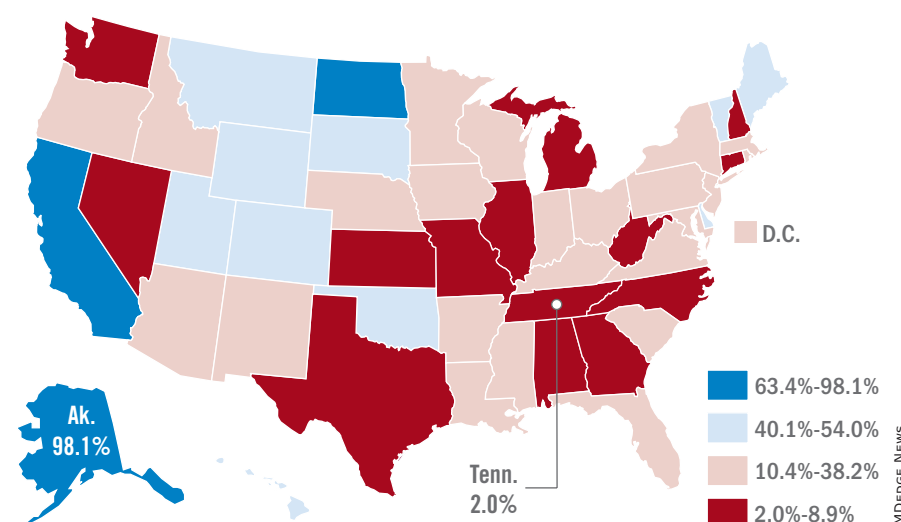
users.” The ALA report points to the steep rise in e-cigarette use among youth with a 20.8% rise in high school students using these products in 2018, a rise from 11.7% in 2017. This trend is not likely to be reversed by the FDA proposals to date, which rely on voluntary action by the

of spending in different program categories. The higher spenders on prevention and control were Alaska at 98.1% and California at 74.5% of the CDC recommended level. The lowest spenders were Tennessee at 2.0% and Missouri at 3.0%.

All but eight states received an F on minimum age for tobacco sales

## State spending on tobacco prevention for fiscal year 2019

Proportion of CDC-recommended level



Note: Based on state revenue data from the Campaign for Tobacco-Free Kids.

Source: American Lung Association

industry to curb youth use, sales restrictions to youth, and restrictions on some flavored tobacco products.

## The report card

Federal government efforts in regulation of tobacco products, taxation, and health insurance coverage of cessation all received an F in this report, while mass media campaigns were given an A.

The states didn’t fare much better. They were graded on prevention and control funding, smoke-free air, taxation, access to cessation services, and minimum age for sales. A total of 19 states received a grade of F in four or five of these areas.

Funding for prevention and control was evaluated as the percentage of the amount recommended by the CDC, adjusted for a variety of state-specific factors such as prevalence of tobacco use, cost and complexity of conducting mass media campaigns, and proportion of the audience below 200% of the federal poverty level. A limitation of this methodology of grading funding is that it doesn’t evaluate effectiveness of the spending or the level

because most have an age limit 18 instead of the ALA and CDC recommendation of age 21.

Harold Wimmer, the CEO of the American Lung Association, wrote, “Aggressive action by our country’s federal and state policymakers is urgently required. However, ‘State of Tobacco Control’ 2019 has found a disturbing failure by federal and state governments to take action to put in place meaningful and proven-effective policies that would have prevented, and reduced tobacco use during 2018. This failure to act places the lung health and lives of Americans at risk. We have also found that this lack of action has emboldened tobacco companies to be even more brazen in producing and marketing products squarely aimed at kids, such as the JUUL e-cigarettes that look like an easily concealed USB drive, which now dominate the market driven by youth use.”

The full report is available for download at the ALA website.

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**SOURCE:** American Lung Association, “State of Tobacco Control 2019.”



# Benralizumab effective for severe asthma at 2 years

BY JIM KLING

MDedge News

**B**enralizumab is safe and effective for the treatment of uncontrolled asthma out to 2 years, according to findings of the BORA trial, an extension study of the phase 3 SIROCCO and CALIMA trials. The study follows up and reinforces previously reported 1-year data and was reported by William W. Busse, MD, of University of Wisconsin, Madison, and his colleagues in the *Lancet Respiratory Medicine*.

Benralizumab is a monoclonal antibody that targets interleukin-5 receptor alpha. It causes rapid depletion of eosinophils through cell-mediated cytotoxicity. A 30-mg dose of benralizumab every 8 weeks is approved for severe asthma treatment in the United States, and other countries.

In the second year, there were no new adverse events associated with depleted eosinophils, and the frequency of opportunistic infections was similar to the first year.

The 48-week SIROCCO trial, the 56-week CALIMA trial, and the 28-week ZONDA trial tested the effect of benralizumab 30 mg given every 4 weeks or 8 weeks, combined with high-dosage inhaled steroids and long-acting beta<sub>2</sub>-agonists. The 8-week dose of the drug reduced annual exacerbations by 51%, compared with placebo in the SIROCCO trial and by 28% in the CALIMA trial. In the ZONDA trial, benralizumab reduced oral glucocorticoid use by 75%, compared with placebo, and by 25% from baseline.

The BORA extension trial included participants in the previous three trials. In the current report, researchers presented results from the analysis from BORA participants recruited from the SIROCCO and CALIMA trials. Data from participants from all three trials will be reported in the future.

The analysis included 1,576 patients who continued to receive benralizumab after being assigned to the treatment arm in SIROCCO or CALIMA, or who had received placebo and then were randomized to benralizumab on the 4-week (n = 783; 265 from placebo) or 8-week dose (n = 793; 281 from placebo) schedule.

A total of 166 patients, or about 10% in each group, discontinued treatment. The frequency of any serious adverse event (SAE) ranged between 10% and 11% in all groups. SAEs associated with infections

ranged from 1% to 3%, indicating that there were no significant differences in SAE frequencies between those who were originally assigned to placebo and those who originally received benralizumab. That suggests

no safety differences between receiving the drug for 1 year or 2 years.

AstraZeneca and Kyowa Hakko Kirin funded the studies. The authors have received fees from AstraZeneca and other pharma-

ceutical companies, and some are employees of AstraZeneca.

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**SOURCE:** Busse WW et al. *Lancet Respir Med*. 2019 Jan 1;7(1):46-59.

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 **CHEST**<sup>TM</sup> Physician  
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# E-cigarettes beat nicotine patch but quit rates still low

BY ANDREW BOWSER

MDedge News

**E**-cigarettes might be more effective for smoking cessation than nicotine replacement therapy, results of a randomized study of almost 900 adults suggest.

Rates of abstinence at 1 year were 18% for adults who used refillable e-cigarettes to wean themselves off smoking, according to the reported results, compared with about 10% for those who tried nicotine replacement therapies.

"This is particularly noteworthy given that nicotine replacement was used under expert guidance, with access to the full range of nicotine replacement products, and with 88.1% of participants using combination treatments," said investigator Peter Hajek, PhD, of Queen Mary University of London, and his coauthors in the *New England Journal of Medicine*.

The findings contrast with those of earlier studies, which showed a lesser effect of e-cigarettes as a stop-smoking strategy, Dr. Hajek and coauthors wrote.

In previous studies, participants used first-generation car-

tridge-based e-cigarettes, while in the present study, they were given second-generation refillable e-cigarettes and free choice of e-liquids, the authors noted. Moreover, those previous studies provided limited face-to-face support, they said, but this study included weekly behavioral support for at least 4 weeks in both the e-cigarette and nicotine replacement groups.

The randomized study by Dr. Hajek and his colleagues included 886 adults in the United Kingdom attending stop-smoking services provided by the U.K. National Health Service. They were randomized to receive either an e-cigarette starter pack and one bottle of nicotine-containing e-liquid, or 3 months' worth of nicotine replacement products of their own choosing. At the 52-week validation visits, the study participants received about the equivalence of about \$26 U.S. dollars for their travel and time.

Abstinence from smoking at 52 weeks, which was verified by measuring expired carbon monoxide levels, was achieved in 18.0% of the e-cigarette group and 9.9% of the

nicotine replacement group (relative risk, 1.83; 95% confidence interval, 1.30-2.58; *P* less than .001), according to the report.

However, the rate of continued e-cigarette use was "fairly high," investigators wrote. Eighty percent of the e-cigarette group was still using their assigned product at 52 weeks, compared with just 9% in the nicotine replacement group.

"This can be seen as problematic if e-cigarette use for a year signals long-term use, which may pose as-yet-unknown health risks," they said.

Tobacco withdrawal symptoms were less severe and satisfaction ratings were higher with e-cigarettes versus nicotine replacement therapy, similar to what had been observed in previous studies, investigators said.

They cited several limitations. For example, product assignments were not blinded. However, the investigators said they tried to "limit expectation effects by recruiting only participants with no strong product preference."

Dr. Hajek reported grants and fees from Pfizer unrelated to the present study. Coauthors reported disclosures related to Pfizer and Johnson

## VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** Cessa-

tion success rates are low in both the e-cigarette group and the nicotine replacement group. "Ces-



sation" in the e-cigarette group meant the group quit traditional cigarettes; most of the quitters were still using e-cigarettes. Maybe e-cigarettes have a role in tobacco cessation. Maybe. That doesn't mean that they are healthy or safe.

and Johnson, along with grants from the U.K. National Institute for Health Research.

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**SOURCE:** Hajek P et al. *N Engl J Med*. 2019;380:629-37. doi: 10.1056/NEJMoa1808779.



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# Immunotherapy's cardiac effects require early monitoring, management

BY NEIL OSTERWEIL

MDedge News

WASHINGTON – Unquestionably, immunotherapy is revolutionizing the care of patients with various solid tumors such as lung cancer and hematologic malignancies.

But it's equally true that there's no such thing as either a free lunch or a cancer therapy free of side effects, whether it's increased risk for heart failure associated with anthracycline-based chemotherapy, or inflammatory conditions, arrhythmias, and thromboembolic events associated with immune checkpoint inhibitors, said R. Frank Cornell, MD, of Vanderbilt University Medical Center in Nashville, Tenn.

"Early awareness and intervention is critical for improved outcomes, and a multidisciplinary approach between oncology, cardiology, the clinic nurse, and other health care providers is critical in managing these patients with these complicated therapies," he said at the American College of Cardiology's Advancing the Cardiovascular Care of the Oncology Patient meeting.

## Checkpoint inhibitors and the heart

Toxicities associated with immune checkpoint inhibitors such as the programmed death 1/ligand 1 (PD-1/PD-L1) inhibitors nivolumab (Opdivo) and pembrolizumab (Keytruda) and the cytotoxic T-lymphocyte antigen 4 antibody ipilimumab (Yervoy) tend to mimic autoimmune conditions, Dr. Cornell said. All three of these agents are used to treat lung cancer and other cancers.

Cardiovascular events associated with these agents, while uncommon, include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis, and venous thromboembolism, he said, citing an American Society of Clinical Oncology (ASCO) clinical practice guideline (J Clin Oncol 2018;36[17]:1714-68).

Dr. Cornell described the case of a 63-year-old woman with disseminated metastatic melanoma who presented to the emergency department 10 days after starting on combination therapy with ipilimumab and nivolumab. She had developed shortness of breath, pleuritic chest pain, and a mild cough for 1 or 2 days.

Her cardiac laboratory markers had been normal at baseline, but were markedly elevated on presentation, and electrocardiograms showed complete heart block and subsequent ventricular tachycardia.

The patient was started on high-dose prednisone, but she died in hospital, and an autopsy showed that the cause of death was infiltration into the myocardium of CD3-positive and CD8-positive T lymphocytes.

"So how do we manage this? This is a good opportunity, I think, for further cardiology and oncology collaboration to develop more robust

guidelines for what we can do to best prevent this," Dr. Cornell said.

Patients started on the ipilimumab/nivolumab combination should be tested weekly for cardiac troponin, creatine kinase (CK) and CK-muscle/brain (CK-MB) weekly for the first 3-4 weeks of therapy. Therapy should be



Dr. R. Frank Cornell said, "Early awareness and intervention is critical for improved outcomes, and a multidisciplinary approach between oncology, cardiology, the clinic nurse, and other health care providers is critical in managing these patients with these complicated therapies."

stopped if troponin levels continue to rise, and the patient should be started on high-dose steroids, he said.

The role of other anti-inflammatory agents such as infliximab (Remicade and biosimilars) is unclear and needs further study, he added.

Dr. Cornell cited a 2018 letter to The Lancet by Javid J. Moslehi, MD, and colleagues from Vanderbilt describing an increase in reports of fatal myocarditis among patients treated with checkpoint inhibitors.

"We highlight the high mortality rate with severe immune checkpoint inhibitor-related myocarditis, which is more frequent with combination PD-1 and CTLA-4 blockade, but can also occur with monotherapy. Myocarditis was observed across immune checkpoint inhibitor regimens, although it remains too early to determine whether the incidence differs between use of anti-PD1 and anti-PD-L1 drugs. Furthermore, this condition occurs early on during therapy and across cancer types," they wrote.

Most of the patients had no preexisting cardiovascular disease, and most were not taking medications for hypertension, cardiovascular disease, or diabetes.

## CAR-T cells and cardiac disease

The primary cardiac complications associated with CAR-T cell therapy are related to the cytokine release syndrome (CRS), a condition marked by progressive elevation in inflammatory cytokines that in turn leads to marked ele-

vations in C-reactive protein (CRP), interferon gamma, tumor necrosis factor alpha, and release of pro-inflammatory cytokines including interleukin (IL)-6, IL-10, IL-12, and IL-1 beta.

In rare instances, CRS can lead to disseminated intravascular coagulation (DIC), capillary leak syndrome, and a hemophagocytic lymphohistiocytosis-like (HLH) syndrome, Dr. Cornell said.

Package inserts for the two Food and Drug Administration-approved CAR-T cell products, axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) show that each was associated in clinical trials with a high incidence of CRS.

Among patients treated with axicabtagene ciloleucel, 94% developed CRS, which was grade 3 or greater in severity in 13%. The median time to onset was 2 days, and the median duration was 7 days. Cardiovascular adverse events included grade 3 or greater tachycardia in 2%, arrhythmias in 7%, edema in 1%, dyspnea in 3%, pleural effusion in 2%, hypotension in 15%, hypertension in 6%, and thrombosis in 1%.

Among patients treated with tisagenlecleucel, 79% treated for B-cell acute lymphoblastic leukemia (B-ALL) and 74% treated for diffuse large B-cell lymphoma (DLBCL) developed CRS, which was grade 3 or greater in 49% and 23% of patients, respectively. The median time to onset was 3 days, and the median duration of CRS was 8 days.

Cardiovascular adverse events of grade 3 or greater among these patients included tachycardia in 4%, fluid overload in 7%, edema in 1%, dyspnea in 12%, pulmonary edema in 4%, hypotension in 22%, and hypertension in 6%.

Risk factors for CRS include high pre-infusion tumor burden, active infections, and concurrent inflammatory processes, Dr. Cornell said.

Prevention of cardiovascular complications of CAR-T cell therapy requires management of CRS. Patients with grade 2 or greater CRS should receive the anti-IL-6 agent tocilizumab (Actemra) 8 mg/kg intravenously over 1 hour to a maximum dose of 800 mg. Tocilizumab infusions can be repeated every 8 hours as needed if the patient is not responsive to intravenous fluids or increasing supplemental oxygen, but should be limited to a maximum of three doses over 24 hours, and a maximum total of four doses.

Patients with grade 3 CRS should also receive intravenous methylprednisolone 1 mg/kg twice daily or the equivalent amount of dexamethasone, with corticosteroids continued until the severity of CRS is grade 1 or less, then tapered over 3 days.

Patients with grade 4 CRS should also receive IV methylprednisolone 1,000 mg per day for 3 days, and if symptoms improve, continue management as per grade 3, Dr. Cornell said.

Dr. Cornell reported having nothing to disclose.

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# SGLT-2 inhibitors promising for heart failure prevention, not treatment

BY DOUG BRUNK

MDedge News

LOS ANGELES – Mounting evidence suggests that the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors helps prevent heart failure.

They also may play a role in the treatment of patients with known heart failure (HF), but further studies are required to prove definite treatment benefit.

“These trials enrolled a minority of patients with known heart failure, and, in those subgroups, the drugs seem to reduce the risk for hospitalization, opening the possibility of treatment benefit,” Javed Butler, MD, said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease. “But there were not enough patients to conclude this. If you are treating diabetes with these agents in patients with heart failure, more power to you. But don’t think you are treating heart failure per se until the results of the dedicated heart failure trials come out.”

Good glycemic control has not been shown to affect heart failure outcomes per se, said Dr. Butler, professor and chairman of the department of medicine at the University of Mississippi Medical Center, Jackson.

“People seem to mix the concepts of prevention and treatment together,” he said. “We have now very good evidence across all trials with SGLT-2 inhibitors for prevention of heart failure. But for treatment, we need more data despite favorable early signals.

“Also, these trials include most patients with ischemic heart disease, but we don’t have data on nonischemic etiology for the development of heart failure from these trials,” Dr. Butler added.

The best available data from clinical trials suggest that patients with American College of Cardiology Foundation/American Heart Association heart failure classification stages A and B benefit the most from aggressive treatment to prevent HF.

“Either they have diseases like high blood pressure or diabetes, but their hearts are normal, or, perhaps, their hearts are abnormal, and they develop left ventricular hypertrophy or atrial fibrillation,” he said. “However, if someone is stage C – manifest heart failure – or stage D

– advanced heart failure – we need further data on novel therapies to improve their outcomes.”

Dr. Butler emphasized that not all heart failure is associated with atherosclerotic vascular disease. In fact, the Health, Aging, and Body Composition Study showed that the incidence of heart failure increased progressively across age groups, both for those with and without a preceding vascular event ( $P = .03$  and  $P$  less than .001,



Dr. Butler

respectively; Eur J Heart Fail. 2014 May;16[5]:526-34). “There’s a whole other world of nonischemic heart failure that we also need to worry about,” he said. “There is a lot of microvascular endothelial dysfunction.”

The combination of heart failure and diabetes is especially lethal. “If you put them together, you’re looking at about a 10-fold higher risk of mortality, which is a horrible prognosis,” Dr. Butler said. “That means that we need to think about prevention and treatment separately.”

Data from the SAVOR-TIMI 53, EXAMINE, and TECOS trials show there is no protective effect of dipeptidyl peptidase-4 inhibitors when it comes to hospitalization for heart failure.

“The other classes of drugs either increase the risk, or we don’t have very good data,” Dr. Butler said. “So far, across the spectrum of therapies for diabetes, the effect on heart failure is neutral and perhaps confers some risk.”

SGLT-2 inhibitors convey a different story.

In the EMPA-REG OUTCOME trial, one inclusion criterion was established cardiovascular disease (CVD) in the form of a prior MI,

coronary artery disease, stroke, unstable angina, or occlusive peripheral artery disease, but not heart failure alone (N Engl J Med. 2015 Nov 26; 373[22]:2117-28).

“This was not a heart failure study, so we don’t know what their New York Heart Association class was, or the details of their baseline HF treatment in the minority of patients who were enrolled who had a history of HF,” Dr. Butler cautioned.

However, the trial found that empagliflozin conferred an overall cardiovascular death risk reduction of 38%, compared with placebo.

When the researchers assessed the impact of treatment on all modes of cardiovascular death, they found that death from heart failure benefited the most (hazard ratio, 0.32;  $P = .0008$ ), while

sudden death benefited as well. Empagliflozin also had a significant impact on reduced hospitalization for heart failure, compared with placebo (HR, 0.65).

“This is a large enough cohort that you should feel comfortable that this drug is preventing heart failure in those with HF at baseline,” said Dr. Butler, who was not involved with the study. “We can have a debate about whether this is a treatment for heart failure or not, but for prevention of heart failure, I feel comfortable that these drugs do that.”

A subsequent study of canagliflozin and cardiovascular and renal events in type 2 diabetes showed the same result (N Engl J Med. 2017 Aug 17; 377[7]:644-57). It reduced hospitalization for heart failure by 33% (HR, 0.67).

Then came the CVD-REAL study, which found low rates of hospitalization for heart failure and all-cause death in new users of SGLT-2 inhibitors. More recently, DECLARE-TIMI 58 yielded similar results.

“One of the criticisms of these findings is that heart failure characteristics were not well phenotyped in these studies,” Dr. Butler said. “I say it really does not matter. Heart failure hospitalizations are associated with a poor prognosis irrespective of whether the hospitalization

occurred in patients without heart failure or in a patient with previously diagnosed heart failure, or whether the patient has reduced or preserved ejection fraction.

“Framingham and other classic studies show us that 5-year mortality for heart failure is about 50%,” he noted. “If you can prevent a disease that has a 5-year mortality of 50%, doesn’t that sound like a really good deal?”

A contemporary appraisal of the heart failure epidemic in Olmstead County, Minn., during 2000-2010 found that the mortality was 20.2% at 1 year after diagnosis, and 52.6% at 5 years after diagnosis. The data include new-onset HF in both inpatient and outpatient settings.

Specifically, new-onset HF hospitalization was associated with a 1-year postdischarge mortality of 21.1% (JAMA Intern Med. 2015;175[6]:996-1004).

“We cannot ignore prevention of heart failure,” Dr. Butler said. “Also, for treatment, once you get hospitalized for heart failure, the fundamental natural history of the disease changes. There is a 30% cumulative incremental death risk between the second and third hospitalizations.”

Dr. Butler concluded his presentation by noting that five randomized, controlled trials evaluating SGLT-2 inhibitors in HF have been launched, and should help elucidate any effects the drugs may have in treating the condition. They include EMPEROR-Preserved (NCT03057951), EMPEROR-Reduced (NCT03057977), Dapa-HF (NCT03036124), and SOLOIST-WHF (NCT03521934) and DELIVER (NCT03619213).

Dr. Butler disclosed that he has received research support from the National Institutes of Health, the European Union, and the Patient-Centered Outcomes Research Institute. He has also been a consultant for numerous pharmaceutical companies, including Boehringer Ingelheim, Janssen, and Astra-Zeneca, which sponsored the EMPA-REG, CANVAS, and DECLARE TIMI 58 trials.

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*Empagliflozin conferred an overall cardiovascular death risk reduction of 38%, compared with placebo.*



# Revised U.S. A fib guidelines revamp anticoagulation

BY MITCHEL L. ZOLER

MDedge News

**T**he first update to U.S. medical-society guidelines for managing atrial fibrillation since 2014 raised the threshold for starting anticoagulant therapy in women, pegged the direct-acting oral anticoagulants (DOACs) as preferred over warfarin, and introduced for the first time weight loss as an important intervention tool for treating patients with an atrial arrhythmia.

On Jan. 28, the American College of Cardiology, American Heart Association, and Heart Rhythm Society posted online a 2019 focused update (Circulation. 2019 Jan 28. doi: 10.1161/CIR.0000000000000665) to the 2014 atrial fibrillation (AF) management guidelines that the groups had previously published (J Am Coll Cardiol. 2014 Dec 2;64[21]:2246-80).

Perhaps the two most important changes, as well as the two that lead off the new document, were a pair of class I recommendations on using oral anticoagulation in AF patients.

One of these updates reset the threshold for initiating oral anticoagulant therapy in women from 2 points on the CHA2DS2-VASc scale to 3 points, while leaving the threshold for men unchanged at 2 points. This brought U.S. guidelines in line with European guidelines, set by the European Society of Cardiology in 2016 (Eur Heart J. 2016 Oct 7;37[38]:2893-962). It will now also mean that, because of the way the CHA2DS2-VASc score is calculated,

women with AF who are at least 65 years old will no longer automatically get flagged as needing oral anticoagulant therapy.

"This is a really important shift. It's recognition that female sex is not



Dr. Calkins

as important a risk factor [for AF-associated stroke] as once was thought," commented Hugh Calkins, MD, professor of medicine at Johns Hopkins Medicine in Baltimore and a

member of the panel that wrote the update. "This will change the number of women with AF who go on anticoagulation," predicted Dr. Calkins, who directs the cardiac arrhythmia service at his center.

The second important change to the anticoagulation recommendations was to specify the DOACs as recommended over warfarin in AF patients eligible for oral anticoagulation and without moderate to severe mitral stenosis or a mechanical heart valve, which also matches the 2016 European guidelines and updates the prior, 2014, U.S. guidelines, which didn't even mention DOACs.

Prescribing a DOAC preferentially to AF patients has already become routine among electrophysiologists, but possibly not as routine among primary care physicians, so this change has the potential to shift practice, said Dr. Calkins. But the higher price for DOACs, compared with warfarin, can

pose problems. "The cost of DOACs remains an issue that can be a serious limitation to some patients," said Craig T. January, MD, professor of medicine at the University of Wisconsin in Madison and chair of the guideline-writing panel.

Another notable change in the 2019 update was inclusion for the first time of weight loss as a recommended intervention, along with other risk factor modification, an addition that Dr. Calkins called "long overdue."

"This is a new recommendation, and it will potentially be important," said Dr. January, although the guidelines do not spell out how aggressive clinicians should be about having patients achieve weight loss, how much loss patients should achieve, or how they should do it. "There are a lot of observational data and basic science data suggesting the importance of weight loss. Most electrophysiologists already address weight loss. The problem is how to get patients to do it," commented Vivek Reddy, MD, professor of medicine and director of cardiac arrhythmia services at Mount Sinai Hospital in New York.

Dr. Reddy expressed surprise over two other features of the updated guidelines. For the first time, the guidelines now address percutaneous left atrial appendage (LAA) occlusion and say: "Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation." The guidelines' text acknowledges

that this runs counter to the Food and Drug Administration labeling for the Watchman LAA occlusion device, which restricts the device to patients "deemed suitable for long-term warfarin (mirroring the inclusion criteria for enrollment in the clinical trials) but had an appropriate rationale to seek a nonpharmacological alternative to warfarin."

Dr. Reddy

"We do not take a position on the FDA's

actions," Dr. January said in an interview.

"The ACC, AHA, and HRS guidelines should reflect what the FDA decided," Dr. Reddy said in an interview. "I'm a little surprised the guidelines said that anticoagulation had to be contraindicated."

The 2019 update also added a class IIb, "may be reasonable" recommendation for catheter ablation of AF in patients with heart failure with reduced ejection fraction.

Dr. Calkins has been a consultant to Abbott, Altathera, Atri-Care, Boehringer-Ingelheim, King, Medtronic, and St. Jude and has received research funding from Boehringer-Ingelheim, Boston Scientific, and St. Jude. Dr. January had no disclosures. Dr. Reddy has been a consultant to, received research funding from, or has an equity interest in more than three dozen companies.

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## Medical advice can drive emergency visits by AF patients

BY MITCHEL L. ZOLER

MDedge News

**BOSTON** – Patients with atrial fibrillation who present to emergency departments, despite being asymptomatic, often go based on their understanding of advice they had previously received from their physicians, according to results from a prospective study of 356 Canadian atrial arrhythmia patients seen in emergency settings.

One way to deal with potentially inappropriate emergency department use is to have concerned patients with atrial fibrillation (AF) record their heart rhythm data with a handheld device or watch, transfer the records to their smartphones, and transmit the information to a remote physician for interpretation and advice, Benedict M. Glover, MD, said at the

annual International AF Symposium.

Dr. Glover and his associates are in the process of developing a prototype system of this design to address the need they identified in a recent



Dr. Glover

registry of 356 patients with a primary diagnosis of AF who sought care in the emergency department of any of seven participating Canadian medical centers, including five academic centers and two community hospitals. The survey results showed that 71% of the patients were symptomatic and 29% were asymptomatic then they first presented to an ED.

Case reviews of the 356 patients showed that 152 (43%) came to the EDs for what were classified as inappropriate reasons. The most common cause by far of an inappropriate ED presentation was prior medical advice the patient had received, cited in 62% of the inappropriate cases, compared with 9% of the

appropriate cases, said Dr. Glover, an electrophysiologist at Sunnybrook Health Sciences Centre in Toronto.

The inappropriate ED use by AF patients could be addressed in at least two ways, he said. One solution might be to give patients an alternative destination, so that instead of going to an ED they could go to an outpatient AF clinic. A second solution is to give patients a way to have their heart rhythm assessed remotely at the time of their concern. Dr. Glover said that his center had the staff capacity to deal with the potential influx of rhythm data from a pilot-sized program of remote heart-rhythm monitoring, but he conceded that scaling up to deal with the data that could come from the entire panel of AF patients managed by Sunnybrook physicians would be a huge challenge.

Dr. Glover had no disclosures.

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# Too much, too little sleep linked to atherosclerosis

BY M. ALEXANDER OTTO

MDedge News

**T**oo little and too much sleep, along with fragmented sleep, were independently linked with increased subclinical, non-cardiac atherosclerotic plaque in healthy middle-aged men and women in a Spanish investigation of bank employees.

“Overall, our findings support the potential role of healthy sleeping in protecting against atherosclerosis. Thus, recommending a good sleep hygiene” – 7-8 hours a night – “should be part of the lifestyle modifications provided in our daily clinical practice,” said investigators led by Fernando Domínguez, MD, PhD, of Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid. The report is in the *Journal of the American College of Cardiology*.

Studies have linked sleep problems to increased cardiovascular risk before, but the investigations tended to focus on patients with obstructive sleep apnea (OSA) and other problems, and often relied on patient self-report. The investigators wanted to see if the relationship held in healthy adults, using an objective measure.

The participants – all with no known cardiovascular disease – wore Acti Trainers accelerometers (Actigraph, Pensacola, Fla.) around their waists for 7 days to record

sleep duration and quality. Subjects also had their plaque burdens assessed by 3-dimensional vascular ultrasound (VUS) at their carotid and femoral arteries bilaterally. Cardiac CT was used to assess coronary artery calcification as a surrogate for coronary artery atherosclerosis.

The 3,974 participants had a mean age of 46 years, and a third were women; they had a low prevalence of both hypertension and diabetes. OSA patients were excluded from the study. Overall, 27% had very short sleep duration (VSSD), less than 6 hours a night; 38% had short sleep duration (SSD), 31% slept from 7 to 8 hours per night, and served as the reference group for healthy sleep habits; and 4% had long sleep duration (LSD), greater than 8 hours.

After adjustment for a wide range of cardiovascular risk factors, including body mass index, hypertension, and smoking, VSSD was independently associated with a higher atherosclerotic burden, compared to the reference group (odds ratio, 1.27; 95% confidence interval, 1.06-1.52;  $P = 0.008$ ). Participants in the highest quintile of sleep fragmentation were more likely to have plaques at multiple sites (OR, 1.34; 95% CI, 1.09-1.64;  $P = 0.006$ ). The Framingham risk score at both 10 and 30 years was significantly higher in participants with VSSD or SSD, and in the highest quintiles of sleep fragmentation.



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LSD was also associated with a higher plaque burden, which reached statistical significance in women. “Too-long sleep duration may not be healthy either ... Recommendations should be restricted to 7 to 8 hours,” the investigators said.

Sleep duration and quality were not associated with inflammation markers or coronary artery calcification. The investigators noted that CT for coronary artery calcification might not be as sensitive as VUS for picking up subclinical atherosclerosis.

Short sleepers tended to have higher intakes of alcohol and caf-

feine than did those in the 7- to 8-hour group.

The work was funded by CNIC and Banco Santander, among others. Dr. Domínguez had no disclosures. Investigator Hector Bueno, MD, PhD, reported research funding and fees from a number of companies, including AstraZeneca and Novartis. The second author, Valentín Fuster, MD, PhD, is the editor of the *Journal of the American College of Cardiology*, which published the report.

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**SOURCE:** Domínguez F et al. *J Am Coll Cardiol* 2019;73:134-44.

## Teens' screen time linked to poor sleep, depression

BY JILL D. PIVOVAROV

MDedge News

**S**creen-based activities and sleep behaviors could be “intervention targets” for adolescents with depressive symptoms, results of a study of almost 3,000 U.S. adolescents suggest.

“Our results indicated that [social messaging, Web surfing, TV/movie watching, and video gaming] were associated with greater depressive symptoms and poorer sleep characteristics,” Xian Li, PhD, and her associates reported in *Sleep Medicine*.

Numerous studies previously have demonstrated a positive link between adolescent depression and exposure to electronic devices, although little is known about the precise mechanism(s) of action involved and to what extent sleep plays a role. To address those gaps, Dr. Li, of the State University of New York at Stony Brook, and her associates examined four types of screen activities to determine whether symptoms of adolescent depression, sleep duration, and symptoms of insomnia – including

problems falling asleep and staying asleep – are influenced in any way by those activities.

Using data from the Fragile Families and Child Wellbeing Study, a longitudinal urban birth cohort study, Dr. Li and her associates evaluated a total of 2,865 adolescents (mean 15.53 years of age; 48.2% female). The investigators assessed depressive symptoms at age 15 years by using five items from Center for Epidemiologic Studies Depression Scale.

Dr. Li and her associates found greater depressive symptoms associated with all four of the screen-based activities ( $P$  less than .01). In addition, more problems were observed with falling and staying asleep as well as shortened duration of sleep during the week for each of the activities monitored.

Social messaging, Web surfing, and time spent watching TV and movies appeared to be directly correlated with sleep characteristics, but the same could not be said for gaming, which showed only partial correlation with sleep characteristics. In that case, the authors speculated that the association be-

tween gaming and depression could be at least partly explained by individual characteristics such as trait neuroticism and self-control or a self-selection behavior in which those exhibiting greater signs of depression turn to gaming as an escape.

The authors also noted a significant link between depressive symptoms at age 9 years and gaming behavior at age 15 years. They did note that, while the relationships in the models might have statistical significance, “the effect size in the study as a whole are small.”

The research was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health, and several private foundations. Dr. Buxton received two subcontract grants to Pennsylvania State University from Mobile Sleep Technologies. Dr. Hale received an honorarium from the National Sleep Foundation.

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**SOURCE:** Li X et al. *Sleep Med*. 2019 Feb 2. doi: 10.1016/j.sleep.2019.01.029.

# Socioeconomic status, race tied to CPAP compliance

BY DOUG BRUNK

MDedge News

SAN DIEGO – Positive indicators of compliance with continuous positive airway pressure (CPAP) included higher apnea-hypopnea index, white race, and higher median household income, results from a large single-center cohort study showed.

“CPAP is the gold standard treatment for OSA [obstructive sleep apnea] and is very effective, especially for those with severe disease,” researchers led by Philip S. LoSavio, MD, wrote in an abstract presented at the Triological Society’s Combined Sections Meeting. “However, CPAP is a significant challenge for patients for various reasons, with reports of only 46%-80%

of OSA patients using CPAP for more than 4 consecutive hours on two out of three nights.”

In an effort to identify and define different factors associated with CPAP compliance, Dr. LoSavio and his colleagues collected data on 578 patients with OSA on CPAP who were treated at Rush University Medical Center, Chicago. The mean patient age was 58 years, 52% were female, 43% were African American, 40% were white, their mean body mass index was 36.91 kg/m<sup>2</sup>, and their mean apnea-hypopnea index was 37.25 events per hour. The researchers recorded CPAP use at office visits via CPAP module or card, and patients were considered CPAP compliant if their machines logged 4 consecutive hours of use for 70% or more of

*Continued on page 29*

## VIEW ON THE NEWS

**Krishna Sundar, MD, FCCP, comments:**

Striking findings of this study are strong effects of median income and race on CPAP compliance. Other studies have shown improved CPAP compliance following a visit with a sleep provider prior to therapy and in patients with greater self-efficacy. These findings together emphasize the importance of patient characteristics (beyond sleep apnea severity or comorbidities) as determinants of PAP adherence.



# More data link short sleep, homocysteine levels, CV risk

BY KARI OAKES

MDedge News

**S**hort sleep’s association with cardiovascular risk may be mediated in part by elevated homocysteine levels, suggests a new analysis of data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES).

The study, published in the *Journal of Clinical Sleep Medicine*, found that elevated homocysteine levels were only associated with short sleep duration for some populations, including women, non-Hispanic white individuals, and participants with obesity.

A total of 4,480 NHANES participants had serum homocysteine levels on record and were included in the study; of these, those with self-reported sleep duration of 7 hours had the lowest serum homocysteine levels. Those with the shortest sleep duration – 5 hours or less per night – had the highest homocysteine levels.

When participants were broken into subgroups by such factors as sex, ethnicity/race, and body mass index, the association between extremely short sleep and elevated homocysteine levels was retained for three groups: women, non-Hispanic white participants, and those with BMIs of 30 kg/m<sup>2</sup> and higher.

“[T]his finding might suggest increased vulnerability to cardiovascular risk or other atherothrombotic events in these groups in the context of short sleep,” wrote Tien-Yu Chen, MD, of Tri-Service General Hospital, Taipei, Taiwan, and coauthors in the abstract accompanying the study.

In the NHANES questionnaire, participants were asked how much sleep they usually got, in whole hours. Serum homocysteine was measured once for each study participant.

Using multivariate linear regression, homocysteine was considered the dependent, continuous variable, and the association between sleep duration and homocysteine was

assessed using three models that accounted for confounders. The first and simplest model accounted for age, sex, and race/ethnicity. The second model added BMI, several cardiometabolic laboratory values, and vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, and folate levels. The third model included all previous factors and added patient characteristics and comorbidities, such as sleep disorders, mental health service use, cardiovascular disease and cancer diagnoses, and alcohol and tobacco use.

Dr. Chen and colleagues dichotomized homocysteine levels to above or below the 75th percentile of the log homocysteine level, which fell at 9.74 nmol/L.

After adjustment, women, but not men, had an association between short sleep and increased odds of elevated homocysteine (odds ratio, 2.691; *P* = .010). This association “persisted in fully adjusted models,” wrote Dr. Chen and coauthors.

For individuals with obesity (BMI of 30 or greater), the association between elevated homocysteine and extremely short sleep (5 hours or less) persisted in fully adjusted models (beta = .062; *P* = .039 for model 3).

When looking at ethnicity, the association between extremely short sleep and elevated homocysteine was only seen among non-Hispanic white participants; again, this association was seen after full adjustment for confounders (beta = .068; *P* = .032). Small sample sizes limited some of the racial/ethnic analyses, noted the investigators.

Homocysteine, explained Dr. Chen and coauthors, is associated with a variety of atherogenic changes, and elevated levels are associated

with increased risk for cardiovascular disease and mortality. Short sleep is also associated with increased cardiovascular risk, as is long sleep in some studies.

Though preliminary work had shown that short sleep had an association with homocysteine levels, the relationship is unclear since that study had many potential cardiovascular confounders, they said.

The association between extremely short sleep duration and cardiovascular events has been well established, with increased inflammation playing a potential role, although the reasons for the association are still being elucidated. “Because increased homocysteine levels are considered an independent risk factor for cardiovascular diseases, further studies are needed to better understand the relationships among short sleep duration, homocysteine levels, and cardiovascular events,” the investigators wrote.

The study’s strengths include the large sample size and ability to control for many demographic and individual characteristics, including comorbidities. However, sleep duration was based on self-report and did not include information about napping or sleep-wake times. Also, sleep quality was not assessed beyond a question about snoring or snorting and a question about a prior diagnosis of a sleep disorder.

One of the coauthors reported financial relationships with multiple pharmaceutical companies and UpToDate.

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**SOURCE:** Chen T-Y et al. *J Clin Sleep Med*. 2019;15(1):139-48.



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nights. During the office visits, patients completed a questionnaire asking if they were suffering from different otolaryngology-related diseases, including sinus headaches, gastroesophageal reflux, and enlarged tonsils. Dr. LoSavio, who heads the section of sleep surgery in the department of otorhinolaryngology at Rush University Medical Center, and his colleagues performed logistic regression to ascertain the effects of race and socioeconomic status on CPAP compliance while adjusting for OSA severity. They also analyzed the adjusted association of median income and self-reported symptoms of sinus headaches, GERD, and enlarged tonsils, on CPAP compliance.

They found that African American patients were less compliant with CPAP, compared with their white counterparts (odds ratio 0.42;  $P$  less than .01). In addition, patients with mild OSA were less likely to be compliant compared with those who had severe disease (OR 0.57;  $P$  less

than .03). Self-reported symptoms of sinus headaches, GERD, and enlarged tonsils were associated with significantly lower levels of compliance, while higher median income was positively associated with higher levels of compliance. When the researchers grouped incomes based on the 2018 federal tax classification brackets, they observed a significant association between compliance and median income ( $P$  less than .001), with a likelihood ratio of 20.4.

“Previous studies have shown that with increases in OSA disease severity, defined by higher [apnea-hypopnea index], comes increases in CPAP compliance, while other studies have alluded to the fact that lower socioeconomic status can affect CPAP compliance,” Dr. LoSavio and his associates wrote in their abstract. “A novel aspect of our study hoped to shed light on different otolaryngology-related diseases and how they might affect compliance. The patients with comorbid GERD, sinus headaches, and enlarged tonsils were less CPAP

*Self-reported symptoms of sinus headaches, GERD, and enlarged tonsils were associated with significantly lower levels of compliance.*



DAVID CANNINGS-BUSH/ELL/ISTOCKPHOTO

compliant in our study. These conditions are relatively easily treated and could therefore provide an avenue to increase CPAP compliance if addressed.” They acknowledged certain limitations of the study, including its single-center design and the self-reported nature of the patient questionnaire.

The researchers reported having no financial disclosures. The meeting was jointly sponsored by the Triological Society and the American College of Surgeons.

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**SOURCE:** LoSavio PS et al. Triological CSM 2019, Abstracts.

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 **CHEST**<sup>TM</sup> Physician  
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

# Sleep problems common in autism spectrum disorder

BY TARA HAELE

MDedge News

Children with a diagnosis of autism spectrum disorder or another developmental delay or disorder that includes autistic characteristics are twice as likely to have sleeping problems, a multisite case-control study has found.

The findings match up with previous similar studies, but this study is among the largest to measure sleeping problems in children with autism spectrum disorder with two control groups.

“The higher reported occurrence of sleep problems in children with autism spectrum disorder may be due to multiple contributing factors, including physiologic differences, sleep disorders, developmental comorbidities, medical comorbidities causing sleep disruption, communication impairments, and behavioral disturbances,” Ann M. Reynolds, MD, of the University of Colorado and Children’s Hospital Colorado, both in Aurora, and her associates reported in *Pediatrics*.

“Children with autism spectrum disorder are more likely to have anxiety, which may predispose them to sleep problems,” the authors added.

The study evaluated sleep habits and problems in 1,987 children aged 2-5 years. The study population included 522 children with autism

spectrum disorder, 228 children with other developmental delays and disorders that have autism spectrum disorder characteristics, 534 children with other developmental delays and disorders, and 703 children from the general population.



DEVANGEORGIEV/THINKSTOCKPHOTOS

Parents completed the Children Sleep Habits Questionnaire (CSHQ), a 33-item assessment tool typically used with a total score cutoff of 41 and above for identification of children with sleep disorders. The researchers also used a second, more conservative cutoff of 48 – the cutoff for the highest quartile in the general population group to avoid overidentification with the lower cutoff.

Scores were adjusted for maternal education and race/ethnicity, family income, child age and sex, and child cognitive scores on the Mullen Scales of Early Learning (MSEL). The researchers also adjusted for genetic and/or neurologic diagnoses, including Down syndrome, fragile X, Rett syndrome, tuberous sclerosis, cerebral palsy, and neurofibromatosis.

Autistic children tended to have lower MSEL scores than the other children. Both the autistic children and those with other developmental disorders and delays were more likely than those in the general population to have neurologic or genetic conditions.

Based on a cutoff score of 48, autistic children had more than double the odds of sleep problems, compared with children in the general population (adjusted odds ratio, 2.37;  $P = .001$ ) and children with other developmental delays (aOR, 2.12;  $P = .001$ ).

With a cutoff of 41, sleep problems in children with autism spectrum disorder were 1.45 times greater than the general population ( $P = .023$ ) and 1.75 times greater than those with developmental delays ( $P = .001$ ). But children with developmental delays who displayed autistic characteristics did not have significantly different prevalence of sleep problems than children with autism spectrum disorder had.

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP,**  
**comments:** More research

in the area of autism is needed. This is a robust study comparing autism to other developmental disorders in ages 2 thru 5 years.



“The phenotypic overlay between children with [autism spectrum disorder] and children with developmental delay with [autism characteristics] may explain the similarities in sleep disturbance among these two groups,” the authors wrote.

The research was funded by the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Award. Dr Reynolds consults for Ovid Therapeutics regarding evaluation of sleep severity and improvement in clinical trials.

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**SOURCE:** Reynolds AM et al. *Pediatrics*. 2019 Feb. 11. doi: 10.1542/peds.2018-0492.

# No increase in severe community-acquired pneumonia after PCV13

BY TARA HAELE

MDedge News

Despite concern about the rise of nonvaccine serotypes following widespread PCV13 immunization, cases of community-acquired pneumonia (CAP) remain nearly as low as after initial implementation of the vaccine and severe cases have not risen at all.

This was the finding of a prospective time-series analysis study from eight French pediatric emergency departments between June 2009 and May 2017. The 12,587 children with CAP enrolled in the study between June 2009 and May 2017 were all aged 15 years or younger and came from one of eight French pediatric EDs.

Pediatric pneumonia cases per 1,000 ED visits dropped 44% after PCV13 was implemented, a decrease from 6.3 to 3.5 cases of CAP per 1,000 pediatric visits from June 2011 to May 2014, with a slight but statistically significant increase to 3.8 cases of CAP per 1,000 pediatric visits from June 2014 to May 2017. However, there was no statistically significant increase in cases with pleural effusion, hospitalization, or high

inflammatory biomarkers.

“These results contrast with the recent increase in frequency of invasive pneumococcal disease observed in several countries during the same period linked to serotype replacement beyond 5 years after PCV13 implementation,” reported Naïm Ouldali, MD, of the Association Clinique et Thérapeutique Infantile du Val-de-Marne in France, and associates. The report is in *JAMA Pediatrics*.

“This difference in the trends suggests different consequences of serotype replacement on pneumococcal CAP vs invasive pneumococcal disease,” they wrote. “The recent slight increase in the number of all CAP cases and virus involvement may reflect changes in the epidemiology of other pathogens and/or serotype replacement with less pathogenic serotypes.”

This latter point arose from discovering no dominant serotype during the study period. Of the 11 serotypes not covered by PCV13, none appeared in more than four cases.

“The implementation of PCV13 has led to the quasi-disappearance of the more invasive serotypes and increase in others in nasopharyngeal flora, which greatly reduces the frequency of the

more severe forms of CAP, but could also play a role in the slight increase in frequency of the more benign forms,” the authors reported.

Among the study’s limitations was lack of a control group, precluding the ability to attribute findings to any changes in case reporting. And “participating physicians were encouraged to not change their practice, including test use, and no other potential interfering intervention.”

Funding sources for this study included the Pediatric Infectious Diseases Group of the French Pediatrics Society, Association Clinique et Thérapeutique Infantile du Val-de-Marne, the Foundation for Medical Research, and a Pfizer Investigator Initiated Research grant.

Dr. Ouldali has received grants from GlaxoSmithKline, and many of the authors have financial ties and/or have received non-financial support from AstraZeneca, Biocodex, GlaxoSmithKline, Merck, Novartis, Pfizer, and/or Sanofi Pasteur.

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**SOURCE:** Ouldali N et al. *JAMA Pediatrics*. 2019 Feb 4. doi: 10.1001/jamapediatrics.2018.5273.



# Mild OSA resolves spontaneously in some children

BY DOUG BRUNK

MDedge News

CORONADO, CALIF. – Mild obstructive sleep apnea (OSA) resolves in about one-third of children younger than age 3 years after an observation period of 3-12 months, results from a single-center study showed.

“OSA affects up to 6% of the pediatric population, and diagnosis of young children can be particularly challenging due to the heterogeneity of presenting symptoms,” Douglas C. von Allmen, MD, said at the Triological Society’s Combined Sections Meeting. “While school-age children may present with snoring, that’s less common in the younger population. Up to one-quarter of infants may have noisy breathing, which may mimic obstructive events throughout the first 3 years of life. Additionally, long-term clinical implications of mild sleep apnea in very young children is unclear.”

According to Dr. von Allmen, a fifth-year otolaryngology resident at the University of Cincinnati, management strategies of children with OSA can include a period of observation, particularly when there’s an absence of concerning findings on polysomnography (PSG), such as

hypoventilation or significant hypoxia, or when the primary etiology of the OSA is unknown. “Additionally, few studies at this point have attempted to characterize the natural history of mild OSA in pediatric patients under 3 years of age,” he said.



Dr. von Allmen

In an effort to assess the effects of observation on the PSG outcomes of children under 3 years with mild OSA, Dr. von Allmen and his colleagues performed a retrospective review of 26 children who had an overnight PSG with a follow-up PSG performed 3-12 months later. They excluded patients with neuromuscular disease, tracheostomy, or interstitial lung disease. All PSGs were performed at the Cincinnati Children’s Hospital Medical Center between 2012 and 2017 and were scored by a board-certified sleep physician. The researchers defined mild OSA as at least one, but fewer than five, events per hour. The mean age of the 26 patients was 7 months, 65% were male, 92% were white, and their median body mass index was in the 39th

percentile. Comorbidities include laryngomalacia (40%), cardiac disease (40%), allergies (34%), asthma (23%), and Down syndrome (11%).

Between baseline and follow-up, the apnea-hypopnea index (AHI) trended downward from 4.3 to 3.4 events per hour ( $P = .19$ ) the obstructive AHI decreased significantly from 2.7 to 1.3 events per hour ( $P = .013$ ), while the central apnea index also trended downward from 1.4 to 1.2 events per hour ( $P = .60$ ). The oxyhemoglobin nadir and sleep efficiency did not change significantly, but there was a decrease in the arousal index (from 14.7 to 13 events per hour;  $P = .027$ ) and in the percentage of REM sleep (from 33% to 30%;  $P = .008$ ).

As for postobservation OSA severity outcomes, eight patients (31%) resolved spontaneously, one patient progressed from mild to moderate OSA, and the rest remained in their mild OSA state. Subanalysis revealed that OSA resolution rate was 36% in patients with laryngomalacia, compared with 27% in those with no laryngomalacia, a difference that did not reach statistical significance ( $P = .98$ ).

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** While retrospective, this study is important because surgery in children, especially 2 years of age and younger, has a higher incidence of complications.

Dr. von Allmen pointed out that the study cohort had comorbidities which may have contributed to the persistence of OSA. He also acknowledged certain limitations of the study, including its retrospective nature, the potential for selection bias, the small sample size, and the fact that it did not include a control sample of normal children.

Dr. von Allmen reported having no financial disclosures. The study received a resident research award at the meeting, which was jointly sponsored by the Triological Society and the American College of Surgeons.

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**SOURCE:** von Allmen DC et al. Triological CSM, Abstracts.

# FDA approves 0.5-mL Fluzone Quadrivalent vaccine for children

BY LUCAS FRANKI

MDedge News

The Food and Drug Administration has approved the 0.5-mL dosage of Fluzone Quadrivalent, an influenza vaccine, for use in children aged 6-35 months, according to Sanofi Pasteur, the vaccine’s manufacturer.

FDA approval was based on results of a phase 4 safety and immunogenicity study of nearly 2,000 children. Children aged 6-35 months who received one or two doses of Fluzone at 0.50 mL had a safety profile similar to that of children who received one or two doses of Fluzone at 0.25 mL. Results from the study were presented at the Pediatric Academic Societies annual meeting in April 2018.

This flu vaccine should not be given to anyone with a severe allergic reaction (anaphylaxis) to egg or

egg products, according to the press release.

In children, the most common adverse events are injection-site reactions, muscle aches, fatigue, and headache; in young children, irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever are common.

“Offering pediatricians the convenience of the same 0.5-mL dose option for children may help streamline immunization efforts. The potentially life-threatening effects of influenza in children reported during the 2017-18 season, especially among those who were not vaccinated, is sobering,” David P. Greenberg, MD, regional medical head of Sanofi Pasteur of North America, said in the press release.

Find the full press release on the Sanofi website.

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## Explore the Moderate to Severe Asthma Center of Excellence

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# CHEST Foundation's NetWorks Challenge is just around the corner

The NetWorks Challenge is an annual fundraising competition that encourages NetWork members to contribute to the CHEST Foundation - supporting clinical research grants and community service programs and creating patient education materials - while earning travel grants for their NetWork members to the CHEST Annual Meeting 2019 in New Orleans. Because of your generosity throughout the 2018 NetWorks Challenge, the CHEST Foundation was able to send 59 early career clinicians to CHEST 2018 in San Antonio - marked growth from the 25 clinicians who received the travel grants in 2017.



As we further improve this program based on feedback from NetWorks members, a few elements of the fundraiser are changing in 2019.

**Length:** This year, the NetWorks Challenge will span 3 months. Contributions made between April 1 and June 30 count toward your NetWork's fundraising total! Just be sure to list your NetWork when making

your contribution on [chestfoundation.org/donate](http://chestfoundation.org/donate). Each month has a unique theme related to CHEST, so be sure to watch our social media profiles to engage with us and each other during the drive.

Additionally, ANY contributions made to the CHEST Foundation during your membership renewal will count toward your NetWorks total amount raised - no matter when your membership is up for renewal. Contributions made in this manner after June 30 will count toward your Network's 2020 amount raised.

**Prizes:** This year, every NetWork is eligible to receive travel grants to CHEST 2019 in New Orleans

based on the amount raised by the NetWork. Our final winners - the NetWork with the highest amount raised, and the NetWork with the highest percentage of participation from their NetWork, will each receive two additional travel grants to CHEST 2019. Plus, the NetWork with the highest amount raised over the course of the challenge receives an additional prize - a seat in a CHEST Live Learning course of the winner's choosing, offered at CHEST's Innovation, Simulation, and Training Center in Glenview, Illinois.

Visit [chestfoundation.org/nc](http://chestfoundation.org/nc) for more detailed information.

## PRACTICE MANAGEMENT

# EHR stress predicts burnout

BY GREGORY TWACHTMAN

MDedge News

Physicians who experience stress related to the use of health information technology are twice as likely to experience burnout.

Rebekah Gardner, MD, of Brown University in Providence, R.I., and her colleagues surveyed all 4,197 Rhode Island physicians in 2017 to learn how the use of electronic health records affected their practices and their job satisfaction.

Just over a quarter (25.0%) of 1,792 respondents reported burnout. Among electronic health record users (91% of respondents), 70% reported health IT-related stress (*J Am Med Inform Assoc.* 2019;26[2]:106-14; doi: 10.1093/jamia/ocy145).

"After adjustment, physicians reporting poor/marginal time for documentation had 2.8 times the odds of burnout (95% confidence interval, 2.0-4.1; *P* less than .0001) compared to those reporting sufficient time," according to the researchers.

The team looked at three stress-related variables: whether the EHR adds to the frustration of one's day; whether physicians felt they had sufficient time for documentation; and the amount of time spent on the EHR at home. Variables were measured on a four- or five-point scale depending on the question related to the specific stress variable.

Almost two-thirds (64.2%) of respondents "agreed" or "strongly agreed" that EHRs add to the frustration of their day.

"It was the most commonly cited HIT-related stress measure in almost every specialty, with the highest prevalence among emergency physicians (77.6%)," the investigators wrote.

More than a third of physicians (37.7%) reported "moderately high" or "excessive" time spent on EHRs at home; this metric was the most commonly cited stress measure among pediatricians (63.6%).

Nearly half (46.4%) of physicians reported "poor" or "marginal" sufficiency of time for documentation.

"Presence of any 1 of the HIT-related stress measures was associated with approximately twice the odds of burnout among physician respondents," Dr. Gardner and her colleagues noted, adding that "measuring and addressing HIT-related stress is an important step in reducing workforce burden and improving the care of our patients."

To alleviate burnout, the authors recommended increased use of scribes, use of medical assistants to help create a more team-based documentation function, improved EHR training, more time during the day for documentation, and streamlined documentation expectations, with certain culture shifts needed in some cases (i.e., banning work-related email and clinical tasks for vacationing physicians).

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**SOURCE:** Gardner R et al. *J Am Med Inform Assoc.* doi: 10.1093/jamia/ocy145.



LEAH-ANNE THOMPSON/THINKSTOCK

## VIEW ON THE NEWS

**Mike Nelson, MD, FCCP, comments:**

I just dictated a note into my EHR about a patient with Buerger disease, thromboangiitis obliterans, translated by my software as thrombo in GI disability her aunts (yes, it is medical software). After laughing, I deleted and tried again only to get the same result. Had I typed this at my electrifying speed of 25 words a minute with eight mistakes it probably would have taken less time by half. Had I written it on a piece of paper it may have taken about 2-3 seconds. Just a few seconds, you say. But multiply it by hundreds of times per day and one can understand the frustration of the 70% in this article. Don't get me started on the 8-page office notes from a problem-focused return visit. Many of you are probably aware that there is an Office of the National Coordinator for Health Information Technology (ONC) that was created in 2004 by an executive order and legislatively mandated in 2009 by the HITECH act. The mission of the organization is to "Improve the health and well-being of individuals and communities through the use of technology and health information that is accessible when and where it matters most." Fifteen years later the ONC is desperately failing in their mission.





# Get ready for the Big Easy

CHEST 2019 will be in New Orleans, Louisiana, this year, October 19-23. Here are a few ways to be engaged leading up to the meeting.

## Submit abstracts and case reports

Do you have original investigative research to share? There's still some time to submit your abstracts and case reports for presentation at CHEST 2019 through Friday, March 15. If accepted, all abstracts and case reports will be published as submitted in an online CHEST® journal abstract supplement. No corrections will be made once submission is complete.

View submission details (<https://chestmeeting.chestnet.org/abstracts-and-case-reports/>).

## Call for moderators

CHEST is currently requesting moderators to facilitate discussions, questions, and answers within assigned sessions on-site at CHEST 2019 in New Orleans. Moderators will be notified June to September of their acceptance as a moderator.

View complete details ([https://docs.google.com/forms/d/e/1FAIpQLSd-SWFSyKAelJfyYgGRF6km\\_95zn-ba63bx6iM9TWl08gpdqzEQ/viewform](https://docs.google.com/forms/d/e/1FAIpQLSd-SWFSyKAelJfyYgGRF6km_95zn-ba63bx6iM9TWl08gpdqzEQ/viewform)).

## CHEST Challenge 2019

US-based CHEST fellows-in-training - does your fellowship have what it takes to win CHEST Challenge 2019? CHEST Challenge is a fun and exciting competition in which CHEST fellows-in-training compete against programs around the country for honor and prizes! The first round of the competition consists of two parts: social media challenges and online quiz. The aggregate score for both of these components will be used to identify the top three highest scoring teams. These top three teams will then be invited to send three fellows each to the CHEST Challenge Championship, a Jeopardy-style game show that takes place live during the CHEST Annual Meeting.

See the rules and how to participate ([chestchallenge.org](http://chestchallenge.org)).

## Apply for CHEST Foundation grants

The CHEST Foundation has awarded more than \$10 million in grant funding to nearly 800 recipients worldwide for clinical research and community service. Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars in a field of expertise.

*The CHEST Foundation has awarded more than \$10 million in grant funding to nearly 800 recipients worldwide for clinical research and community service.*

The CHEST Foundation is accepting grant applications now through April 8, 2019, in the following areas:

- CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP – Up to \$15,000 (multiple recipients selected)\*
- The GlaxoSmithKline Distinguished Scholar in Respiratory Health – \$150,000\*
- CHEST Foundation Research Grant in Asthma – \$15,000 – \$30,000\*
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease – \$25,000 – \$50,000\*
- CHEST Foundation Research Grant in Cystic Fibrosis – \$15,000 – \$30,000\*
- CHEST Foundation Research Grant in Lung Cancer – \$50,000 – \$100,000\*
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria Diseases – \$30,000 – \$60,000\*
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension – \$25,000 – \$50,000\*
- CHEST Foundation Research Grant in Pulmonary Fibrosis – \$25,000 – \$50,000\*
- CHEST Foundation Research Grant in Venous Thromboembolism – \$15,000 – \$30,000\*
- CHEST Foundation Research Grant in Women's Lung Health – \$10,000\*

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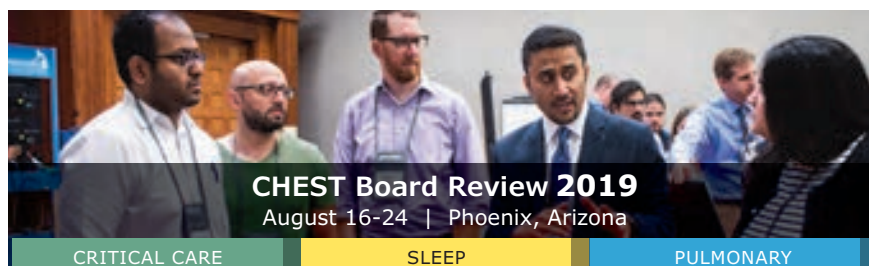
# 2019 Education Calendar



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March 7 - 9	Ultrasonography: Essentials in Critical Care
March 21-23	Lung Cancer: A Multidisciplinary Update
April 4 - 6	Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers
May 3 - 4	Bronchoscopy Procedures for the ICU
May 30 - June 1	Advanced Critical Care Echocardiography
June 6 - 8	Difficult Airway Management
June 28 - 29	Therapeutic Bronchoscopy for Airway Obstruction
July 25 - 27	Mechanical Ventilation: Advanced Critical Care Management
August 8 - 10	Cardiopulmonary Exercise Testing (CPET)
September 5 - 7	Difficult Airway Management
September 12 - 14	Ultrasonography: Essentials in Critical Care
September 19 - 21	Comprehensive Bronchoscopy With Endobronchial Ultrasound
November 7-9	Extracorporeal Support for Respiratory and Cardiac Failure in Adults
November 14 - 16	Critical Care Ultrasound: Integration into Clinical Practice
November 22 - 23	Comprehensive Pleural Procedures
December 5 - 7	Ultrasonography: Essentials in Critical Care
December 13 - 14	Advanced Critical Care Echocardiography Board Review Exam Course



Calendar subject to change. For most current course list and more information, visit [livelearning.chestnet.org](http://livelearning.chestnet.org).

# CHEST reaccruited by Society for Simulation in Healthcare

**T**he American College of Chest Physicians (CHEST) received reaccreditation from the Society for Simulation in Healthcare (SSH) for the 2018-2023 term in the areas of Teaching/Education, Assessment, and Research.

In 2013, CHEST became the first and only medical specialty society to achieve SSH accreditation, a distinction that continues today. Currently, CHEST joins over 125 SSH-accredited programs worldwide, including universities, hospitals, and medical education companies.

The reaccreditation process was the result of months of preparation on behalf of CHEST Simulation Program staff, CHEST Accreditation staff, CHEST Outcomes staff, as well as CHEST's Live

Learning Domain Task Force chairs and other education leadership. This culminated in mid-November at a face-to-face on-site interview with site reviewers representing SSH and CHEST Simulation Program faculty and staff and CHEST leadership.

Throughout the process, CHEST was given the opportunity to highlight the unique and innovative ways in which we are utilizing simulation-based education to provide greater clinical insights to enhance patient care.

We recognize that this isn't only an every-4-year commitment, but it is resultant of the ongoing efforts from a group of dedicated individuals.

Thank you to all whose contributions ensured our success!

# This month in the journal *CHEST*®

## Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Editor in Chief

**Giants in Chest Medicine – Paul D. Stein, MD, Master FCCP**

**Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials.**

By Dr. E. J. Schenck, et al.

**The Accuracy of Clinical Staging of Stage I-IIIa Non-Small Cell Lung Cancer: An Analysis Based on Individual Participant Data.**

By Dr. N. Navani, et al.

**A Simple Clinical Risk Score (C2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects.**

By Dr. Y-G Li, et al.

**A Sleep Medicine Curriculum for Pulmonary and Pulmonary/Critical Care Fellowship**

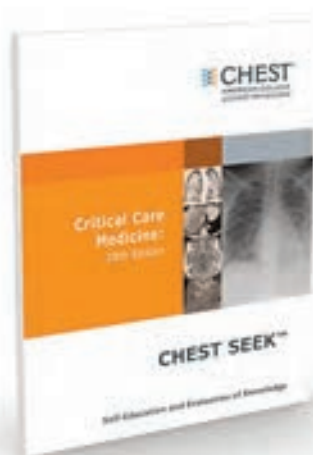


**Programs: A Multisociety Expert Panel Report.**

By Dr. D. A. Schulman, et al.

**Therapy for Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report.**

By J. R. Klingler, et al.



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## SLEEP STRATEGIES

# Phrenic nerve stimulation for treatment of central sleep apnea

BY SHAHROKH JAVAHERI, MD, FCCP; ROBIN GERMANY, MD; WILLIAM T. ABRAHAM, MD; AND MARIA ROSA COSTANZO, MD

Compared with obstructive sleep apnea (OSA), the prevalence of central sleep apnea (CSA) is low in the general population. However, in adults, CSA may be highly prevalent in certain conditions, most commonly among those with left ventricular systolic dysfunction, left ventricular diastolic dysfunction, atrial fibrillation, stroke, and opioid users (Javaheri S, et al. *J Am Coll Cardiol*. 2017; 69:841). CSA may also be found in patients with carotid artery stenosis, cervical neck injury, and renal dysfunction. CSA can occur when OSA is treated (treatment-emergent central sleep apnea, or TECA), notably, and most frequently, with continuous positive airway pressure (CPAP) devices. Though in many individuals, this frequently resolves with continued use of the device.

In addition, unlike OSA, adequate treatment of CSA has proven difficult. Specifically, the response to CPAP, oxygen, theophylline, acetazolamide, and adaptive-servo ventilation (ASV) is highly variable, with individuals who respond well, and individuals in whom therapy fails to fully suppress the disorder.

Our interest in phrenic nerve stimulation increased after it was shown that CPAP therapy failed to improve morbidity and mortality of CSA in patients with heart failure and reduced ejection fraction (HFrEF) (CANPAP trial, Bradley et al. *N Engl*

*J Med*. 2005;353[19]:2025). In fact, in this trial, treatment with CPAP was associated with significantly increased mortality during the first few months of therapy. We reason that a potential mechanism was positive airway pressure that had adverse cardiovascular effects (Javaheri S. *J Clin Sleep Med*. 2006;2:399). This is because positive airway pressure therapy decreases venous return to

the right side of the heart and increases lung volume. This could increase pulmonary vascular resistance (right ventricular afterload), which is lung volume-dependent. Therefore, the subgroup of individuals with heart failure whose right ventricular function is preload-dependent and has pulmonary hyperten-

sion is at risk for premature mortality with any PAP device.

Interestingly, investigators of the SERVE-HF trial (Cowie MR, et al. *N Engl J Med*. 2015;373:1095) also hypothesized that one reason for excess mortality associated with ASV use might have been due to an ASV-associated excessive rise in intrathoracic pressure, similar to the hypothesis we proposed earlier for CPAP. We expanded on this hypothesis and reasoned that based on the algorithm of the device, in some patients, it could have generated excessive minute ventilation and pressure contributing to excess mortality, either at night or daytime (Javaheri S, et al. *Chest*. 2016;149:900). Other deficiencies of the algorithm of the ASV device could have contributed to excess mortality as well (Javaheri S, et al. *Chest*. 2014;146:514). These deficiencies of the ASV device used in the SERVE-HF trial have been significantly improved in the new generation of ASV devices.

Undoubtedly, therefore, mask therapy with positive airway pressures increases intrathoracic pressure and will adversely affect cardiovascular function in some patients with heart failure. Another issue for mask therapy is adherence to the device remains poor, as demonstrated both in the CANPAP and SERVE-HF trials, confirming the need for new approaches uti-

lizing non-mask therapies both for CSA and OSA.

Given the limitations of mask-based therapies, over the last several years, we have performed studies exploring the use of oxygen, acetazolamide, theophylline, and, most recently, phrenic nerve stimulation (PNS). In general, these therapies are devoid of increasing intrathoracic pressure and are expected to be less reliant on patients' adherence than PAP therapy. Long-term randomized clinical trials are needed, and, most recently, the NIH approved a phase 3 trial for a randomized placebo-controlled low flow oxygen therapy for treatment of CSA in HFrEF. This is a modified trial proposed by one of us more than 20 years ago!

Regarding PNS, CSA is characterized by intermittent phrenic nerve (and intercostal nerves) deactivation. It, therefore, makes sense to have an implanted stimulator for the phrenic nerve to prevent development of central apneas during sleep. This is not a new idea. In 1948, Sarnoff and colleagues demonstrated for the first time that artificial respiration could be effectively administered to the cat, dog, monkey, and rabbit in the absence of spontaneous respiration by electrical stimulation of one (or both) phrenic nerves (Sarnoff SJ, et al. *Science*. 1948;108:482). In later experiments, these investigators showed that unilateral phrenic nerve stimulation is also equally effective in man as that shown in animal models.

The phrenic nerves come in contact with veins on both the right (brachiocephalic) and the left (pericardiophrenic vein) side of the mediastinum. Like a cardiac pacemaker, an electrophysiologist places the stimulator within the vein at the point of encounter with the phrenic nerve. Only unilateral stimulation is needed for the therapy. The device is typically placed on the right side of the chest as many patients may already have a cardiac implanted electronic device such as a pacemaker. Like the hypoglossal nerve stimulation, the FDA approved this device for the treatment of OSA. The system can be programmed using an external programmer in the office.

Phrenic nerve stimulation system is initially activated 1 month after the device is placed. It is

programmed to be automatically activated at night when the patient is at rest. First, a time is set on the device for when the patient typically goes to bed and awakens. This allows the therapy to activate. The device contains a position sensor and accelerometer, which determine position and activity level. Once appropriate time, position, and activity are confirmed, the device activates automatically. Therapy comes on and can increase in level over several minutes. The device senses transthoracic impedance and can use this measurement to make changes in the therapy output and activity. If the patient gets up at night, the device automatically stops and restarts when the patient is back in a sleeping position. How quickly the therapy restarts and at what energy is programmable. The device may allow from 1 to 15 minutes for the patient to get back to sleep before beginning therapy. These programming changes allow for patient acceptance and comfort with the therapy, even in very sensitive patients. Importantly, no patient activation is needed, so therapy delivery is independent of patient's adherence over time.

In the prospective, randomized pivotal trial (Costanzo et al. *Lancet*. 2016;388:974), 151 eligible patients with moderate-severe central sleep apnea were implanted and randomly assigned to the treatment (n=73) or control (n=78) groups. Participants in the active arm received PNS for 6 months. All polysomnograms were centrally and blindly scored. There were significant decreases in AHI (50 to 26/per hour of sleep), CAI (32 to 6), arousal index (46 to 25), and ODI (44 to 25). Two points should be emphasized: first, changes in AHI with PNS are similar to those in CANPAP trial, and there remained a significant number of hypopneas (some of these hypopneas are at least in part related to the speed of the titration when the subject sits up and the device automatically is deactivated, only to resume therapy in supine position); second, in contrast to the CANPAP trial, there was a significant reduction in arousals. Probably for this reason, subjective daytime sleepiness, as measured by the ESS, improved. In addition, PNS improved quality

*Continued on page 46*

## In memoriam

CHEST has been notified of the following deaths. We extend our sincere condolences.

Faroque A. Khan, MBBS  
Venessa Holland, MD, FCCP

## CHEST NetWorks

# Disaster response, practice operations, transplant, women's health

## Disaster Response and Global Health

### Epigenetics and disasters

The configuration of the DNA bordering a gene dictates under what conditions a gene is expressed. Random errors or mutations affecting the neighboring DNA or the gene itself can affect how the gene functions. Epigenetics is an emerging field of science looking at environmental and psychosocial factors that do not directly cause mutations but still affect how genes are expressed with implications for the development and inheritance of disease. These external influences are thought to affect why some segments of DNA become accessible for protein production while other segments may not.

Disasters represent stressors with potential for epigenetic impact. Women who were pregnant during the 1998 Quebec ice storm were found to have a correlation between maternal objective stress and a dis-

tinctive pattern of DNA methylation in their children 13 years later (Cao-Lei, et al. *PLoS ONE*. 2014;9[9]:e10765). Methylation is known to affect the activity of a DNA segment and how genes are expressed. Associations have also been found between the severity of hurricanes and the prevalence of autism in the offspring of pregnant women experiencing these disasters (Kinney DK, et al. *J Autism Dev Disord*. 2008;38:481).

Anthropogenic hazards may also affect the offspring of survivors as suggested by studies of civil war POWs and Dutch Hunger Winter during WW II (Costa, et al. *Proc Nat Acad Sci* 2018; 115:44; Heijmans, et al. *Proc Nat Acad Sci*. 2008;105[44]: 17046-9).

Epigenetics represents an area for additional research as natural and man-made disasters increase.

Omesh Toolsie, MBBS  
Steering Committee  
Fellow-in-Training

## Practice Operations

### Medicare Competitive Bidding Program update

Medicare's Competitive Bidding Program (CBP), mandated since 2003, asks providers of specific durable medical equipment (including oxygen) to submit competing proposals for services. The best offer is then awarded a 3-year contract. Recently, several reforms to CBP have been proposed. The payment structure has changed to "lead-item pricing," where a single bid in each category is selected and payment amounts for each product are then calculated based on pricing ratios and fee schedules (CMS DMEPOS Competitive Bidding). This is in contrast to the prior method of



Dr. Dempsey



Dr. Sisk

median pricing, which caused financial difficulty and access concerns (Council for Quality Respiratory Care. The Rationale for Reforming Medicare Home Respiratory Therapy Payment Methodology. 2018). Budget neutrality requirements should relax, and oxygen payment

*Continued on following page*

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of life, in contrast to lack of effect of CPAP or ASV in this domain. Regarding side effects, 138 (91%) of 151 patients had no serious-related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group.—3.4% needed lead repositioning, a rate which is like that of cardiac implantable devices. Seven patients died (unrelated to implant, system, or therapy), four deaths (two in treatment group and two in control group) during the 6-month randomization period when neurostimulation was delivered to only the treatment and was off in the control group, and three deaths between 6 months and 12 months of follow-up when all patients received neurostimulation. Of 73 patients in the treatment group, 27 (37%) reported nonserious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients but was unresolved in one (1%) patient.

Long-term studies have shown sustained effects of PNS on CSA with improvement in both sleep metrics and QOL, as measured by the Minnesota Living with Heart Failure Questionnaire (MLWHF) and patient global assessment (PGA). Furthermore, in the subgroup of patients with concomitant heart failure with LVEF ≤ 45%, PNS was associated with both improvements in LVEF and a trend toward

lower hospitalization rates (Costanzo, et al. *Eur J Heart Fail*. 2018; doi:10.1002/ejhf.1312).

Several issues must be emphasized. One advantage of PNS is complete adherence resulting in a major reduction in apnea burden across the whole night. Second, the mechanism of action prevents any potential adverse consequences related to increased intrathoracic pressure. However, the cost of this therapy is high, similar to that of hypoglossal nerve stimulation. Large scale, long-term studies related to mortality are not yet available, and continued research should help identify those patients most likely to benefit from this therapeutic approach.

Dr. Javaheri is Medical Director, Bethesda Montgomery Sleep Laboratory, Cincinnati; Emeritus Prof of Med, Div of Pulmonology, Sleep and Critical Care Med, Univ of Cincinnati College of Med and Adjunct Prof of Med, Div of Cardiology, The Ohio State Univ, Columbus, OH. Dr. Germany is Clinical Assist Prof of Med, University of Oklahoma, OK, and Chief Med Officer, Respicardia, Inc., Minnetonka, MN. Dr. Abraham is Prof of Med, Physiology and Cell Biology, Chair of Excellence in Cardiovascular Med, College of Med Distinguished Professor and Deputy Director, Davis Heart and Lung Research Institute, The Ohio State Univ, Columbus, OH. Dr. Costanzo is Med Director, Heart Failure Research, Advocate Heart Institute, Naperville, IL.

## 2019 GRANTS CYCLE

Grant Portal Open | February - April 2019  
Grants Reviewed | April - June 2019  
Winners Notified | July 2019  
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- Women's Lung Health

Visit [chestfoundation.org/grants](http://chestfoundation.org/grants) for a complete listing of funding opportunities available in 2019.

For more information about the 2019 grants cycle, contact Andrew Gillen at [agillen@chestnet.org](mailto:agillen@chestnet.org)

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Continued from previous page

structures improve. These proposed changes also include improved coverage of liquid oxygen and addition of home ventilator supplies.

However, effective January 1, 2019, all CBP is suspended through CMS. During the anticipated 2-year gap, any Medicare-enrolled supplier will be able to provide items until new contracts are awarded. Pricing during the gap period is based on a current single price plus consumer price index. These changes will impact CHEST members and their patients moving forward. During the temporary gap period, some areas are seeing decreased accessibility of some DME due to demand. Once reinstated, the changes to the oxygen payment structure should improve access and reduce out-of-pocket costs. The Practice Operations NetWork will continue to provide updates on this topic as they become available.

Timothy Dempsey, MD, MPH  
Steering Committee Fellow-in-Training

Megan Sisk, DO  
Steering Committee Member

## Transplant

### Medicare Part D plans can deny coverage of select immunosuppressant medications in solid organ transplant recipients

An alarming problem has emerged with some solid organ transplant recipients experiencing immunosuppressant medication claim denials by Medicare Part D plans. Affected patients are those who convert from some other insurance (ie, private insurance or state Medicaid) to Medicare after their transplant and,

therefore, rely on Medicare Part D for immunosuppressant drug coverage.

Insurance companies that offer Medicare Part D plans must follow the rules described in the Medicare



Dr. McDermott

Prescription Drug Benefit Manual.<sup>1</sup> Although the Manual mandates that all immunosuppressant medications are on plan formularies, Part D plans are only required to cov-

er immunosuppressant medications when used for indications approved by the Food and Drug Administration (FDA) or for off-label indications supported by the Centers for Medicare & Medicaid Services (CMS)-approved compendia (Drugdex® and AHFS Drug Information®).

A recent study examining the extent of the problem demonstrated non-renal organ transplant recipients are frequently prescribed and maintained on at least one medication vulnerable to Medicare Part D claim denials at 1 year posttransplant (lung: 71.1%; intestine: 39.7%; pancreas: 36.8%; liver: 19.7%; heart: 18.5%).<sup>2</sup> Lung transplant recipients are most vulnerable since no immunosuppressant is FDA-approved for use in lung transplantation, and CMS-approved compendia only support off-label use for tacrolimus and cyclosporine in this population. Therefore, mycophenolate mofetil, mycophenolic acid, azathioprine, everolimus, and sirolimus are vulnerable to denial by Medicare Part D plans when used in lung transplant recipients. Over 95% of lung trans-

plant recipients are maintained on an anti-metabolite, with the majority (88%) maintained on mycophenolate, so this is frequently impacted.<sup>2,3</sup> While the transplant community is aware of this issue and has begun work to correct it, it has yet to be solved.<sup>2,4</sup> In the meantime, if transplant recipients have been denied for this off-label and off-compendia reason, and appeals of those decisions have also been denied, options for obtaining the denied immunosuppressant medication include discount programs, foundation/grant funding, and industry-sponsored assistance programs.

Jennifer K. McDermott, PharmD  
NetWork Member

1. Prescription Drug Benefit Manual. Centers for Medicare & Medicaid Services. Chapter 6: Part D Drugs and Formulary Requirements. Available at: <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf>
2. Potter LM et al. Transplant recipients are vulnerable to coverage denial under Medicare Part D. *Am J Transplant*. 2018;18:1502.
3. Valapour M et al. OPTN/SRTR 2016 Annual Data Report: Lung. *Am J Transplant*. 2018;18 (Suppl 1): 363.
4. Immunosuppressant Drug Coverage Under Medicare Part D Benefit. American Society of Transplantation. Available at: [www.myst.org/public-policy/key-position-statements/immunosuppressant-drug-coverage-under-medicare-part-d-benefit](http://www.myst.org/public-policy/key-position-statements/immunosuppressant-drug-coverage-under-medicare-part-d-benefit).

## Women's Health

### Cannabis use affects women differently

As we enter an era of legalization, cannabis use is increasingly prevalent. Variances in the risks for women and men have been observed. For most age groups, men have higher rates of use or dependence on illicit drugs than women. However, women are equally likely as men to progress to a substance

use disorder. Women may be more susceptible to craving and relapse, which are key phases of the addiction cycle.



Dr. Rajagopal

A study on use among adolescents concluded there was preliminary evidence of a faster transition from initiation of marijuana use to regular use in women, when

compared with men (Schepis, et al. *J Addict Med*. 2011;5[1]:65).

Research studies suggest that marijuana impairs spatial memory in women more so than in men. Studies have suggested that teenage girls who use marijuana may have a higher risk of brain structural abnormalities associated with regular marijuana exposure than teenage boys (Tapert, et al. *Addict Biol*. 2009;14[4]:457).

A study published in *Psychoneuroendocrinology* showed that cannabinoid receptor binding site densities exhibit sex differences and can be modulated by estradiol in several limbic brain regions. These findings may account for the sex differences observed with respect to the effects of cannabinoids (Riebe, et al. *Psychoneuroendocrinology*. 2010;35[8]:1265).

Further research is needed to expand our understanding of the interactions between cannabinoids and sex steroids. Detoxification treatments tailored toward women and men with cannabis addiction show a promising future and necessitate further research.

Anita Rajagopal, MD  
Steering Committee Member

# CHEST updates guidelines on PAH

The American College of Chest Physicians® (CHEST) has published updates to the evidence-based guidelines on therapy for pulmonary arterial hypertension (PAH). In the latest evidence-based guideline, Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report, experts provide 78 evidence-based recommendations for appropriate use in treating patients with PAH.

"New recommendations and ungraded consensus-based statements were developed in this update based on new studies that were published

since the 2014 guidelines. In addition, an evidence-based and consensus-driven treatment algorithm was created to guide the clinician through an organized approach to management," says CHEST Pulmonary Arterial Hypertension Guidelines Committee Co-Chair, Deborah Jo Levine, MD, FCCP.

As part of the guideline development process, the panel updated the systematic review on the same clinical questions and criteria. Based on the results of the systematic review, the panel developed two new recommendations about pharmacologic therapy for PAH:

- For treatment-naïve patients with PAH who are World Health Organization (WHO) functional class II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD).

- For stable or symptomatic patients with PAH on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD.

The complete guideline article is free to view in the Online First section ([https://journal.chestnet.org/article/S0012-3692\(19\)30002-9/full-text](https://journal.chestnet.org/article/S0012-3692(19)30002-9/full-text)) of the journal *CHEST*®.

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