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CHEST Physician®

Catherine Hackett/MDedge News

Dr. John J.V. McMurray, professor of medical cardiology at the University of Glasgow

Pneumonia, death risks soar in heart failure patients

BY RICHARD MARK KIRKNER
MDedge News

Patients with heart failure get pneumonia at a rate almost three times greater than expected and, once they do get pneumonia, have about a fourfold greater risk of death, investigators for a retrospective analysis of 13,000 patients from two landmark randomized HF trials have found.

The investigators also found that HF patients with preserved ejection fraction (HFpEF) are at the highest risk of developing pneumonia.

The analysis showed that 6.3% of patients in the PARADIGM-HF trial and 10.6% of those in the PARAGON-HF trial developed pneumonia, reported the study authors, led by John J.V. McMurray, MD, of the British Heart Foundation Cardiovascular Research Center at the University of Glasgow (J Am Coll Cardiol. 2021;77:1961-73).

"The main reason for doing this study was the fact that many heart failure patients are not vaccinated, as they should be, against pneumonia – both pneumococcus and influenza vaccination," Dr. McMurray said in an interview.

PARADIGM-HF and PARAGON-HF

The post hoc analysis consisted of 8,399 patients with HF with reduced ejection fraction (HFrEF) in PARADIGM-HF (Eur J Heart Fail. 2013 Sep;15[9]:1062-73) and 4,796 patients with

PNEUMONIA // *continued on page 6*

COVID-19 infection conveys only partial immunity

BY NEIL OSTERWEIL
MDedge News

Do your patients think that getting COVID-19 is fully protective against subsequent reinfection? Tell it to the Marines.

A study of U.S. Marine recruits on their way to boot camp at Parris Island, S.C., showed that those who were seropositive at baseline, indicating prior exposure to SARS-CoV-2, remained at some risk for reinfection. They had about one-fifth the risk of subsequent infection, compared with seronegative recruits during basic training, but reinfections did occur.

The study, by Stuart C. Sealfon, MD, of Icahn School of Medicine at Mount Sinai in New York, and colleagues, was published The Lancet Respiratory Medicine (2021 Apr 15. doi: 10.1016/S2213-2600[21]00158-2).

"Although antibodies induced by initial infection are largely protective, they do not guarantee effective SARS-CoV-2 neutralization activity or immunity against subsequent infection," they wrote.

An infectious disease specialist who was not involved in the study said that the findings

IMMUNITY // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

SLEEP STRATEGIES

Obstructive sleep apnea and COVID-19

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Why we write Esbriet

Your patients trust you. That's why you trust Esbriet for efficacy, safety, and tolerability.

INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

Elevated liver enzymes and drug-induced liver injury (DILI): DILI has been observed with Esbriet. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3x ULN (3.7%) compared with placebo patients (0.8%). Increases in ALT and AST ≥3x ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with Esbriet, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) vs placebo (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, vs 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modification may be necessary.

Adverse reactions: The most common adverse reactions (≥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 reduction of Esbriet is 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.

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ESBRIET OFFERS ESTABLISHED SAFETY BUILT ON MULTIPLE CLINICAL STUDIES

Esbriet was rigorously analyzed in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients with idiopathic pulmonary fibrosis (IPF)[1]

Serious adverse events (AEs), including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet[1]

The most common AEs (>1%) leading to discontinuation were rash and nausea. The most common AEs (>3%) leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

Some AEs with Esbriet were mild to moderate, occurred early, and decreased over time[1,2]

Photosensitivity reactions and GI events typically occurred in the first 3 to 6 months of treatment and infrequently led to discontinuation

<9% of photosensitivity events and <8% of GI events in three phase 3 trials were severe. The remaining photosensitivity and GI events were mild to moderate in severity[2]

>1400 patients were evaluated for safety of Esbriet, with >170 on treatment for more than 5 years in clinical trials[1]

Dose modifications, interruptions, and discontinuations with Esbriet 267 mg may help manage potential AEs like GI events and photosensitivity reactions[1]

Demonstrated efficacy

In ASCEND and CAPACITY 004, Esbriet delayed disease progression by slowing lung function decline vs placebo[1,3]

In CAPACITY 006, no statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed[1,4]

Learn more at **EsbrietHCP.com**

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.

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 on Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or 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.

Study design: 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).[1] 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_{co}) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[1,3] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥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_{co} ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[1,4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1] 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).[1] **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.[1]**

References: 1. Esbriet Prescribing Information. Genentech, Inc. July 2019. **2.** Data on file. Genentech, Inc. 2019. **3.** 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. **4.** 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.

Esbriet® (pirfenidone) tablets 267 mg 801 mg

Airborne virus is driver of SARS-CoV-2 transmission

BY DAMIAN MCNAMARA

The scientific evidence for airborne transmission of the SARS-CoV-2 virus from different researchers all point in the same direction – that infectious aerosols are the principal means of person-to-person transmission, according to experts.

Not that it's without controversy. The science backing aerosol transmission "is clear-cut, but it is not accepted in many circles," Trisha Greenhalgh, PhD, said in an interview. "In particular, some in the evidence-based medicine movement and some infectious diseases clinicians are remarkably resistant to the evidence," added Dr. Greenhalgh, professor of primary care health sciences at the University of Oxford (England).

"It's very hard to see why, since

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BRIEF SUMMARY

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

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 and Drug-Induced Liver Injury

Cases of drug-induced liver injury (DILI) have been observed with ESBRIET. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet 2403 mg/day in three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3x ULN than placebo patients (3.7% vs 0.8%, respectively). Elevations ≥10x 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 ≥3x ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration (2.1, 2.3)]*.

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 and Drug-Induced Liver Injury *[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 (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[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

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

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

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
Drug-induced liver injury *[see Warnings and Precautions (5.1)]*

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

the evidence all stacks up," Dr. Greenhalgh said.

"The scientific evidence on spread from both near-field and far-field aerosols has been clear since early on in the pandemic, but there was resistance to acknowledging this in some circles, including the medical journals," Joseph G. Allen, DSc, MPH, told this news organization when asked to comment.

"This is the week the dam broke. Three new commentaries came out … in top medical journals – BMJ, The Lancet, JAMA – all making the same point that aerosols are the dominant mode of transmission," added Dr. Allen, associate professor of exposure assessment science at the Harvard School of Public Health in Boston.

The investigators point to an increase in COVID-19 cases in the aftermath of so-called "super-spreader" events, spread of SARS-CoV-2 to people across different hotel rooms, and the relatively lower transmission detected after outdoor events.

Top 10 reasons

They outlined 10 scientific reasons backing airborne transmission in a commentary published online April 15 in The Lancet (2021. doi: 10.1016/S0140-6736[21]00869-2):

- The dominance of airborne transmission is supported by long-range transmission observed at super-spreader events.
- Long-range transmission has been reported among rooms at COVID-19 quarantine hotels, settings where infected people never spent time in the same room.
- Asymptomatic individuals account for an estimated 33%-59% of SARS-CoV-2 transmission, and could be spreading the virus through speaking, which produces thousands of aerosol particles and few large droplets.
- Transmission outdoors and in well-ventilated indoor spaces is lower than in enclosed spaces.
- Nosocomial infections are reported in health care settings where protective measures address large droplets but not aerosols.
- Viable SARS-CoV-2 has been detected in the air of hospital rooms and in the car of an infected person.
- Investigators found virus in hospital air filters and building ducts.
- It's not just humans – infected animals can infect animals in other cages connected only through an air duct.
- No strong evidence refutes airborne transmission, and contact tracing supports secondary transmission in crowded, poorly ventilated indoor spaces.
- Only limited evidence supports other means of SARS-CoV-2 transmission, including through fomites or large droplets.

"We thought we'd summarize [the evidence] to clarify the arguments for and against. We looked hard for evidence against but found none," Dr. Greenhalgh said.

"Although other routes can contribute, we believe that the airborne route is likely to be dominant," the authors note.

The evidence on airborne transmission was there very early on but the Centers for Disease Control and Prevention, World Health Organization, and others repeated the message that the primary concern was droplets and fomites.

The National Institute for Health Research, Economic and Social Research Council, and Wellcome support Dr. Greenhalgh's research. Dr. Greenhalgh and Dr. Allen reported no relevant financial relationships.

A version of this article first appeared on Medscape.com.

ESBRIET® (pirfenidone)

ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A2 Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

7.2 CYP1A2 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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]*.

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.

Data

Animal Data

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^2 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^2 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^2 basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

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.

Data

Animal Data

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.

ESBRIET® (pirfenidone)

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

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

8.7 Renal Impairment

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

8.8 Smokers

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

10 OVERDOSAGE

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

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

17 PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions (5.1)]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.3)]*.

Smokers

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

Take with Food

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

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Pneumonia vaccination is key

// continued from page 1

HFpEF in PARAGON-HF (N Engl J Med. 2014 Sep 11;371[11]:993-1004). The analysis focused on the 528 and 510 patients in each study, respectively, who developed pneumonia. Those rates translated to an incidence rate of 29 per 1,000 patient-years (95% confidence interval, 27-31) in PARADIGM-HF and 39 per 1,000 patient-years (95% CI, 36-42) in PARAGON-HF.

After pneumonia, the risk of death in patients increased substantially. In PARADIGM-HF, the adjusted hazard ratio for the risk of death from any cause after pneumonia was 4.34 (95% CI, 3.73-5.05). In PARAGON-HF, it was 3.76 (95% CI, 3.09-4.58). HF patients who contracted pneumonia also tended to have HF longer than their counterparts who didn't develop pneumonia, but the frequency of previous hospitalization for HF didn't vary between the pneumonia and no-pneumonia groups.

Dr. Ludmir

Patients who developed pneumonia tended to be older (average age of 66.9 years vs. 64.6 years, $P < .001$) and male (83.9% vs. 77.8%, $P < .001$). The mean age of patients in PARADIGM-HF was almost a decade younger than those in PARAGON-HF, 64 vs. 73 years.

Pneumonia patients also had worse Kansas City Cardiomyopathy Questionnaire scores (76 vs. 80 on average), but no difference in New York Heart Association functional class. "In general, patients who developed pneumonia had more symptoms and signs and HF than those who did not develop pneumonia," Dr. McMurray and colleagues wrote.

Pneumonia patients also had higher rates of chronic obstructive pulmonary disease (26% vs. 12%), diabetes (43% vs. 34%), and atrial fibrillation (46% vs. 36%).

Another reason for conducting the study, Dr. McMurray said, "was the prior findings in patients with coronary disease and acute myocardial infarction that the risk associated with an episode of pneumonia [e.g., in subsequent vascular events and deaths] persisted long after the acute event. We wanted to see if this was also the case for heart failure, and indeed it was."

For example, the adjusted HR for cardiovascular death or hospitalization in the first month following an episode of pneumonia was 9.48 (range of 6.85-13.12, $P < .001$), leveling off to 1.59 after 3 months or more.

Vaccination crucial in HF patients

Dr. McMurray noted that this study emphasizes the importance of pneumonia vaccination for patients with HF. "Given that we have so few treatments to offer patients with HFpEF, this makes the potential value of vaccination in these patients all the greater," he said.

The COVID-19 pandemic, Dr. McMurray said, is a "good reminder of the dangers of a respiratory infection and the importance of vaccination in these patients. COVID-19 has interesting parallels in being a systemic disease and one with postacute, persisting effects."

Jonathan Ludmir, MD, critical care cardiologist at the Corrigan Minehan Heart Center ICU at Mass General and an instructor of medicine at Harvard Medical School, both in Boston said in an interview, "While the study provides an interesting perspective, heart failure patients are at increased risk for many infections and in general have poorer outcomes. In addition, there have been studies similar to this in the past. That being said, this is an important concept to emphasize – heart failure patients have significantly poorer outcomes, are at higher risk for developing pneumonia, and have higher mortality once they develop pneumonia. Clinicians need to be vigilant when heart failure patients develop pneumonia, given their overall poorer outcomes. This study also emphasizes the importance of adopting a preventative approach to all patients, including heart failure patients, by emphasizing the importance of vaccines."

The persistent risk for adverse cardiovascular events 3 months and later after pneumonia is a novel finding of the study, wrote Donna Mancini, MD, and Gregory Gibson, MD, in an invited commentary (J Am Coll Cardiol. 2021;77:1974-6). Both are with the Icahn School of Medicine at Mt. Sinai in New York.

Novartis provided funding for the PARADIGM-HF and PARAGON-HF trials, and Dr. McMurray and coauthors disclosed financial relationships with Novartis. Dr. Mancini and Dr. Gibson have no relevant financial relationships to disclose.

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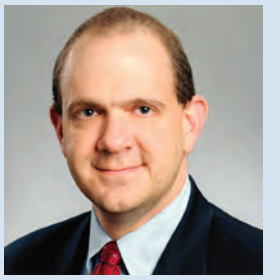

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List of COVID-19 high-risk comorbidities expanded

BY RICHARD FRANKI
MDedge News

The list of medical comorbidities associated with high risk for severe COVID-19 now includes moderate to severe asthma, diabetes, and substance use disorders, according to the Centers for Disease Control and Prevention.

The CDC's latest list consists of 17 conditions or groups of related conditions that may increase patients' risk of developing severe outcomes of COVID-19, the CDC said on a web page intended for the general public.

On a separate page, the CDC defines severe outcomes "as hospitalization, admission to the intensive care unit, intubation or mechanical ventilation, or death."

Asthma is included in the newly expanded list with other chronic lung diseases such as chronic obstructive pulmonary disease and cystic fibrosis; the list's heart disease entry covers coronary artery disease, heart failure, cardiomyopathies, and hypertension, the CDC said.

rfranki@mdedge.com

Comorbidities associated with high risk for severe COVID-19

Cancer	Liver disease
Chronic kidney disease	Overweight and obesity
Chronic lung diseases	Pregnancy
Dementia or other neurological conditions	Sickle cell disease or thalassemia
Diabetes (type 1 or type 2)	Smoking, current or former
Down syndrome	Solid organ or blood stem cell transplant
Heart conditions	Stroke or cerebrovascular disease
HIV infection	Substance use disorders
Immunocompromised state	

MDEDGE NEWS

Note: "Severe" defined as hospitalization, admission to intensive care unit, intubation or mechanical ventilation, or death.

Source: Centers for Disease Control and Prevention

Young people who have had COVID-19 may overestimate their immunity

// *continued from page 1*

provide further evidence about the level of immunity acquired after an infection.

"It's quite clear that reinfections do occur, they are of public health importance, and they're something we need to be mindful of in terms of advising patients about whether a prior infection protects them from reinfection," Mark Siedner, MD, MPH, FCCP, a clinician and researcher in the division of infectious diseases at Massachusetts General Hospital, Boston, said in an interview.

The study results reinforce that "not all antibodies are the same," said Sachin Gupta, MD, an attending physician in pulmonary and critical care medicine at Alameda Health System in Oakland, Calif. "We're seeing still that 10% of folks who have antibodies can get infected again," he said in an interview.

CHARM initiative

Dr. Sealfon and colleagues presented an analysis of data from the ironically named CHARM (COVID-19 Health Action Response for Marines) prospective study.

CHARM included U.S. Marine recruits, most of them male, aged 18-20 years, who were instructed to follow a 2-week unsupervised quarantine at home, after which they reported to a Marine-supervised facility for an additional 2-week quarantine.

At baseline, participants were tested for SARS-CoV-2 immunoglobulin G (IgG) seropositivity, defined as a dilution of 1:150 or more on receptor-binding domain and full-length spike protein enzyme-linked immunosorbent assay (ELISA).

The recruits filled out questionnaires asking them to report any of 14 specific COVID-19–related symptoms or any other unspecified symptom, as well as demographic information, risk factors, and a brief medical history.

Investigators tested recruits for SARS-CoV-2 infection by polymerase chain reaction (PCR) assay at weeks 0, 1, and 2 of quarantine, and any who had positive PCR results during quarantine were excluded.

Participants who had three negative swab PCR results during quarantine and a baseline serology test at the beginning of the supervised quarantine period – either seronegative or seropositive – then went on to their basic training at the Marine Corps Recruit Depot, Parris Island.

The participants were followed prospectively with PCR tests at weeks 2, 4, and 6 in both the seropositive and seronegative groups, and sera were obtained at the same time.

Holes in immunologic armor

Full data were available for a total of 189 participants who were seropositive and 2,247 who were seronegative at enrollment.

In all, 19 of 189 seropositive recruits (10%) had at least one PCR test positive for SARS-CoV-2 infection during the 6-week follow-up period. This translated into a an incidence of 1.1 cases per person-year.

Of the 2,247 participants seronegative at baseline, 1,079 tested positive (6.2 cases per person-year; incidence rate ratio 0.18).

It appeared that antibodies provided some protection for seropositive recruits, as evidenced by a higher likelihood of infection among those with lower baseline full-length spike protein IgG titers than in those with higher baseline titers (hazard ratio 0.4, $P < .001$).

Among the seropositive participants who did acquire a second SARS-CoV-2 infection, viral loads in mid-turbinate nasal swabs were about 10-fold lower than in seronegative recruits who acquired infections during follow-up.

"This finding suggests that some reinfected individuals could have a similar capacity to transmit infection as those who are infected for the first time. The rate at which reinfection occurs after vaccines and natural immunity is important for estimating the proportion of the population that needs to be vaccinated to suppress the pandemic," the investigators wrote.

Dr. Gupta

Baseline neutralizing antibody titers were detected in 45 of the first 54 seropositive recruits who remained PCR negative throughout follow-up, but also in 6 of 19 seropositive participants who became infected during the 6 weeks of observation.

Lessons

Both Dr. Siedner and Dr. Gupta agreed with the authors that the risks for reinfection that were observed in young, physically fit people may differ for other populations, such as women (only 10% of seropositive recruits and 8% of seronegative recruits were female), older patients, or those who are immunocompromised.

Given that the adjusted odds ratio for reinfection in this study was nearly identical to that of a recent British study comparing infection rates between seropositive and seronegative health care workers, the risk of reinfection for other young adults and for the general population may be similar, Dr. Sealfon and colleagues wrote.

Adding to the challenge of reaching herd immunity is the observation that some patients who have recovered from COVID-19 are skeptical about the need for further protection.

"There are patients who feel like vaccination is of low benefit to them, and I think these are the same people who would be hesitant to get the vaccine anyway," Dr. Gupta said.

Although no vaccine is perfect – the vaccine failure rate from the mRNA-based vaccines from Moderna and Pfizer/Biontech is about 5% – the protections they afford are unmistakable, Dr. Siedner said.

The investigators stated, "Young adults, of whom a high proportion are asymptomatically infected and become seropositive in the absence of known infection, can be an important source of transmission to more vulnerable populations. Evaluating the protection against subsequent SARS-CoV-2 infection conferred by seropositivity in young adults is important for determining the need for vaccinating previously infected individuals in this age group."

The study was funded by the Defense Health Agency and Defense Advanced Research Projects Agency. Dr. Sealfon, Dr. Siedner, and Dr. Gupta have no conflicts of interest to report. Dr. Gupta is a member of the editorial advisory board for this publication.

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Guidelines advise expanded use of high-flow oxygen

BY HEIDI SPLETE
MDedge News

Hospitalized patients with acute respiratory failure can benefit from high-flow nasal oxygen in certain settings, according to a new clinical guideline from the American College of Physicians.

High-flow nasal oxygen (HFNO) has demonstrated advantages including improved oxygenation and ventilation, wrote Arianne K. Baldomero, MD, of Minneapolis Veterans Affairs Health Care System and the University of Minnesota, Minneapolis, and colleagues. "However, the comparative benefits and harms of HFNO in clinical outcomes, including mortality, intubation, hospital length of stay, patient comfort, clearance of airway secretions, and reduced work of breathing are not well known."

In the guideline, published in Annals of Internal Medicine (2021 Apr 27. doi: 10.7326/M20-4675), the authors recommend the use of high-flow nasal oxygen in hospitalized patients for initial or postextubation management of acute respiratory failure. The target population includes those patients treated in hospital wards, EDs, intermediate/step-down units, and ICUs.

Use of HFNO therapy as a form of noninvasive respiratory support for hospitalized patients has increased in recent years. The treatment involves delivering warm, humidified oxygen via nasal cannula at a flow level higher than the patient's inspiratory flow.

Potential benefits of HFNO include greater patient comfort, improved compliance, and psychological benefits, according to the authors. HFNO also can be used as respiratory support in critically ill patients for a number of indications including respiratory failure or support post extubation; however, treatment of patients with COVID-19 and related conditions were not considered in the guideline.

The guideline was based on evidence comparing HFNO with conventional oxygen therapy (COT) and noninvasive ventilation (NIV). The authors reviewed 29 randomized, controlled trials that showed clinically meaningful outcomes in HFNO patients, as well as similar rates of, or reductions in, mortality, intubations, and hospital-acquired pneumonia, and increased reports of patient comfort. Data also supported the safety of HFNO with few, if any, contraindications other than problems with fitting the nasal cannula.

Across several trials comparing HFNO and NIV for initial management of acute respiratory failure, HFNO reduced all-cause mortality, intubation, and hospital-acquired pneumonia, although the authors categorized the results as "low-certainty evidence." HFNO was not more effective than NIV for postextubation management. Based on trials comparing HFNO and COT for postextubation management, the authors concluded that HFNO may reduce rates of reintubation and improve patient comfort, also with low-certainty evidence.


Dr. Fincher

The research was limited by a lack of studies comparing HFNO with NIV or COT for acute respiratory failure in patients who were post lung transplantation, or for those with pulmonary embolism, pulmonary arterial hypertension, or asthma, the authors said. Other limitations included the variation in study design, study populations, and treatment protocols across the included studies. Despite these limitations, the results support the guideline recommendation for HFNO in cases of acute respiratory failure and postextubation management. However, "broad applicability, including required clinician and health system experience and resource use, remains unknown," the authors concluded.

Research catches up with practice

The guidelines are important at this time because "the medical literature over the past 3-4 years is catching up to what hospitalists, pulmonologists, and critical care specialists have been doing clinically over the past 6-8 years with perceived better results, Jacqueline W. Fincher, MD, MACP, President of the American College of Physicians, said in an interview.

"HFNO has been used to a varying degree over the last 6-8 years by physicians with much-perceived improved benefit in patients who are hypoxemic on usual noninvasive therapy or conventional oxygen therapy with the impending need for intubation or post extubation," Dr. Fincher said. "During the COVID pandemic particularly with the attack on the respiratory system with COVID pneumonia and frequently associated ARDS [acute respiratory distress syndrome], the use of HFNO has been enormously helpful in trying to keep patients well oxygenated without having to intubate or reintubate them.

"We now have the medical literature that supports what has been seen clinically to make the recommendations and guidelines based on the scientific evidence," Dr. Fincher added. "If we can avoid intubation associated with the patient being sedated, unable to eat, talk, or meaningfully participate in their care or get the patient off the ventilator sooner for the same reasons, then we have significantly improved the quality of their care, decreased their risk of infection, decreased their days in the ICU and the hospital, we will have succeeded in providing the best care possible. The availability of HFNO, with much greater comfort to the patient than being intubated, is a great tool in the toolbox of respiratory care.

"The good news is that HFNO is readily available at most hospitals, but it really requires an intensive care unit and a team of physicians, nurses, and respiratory therapists to be familiar with its use and work closely together to monitor the patient for significant changes in their respiratory status to titrate therapy," she noted.

In the future, some areas in need of more research that might impact updates to the guidelines include "What are some areas in need of more research that might impact future updates to these guidelines? Specifics on whether initiating HFNO earlier in the course of the patient's hypoxemic illness is better or worse, as well as the use of HFNO outside of the ICU setting," Dr. Fincher said. "The needed monitoring of the patient to know whether their respiratory status was deteriorating and how fast would be critical along with the specific indications for titration of the HFNO."

The evidence review was commissioned and funded by the ACP. The data come from work supported by and conducted at the Minneapolis VA Health Care System. Lead author Dr. Baldomero was supported in part by the National Institutes of Health National Center for Advancing Translational Sciences.

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COVID-19 can be severe in children: 12% hospitalized

BY CAROLYN CRIST

About 12% of U.S. children with COVID-19 were hospitalized in 2020, and nearly a third of those had severe disease that required mechanical ventilation or admission to an intensive care unit, according to a new study published in JAMA Network Open on April 9 (2021. doi: 10.1001/jamanetworkopen.2021.5298).

That means about 1 in 9 children with COVID-19 needed hospitalization, and about 1 in 28 had severe COVID-19.

"Although most children with COVID-19 experience mild illness, some children develop serious illness that leads to hospitalization, use of invasive mechanical ventilation, and death," the researchers wrote.

The research team analyzed discharge data from 869 medical facilities in the Premier Healthcare Database Special COVID-19 Release. They looked for COVID-19 patients ages 18 and under who had an in-patient or emergency department visit between March and October 2020.

More than 20,700 children with COVID-19 had an inpatient or emergency department visit, and 2,430 were hospitalized with COVID-19. Among those, 756 children had severe COVID-19 and were admitted to an intensive care unit or needed mechanical ventilation.

About 53% of the COVID-19 patients were girls, and about 54% were between ages 12 and 18. In addition, about 29% had at least one chronic condition.

As with COVID-19 studies in adults, Hispanic, Latino, and Black patients were overrepresented. About 39% of the children were Hispanic or Latino, and 24% were Black. However, the researchers did not find an association between severe COVID-19 and race or ethnicity.

The likelihood of severe COVID-19 increased if the patient had at least one chronic condition, was male, or was between ages 2 and 11.

"Understanding factors associated with severe COVID-19 disease among children could help inform prevention and control strategies," they added. "Reducing infection risk through community mitigation strategies is critical for protecting children from COVID-19 and preventing poor outcomes."

As of April 8, more than 3.54 million U.S. children had tested positive for COVID-19, according to the latest report from the American Academy of Pediatrics and Children's Hospital Association. Cases among children are increasing slightly, with about 73,000 new cases reported during the first week of April.

Children represent about 13.5% of the COVID-19 cases in the country, according to the report. Among the 24 states that provide data, children represented 1%-3% of all COVID-19 hospitalizations, and less than 2% of all child COVID-19 cases resulted in hospitalization.

A version of this article first appeared on Medscape.com.

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*Patient-reported results after 12 months with Philips InCourage vest therapy supported by the RespirTech outcomes program.[1,2]

References: 1. Methodology: As of 3/31/2020, self-reported data from nearly 18,000 bronchiectasis patients. **2.** RespirTech's bronchiectasis patient outcomes program consists of follow-up calls at periodic intervals for up to two years to encourage HFCWO adherence and ensure the device is properly set for individual needs.

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Black nonsmokers still at high risk for secondhand smoke exposure, mostly at home

BY WALTER ALEXANDER
MDedge News

Despite 30+ years of anti-smoking public policies and dramatic overall decline in secondhand smoke (SHS) exposure, nonsmoking low-income and non-Hispanic Black people remain at high risk for exposure to smoke.

No risk-free SHS exposure

Surendranath S. Shastri, MD, of MD Anderson Cancer Center, Houston, and colleagues underscored the U.S. Surgeon General's determination that there is no risk-free level of SHS exposure in a recent JAMA Internal Medicine research letter (2021;181[1]:134-7. doi: 10.1001/jamainternmed.2020.3975).

"With the outbreak of the coronavirus disease 2019, which affects lung function, improving smoke-free policies to enhance air quality should be a growing priority," they wrote.

Dr. Shastri and colleagues looked at 2011-2018 data from the National Health and Nutrition Examination Survey (NHANES), which detailed prevalence of SHS exposure in the U.S. population aged 3 years and older using interviews and biological specimens to test for cotinine levels. For the survey, nonsmokers having serum cotinine levels from 0.05 to 10 ng/mL were considered to have SHS exposure.

While the prevalence of SHS exposure among nonsmokers declined from 87.5% to 25.3% between 1988 and 2012, levels have stagnated since 2012 and racial and economic disparities are evident. Higher smoking rates, less knowledge about health risks, higher workplace exposure, greater likelihood of living in low-income, multi-unit housing, plus having their communities targeted by tobacco companies, may all help explain higher serum levels of cotinine in populations with lower socioeconomic status.

"Multivariable logistic regression identified younger age (odds ratio, 1.88, for 12-19 years, and OR, 2.29, for 3-11 years), non-Hispanic Black race/ethnicity (OR, 2.75), less than high school education (OR, 1.59), and living below the poverty level (OR, 2.61) as risk factors for SHS exposure in the 2017-2018 cycle, with little change across all data cycles," the researchers wrote.

Disparities in SHS exposure

A second report from NHANES data for 2015-2018, published in a National Center for Health Statistics Data Brief (No. 396, February 2021) showed that 20.8% of nonsmoking U.S. adults had SHS exposure, again with greater prevalence among non-Hispanic Black adults (39.7%), than for non-Hispanic White (18.4%), non-Hispanic Asian (20.9%), and Hispanic (17.2%) adults. Exposure was also greater in the younger age groups, with SHS rates for adults aged 18-39 years, 40-59 years, and ≥60 years at 25.6%, 19.1%, and 17.6%, respectively. Lower education (high school or less vs. some college education) and lower income levels were also associated with higher levels of SHS exposure. The investigators noted that, among households with smokers, non-Hispanic Black adults are less likely to have complete smoking bans in homes, and among Medicaid or uninsured parents of any race or ethnicity, bans on smoking in family vehicles are less likely.

Overall, the prevalence of SHS exposure declined from 27.7% to 20.7% from 2009 to 2018, but the decreases were mediated by race and income.

SHS exposure in private spaces

A research brief from the Centers for Disease Control and Prevention on SHS exposure in homes and vehicles in the U.S. among middle and high school students also found a general decline in SHS exposure over 2011-2018 in homes (26.8%-20.9%; $P < .001$) and vehicles (30.2%-19.8%; $P < .001$). The findings, derived from the National Youth Tobacco Survey for 2011-2019, showed that no reduction occurred in homes among non-Hispanic Black students (Prev Chronic Dis. 2020;17:200107. doi: 10.5888/pcd17.200107). Overall, a significant difference in home SHS exposure was observed by race/ethnicity: non-Hispanic Black (28.4%) and non-Hispanic White (27.4%) students both had a higher prevalence compared with Hispanic (20.0%) and non-Hispanic other (20.2%) students ($P < .001$).

Progress in reducing SHS exposure in public spaces has been made over the last 2 decades, with 27 states and more than 1,000 municipalities implementing comprehensive smoke-free laws that prohibit smoking in indoor public places, including workplaces, restaurants, and bars. While the prevalence of voluntary smoke-free home (83.7%) and vehicle (78.1%) rules has increased over time, private settings remain major sources of SHS exposure for many people, including youths. "Although SHS exposures have declined," the authors wrote, "more than 6 million young people remain exposed to SHS in these private settings."

Dr. Cataletto

The study "highlights the need for implementation of smoke-free policies to reduce exposure to secondhand smoke, especially in homes and cars and with focused advocacy efforts in highly affected communities."

In reviewing the data, Mary Cataletto, MD, FCCP, clinical professor of pediatrics at NYU Long Island School of Medicine, stated that the study "highlights the need for implementation of smoke-free policies to reduce exposure to secondhand smoke, especially in homes and cars and with focused advocacy efforts in highly affected communities."

Panagis Galiatsatos, MD, MHS, assistant professor of medicine at Johns Hopkins University, Baltimore, emphasized implementation of smoke-free policies but also treatment for smokers. "I'm not at all surprised by these statistics," he noted in an interview. "Public health policies have helped us to get to where we are now, but there's a reason that we have plateaued over the last decade. It's hard to mitigate secondhand smoke exposure because the ones who are smoking now are the most refractory, challenging cases. ... You need good clinical interventions with counseling supported by pharmacological agents to help them if you want to stop secondhand smoke exposure." He added, "You have to look at current smokers no differently than you look at patients with stage IV cancer – a group that requires a lot of resources to help them get through. Remember, all of them want to quit, but the promise of well-designed, precision-medicine strategies to help them quit has not been kept. Public health policy isn't going to do it. We need to manage these patients clinically."

The investigators had no conflict disclosures.

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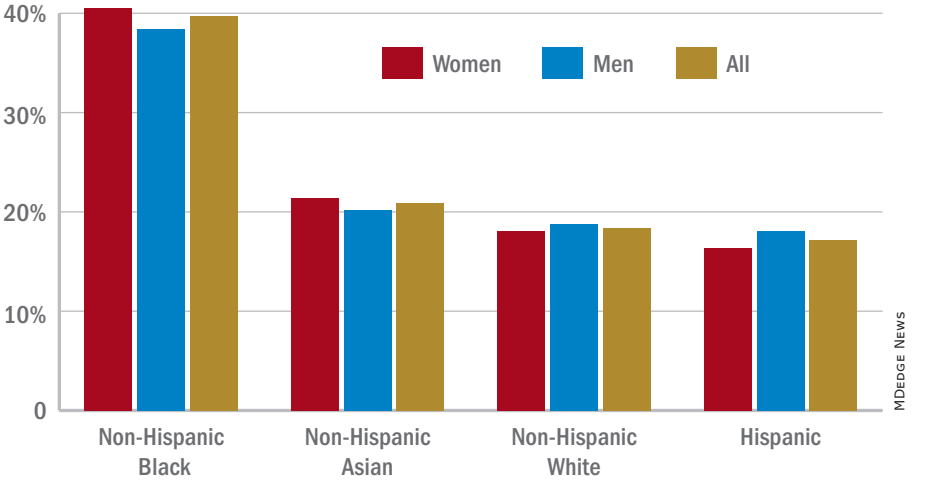
Prevalence of secondhand smoke exposure in nonsmoking adults



Note: Based on data from the National Health and Nutrition Examination Survey, 2015-2018.
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Is pediatric subspecialty training financially worth it?

BY JALEESA BAULKMAN

Pursuing fellowship training is often financially costly in terms of lifetime earnings, compared with starting a career as a general pediatrician immediately after residency, a report suggests.

Researchers found that most pediatric subspecialists – including those practicing neurology, pulmonology, and adolescent medicine – do not see a financial return from additional training because of the delays in receiving increased compensation and the repayment of educational debt.

"Most pediatric subspecialists don't experience a relative increase in compensation after training compared to a general pediatrician, so there isn't a financial benefit to additional training," lead author Eva Catenaccio, MD, from the division of pediatric neurology, department of neurology, Johns Hopkins University, Baltimore, told this news organization.

Comparing results from the two study periods showed that the financial gap between general pediatrics and subspecialty pediatrics worsened over time.

The findings, published online March 8 in Pediatrics (2021 Mar 1. doi: 10.1542/peds.2020-027771), contribute to the ongoing debate about the length of pediatric fellowship training programs. The data also provide evidence for the potential effect of a pediatric subspecialty loan repayment program.

Pediatric subspecialty training rarely pays off

However, not all practitioners in pediatric subspecialties would find themselves in the red relative to their generalist peers. Three subspecialties had a positive financial return: cardiology, critical care, and neonatology. Dr. Catenaccio explained that this may be because these subspecialties tend to be "inpatient procedure oriented, which are often more [lucrative] than outpatient cognitive–oriented subspecialties, such as pediatric infectious diseases, endocrinology, or adolescent medicine."

Enrolling in a pediatric fellowship program resulted in lifetime financial returns that ranged from an increase of $852,129 for cardiology, relative to general pediatrics, to a loss of $1,594,366 for adolescent medicine, researchers found.

For the study, researchers calculated the financial returns of 15 pediatric subspecialties – emergency medicine, neurology, cardiology, critical care, neonatology, hematology and oncology, pulmonology, hospitalist medicine, allergy and immunology, gastroenterology, rheumatology, nephrology, adolescent medicine, infectious diseases, and endocrinology – in comparison with returns of private practice general pediatrics on the basis of 2018-2019 data on fellowship stipends, compensation, and educational debt.

They obtained most of the data from the Association of American Medical Colleges Survey of Resident/Fellow Stipends and Benefits, AAMC's annual Medical School Faculty Salary Report, and the AAMC Medical School Graduation Questionnaire.

Richard Mink, MD, department of pediatrics, Harbor–UCLA Medical Center, Torrance, Calif., noted that it would have been helpful to have also compared the lifetime earnings of practitioners in pediatric subspecialties to academic general pediatricians and not just those in private practice.

The financial gap has worsened

To better understand which aspects of fellowship training have the greatest effect on lifetime compensation, Dr. Catenaccio and colleagues evaluated the potential effects of shortening fellowship length, eliminating school debt, and implementing a federal loan repayment plan. These changes enhanced the returns of cardiology, critical care, and neonatology – subspecialties that had already seen financial returns before these changes – and resulted in a positive financial return for emergency medicine.

The changes also narrowed the financial gap between subspecialties and general pediatrics. However, the remaining subspecialties still earned less than private practice pediatrics.

The new study is an update to a 2011 report, which reflected 2007-2008 data for 11 subspecialties. This time around, the researchers included the subspecialty of hospitalist medicine, which was approved as a board-certified subspecialty by the American Board of Pediatrics in 2014, as well as neurology, allergy and immunology, and adolescent medicine.

"I was most surprised that the additional pediatric subspecialties we included since the 2011 report followed the same general trend, with pediatric subspecialty training having a lower lifetime earning potential than general pediatrics," Dr. Catenaccio said.

Comparing results from the two study periods showed that the financial gap between general pediatrics and subspecialty pediatrics worsened over time. For example, the financial return for pediatric endocrinology decreased an additional $500,000 between 2007 and 2018.

The researchers believe a combination of increased educational debt burden, slow growth in compensation, and changing interest rates over time have caused the financial differences between general pediatrics and subspecialty pediatrics to become more pronounced.

'Pediatric subspecialty training is worth it!'

Despite the financial gaps, Dr. Catenaccio and colleagues say pediatric subspecialty training is still worthwhile but that policymakers should address these financial differences to help guide workforce distribution in a way that meets the needs of patients.

"I think pediatric subspecialty training is worth it," said Dr. Catenaccio, who's pursuing pediatric subspecialty training. "There are so many factors that go into choosing a specialty or subspecialty in medicine, including the desire to care for a particular patient population, interest in certain diseases or organ systems, lifestyle considerations, and research opportunities."

But it's also important for trainees to be aware of economic considerations in their decision-making.

Dr. Mink, who wrote an accompanying commentary, agrees that young clinicians should not make career decisions on the basis of metrics such as lifetime earning measures.

"I think people who go into pediatrics have decided that money is not the driving force," said Dr. Mink. He noted that pediatricians are usually not paid well, compared with other specialists. "To me the important thing is you have to like what you're doing."

A 2020 study found that trainees who chose a career in pediatric pulmonology, a subspecialty, said that financial considerations were not the driving factor in their decision-making. Nevertheless, Dr. Mink also believes young clinicians should take into account their educational debt.

The further widening of the financial gap between general pediatrics and pediatric subspecialties could lead to shortages in the pediatric subspecialty workforce.

The authors and Dr. Mink have disclosed no relevant financial relationships.

A version of this article first appeared on Medscape.com.

Brandon M. Seay, MD, comments: I agree with Dr. Cartenaccio and Dr. Mink that pediatric subspecialty training/work is definitely worth it, but the lifetime earnings are not the only consideration.

When I was in my pediatric residency, I considered whether going into pediatric pulmonology, which had always been an area of medicine that I was interested in, was the best choice for me. I knew I wanted to make the most difference in the lives of as many children as I could. With respiratory issues being one of the most common in pediatrics, I felt I could have the most impact by becoming a pediatric pulmonologist. That was the foremost consideration for me, not how much money I would earn.

During my fellowship training I got exposure to advocacy as a tool to improve the lives of children as well. Having a specific focus in pulmonology gave me insight into specific things that could be advocated for through community engagement and legislative advocacy. By having specific areas to focus on like addressing the dangers of vaping and delaying school start times to encourage more sleep in teenagers, I can have more impact as an advocate. The impact I can make on the lives of kids makes the extra years of training, delay in repaying student loans, and decreased overall lifetime earnings worth it to me.

FDA expands use of SLIT pollen allergy treatment to children

BY JALEESA BAULKMAN

The Food and Drug Administration has approved a new indication for ALK's sublingual immunotherapy (SLIT) tablet Ragwitek to treat ragweed pollen–induced hay fever in children aged 5-17 years.

Ragwitek received FDA approval in 2014 to treat short ragweed pollen–induced hay fever, with or without allergic rhinoconjunctivitis, in adults aged 18-65 years. This new indication expanded that age group to include children.

The approval for Ragwitek comes with a boxed warning regarding a risk for life-threatening allergic reactions associated with the immunotherapy treatment, including anaphylaxis and severe laryngopharyngeal restriction. The package insert specifies that physicians should prescribe autoinjectable epinephrine with the drug.

"Ragwitek tablets provide a new immunotherapy treatment option for children and adolescents with seasonal ragweed allergies which often causes uncomfortable nasal symptoms and red, itchy eyes during the late summer and early fall," David I. Bernstein, MD, University of Cincinnati, Bernstein Clinical Research, said in a company press release.

Short ragweed pollen is one of the most common weed allergies. Allergic rhinitis, or hay fever, affects 10%-30% of the population worldwide, according to the American Academy of Allergy Asthma & Immunology. In the United States, approximately 7.7% of adults and 7.2% of children were diagnosed with it annually, according to the Centers for Disease Control and Prevention.

The new indication was based partly on data from a phase 3 clinical trial in children with short ragweed–induced allergic rhinitis, or hay fever, published in the Journal of Allergy and Clinical Immunology (2021 Apr 15. doi: 10.1016/j.jaip.2020.03.041).

In the study, researchers evaluated the efficacy and safety of the treatment in 1,022 participants aged 5-17 years with a history of ragweed-induced rhinoconjunctivitis and sensitivity to ragweed over a 20- to 28-week treatment period.

Researchers found that Ragwitek improved symptoms in children and adolescents and decreased their use of symptom-relieving medication, compared with placebo.

Among children and adolescents aged 5-17 years, the most common adverse reactions reported were throat irritation/tickle (48.3% in the Ragwitek group vs. 17.7% in the placebo group), itching in the mouth (47.8% vs. 11.2%), itching in the ear (33.9% vs. 6.3%), mouth pain (18.9% vs. 4.5%), swelling of the lips (13.8% vs. 1.2%), nausea (11.5% vs. 3.3%), swelling of the tongue (11.3% vs. 0.8%), throat swelling (10.7% vs. 1.6%), and stomach pain (10.1% vs. 4.5%).

The FDA recommends that SLIT not be prescribed to people with severe, unstable, or uncontrolled asthma, those with a history of severe systemic allergic reactions, and those with a history of eosinophilic esophagitis.

The FDA also recommends that Ragwitek not be prescribed to people with severe, unstable, or uncontrolled asthma, those with a history of severe systemic allergic reactions, and those with a history of eosinophilic esophagitis. The immunotherapy treatment also may not be suitable for people who are unresponsive to epinephrine or inhaled bronchodilators.

In addition, the treatment is not approved for the immediate relief of allergic symptoms in children or adults. The once-daily treatment, which contains an extract from short ragweed pollen, should begin 12 weeks before the start of ragweed pollen season and continue throughout the season, according to the FDA.

Dr. Bernstein said that the under-the-tongue immunotherapy works by targeting the specific allergy trigger and reducing allergy symptoms by "stimulating the immune system."

A version of this article first appeared on Medscape.com.

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Gene dysregulation links cancer risk and night work

BY ROXANNE NELSON, RN, BSN

Working night shifts has been associated with an increased risk for certain cancers, as well as other health disorders. Indeed, the World Health Organization's International Agency for Research on Cancer has classified night-shift work as "probably carcinogenic to humans."

But why night shift should elevate the risk for cancer has been unclear.

A new study shows that a simulated night-shift schedule significantly altered the normal circadian rhythmicity of genes that are involved in cancer hallmark pathways. It also found that this circadian misalignment caused circadian dysregulation of genes involved in key DNA repair pathways.

"Taken together, these findings suggest that night-shift schedules throw off the timing of expression of cancer-related genes in a way that reduces the effectiveness of the body's DNA repair processes when they are most needed," said co–corresponding author Jason McDermott, a computational scientist with the Pacific Northwest National Laboratory's biological sciences division in Richland, Wash.

The study was published online in the Journal of Pineal Research (2021 Feb 27. doi: /10.1111/jpi.12726).

Study conducted among volunteers

The study was carried out among healthy volunteers who were subjected to simulated night-shift or day-shift schedules.

The cohort comprised 14 adults between the ages of 22 and 34 years who had normal nighttime sleep schedules. They were randomly assigned (seven in each group) to a simulated day-shift schedule that involved 3 days of daytime wakefulness (6 a.m.-10 p.m.), or a simulated night-shift schedule involving 3 days of nighttime wakefulness (6 p.m.-10 a.m.).

After the 3 days of simulated shift work, all participants were then kept in a constant routine protocol (used to study humans' internally generated biological rhythms independent of any external influences). As part of the protocol, they were kept awake for 24 hours in a semi-reclined posture under laboratory conditions with constant light exposure and room temperature and evenly distributed food intake (hourly isocaloric snacks).

Blood samples were collected at 3-hour intervals and used for leukocyte transcriptome analysis and DNA damage assessment.

The authors found that the circadian expression of canonical clock genes was substantially altered by the simulated night-shift schedule vs. the day-shift schedule. Four genes (CRY1, CRY2, PER2, and NR1D2) lost their normal day-shift rhythmicity following the night-shift schedule, and NPAS2 gene expression was not rhythmic during the day shift but exhibited circadian rhythmicity in the simulated night-shift condition. Three other genes (NR1D1, PER3, and DBP) were significantly rhythmic during both shifts.

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3 indications[1]

1 The treatment of IPF

2 The treatment of chronic fibrosing ILDs with a progressive phenotype

3 Slowing the rate of decline in pulmonary function in patients with SSc-ILD

6+ years since first approved for IPF[1,2]

Experience adds up with OFEV

ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hepatic Impairment: OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Elevated Liver Enzymes and Drug-Induced Liver Injury

- Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and post-marketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the post-marketing period. The majority of hepatic events occur within the first three months of treatment. OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases.
- In IPF studies, the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN.
- In the chronic fibrosing ILDs with a progressive phenotype study, the majority (95%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (94%) of patients with bilirubin elevations had elevations less than 2 times ULN.

The team also looked at the effect of night shift on circadian rhythmicity in cancer hallmark genes, using a panel of 726 genes. The analysis showed that:

- 257 (35.4%) were rhythmic after at least one of the two simulated shift-work conditions.
- 113 (15.6%) were rhythmic in day shift only.
- 96 (13.2%) were rhythmic during night shift only.
- 48 (6.6%) were rhythmic during both shifts.

"Night shift workers face considerable health disparities, ranging from increased risks of metabolic and cardiovascular disease to mental health disorders and cancer."

A subset of 10 (1.4%) genes exhibited a significant phase advance (3.7 to 8.3 hours) or phase delay (2.8 to 7.0 hours) during the night shift, compared with the day shift.

Thus, the authors concluded, shift work caused significant disturbances in the rhythmicity of gene expression in cancer hallmark pathways.

Findings also showed that night-shift work increases endogenous and exogenous DNA damage. Endogenous DNA damage was

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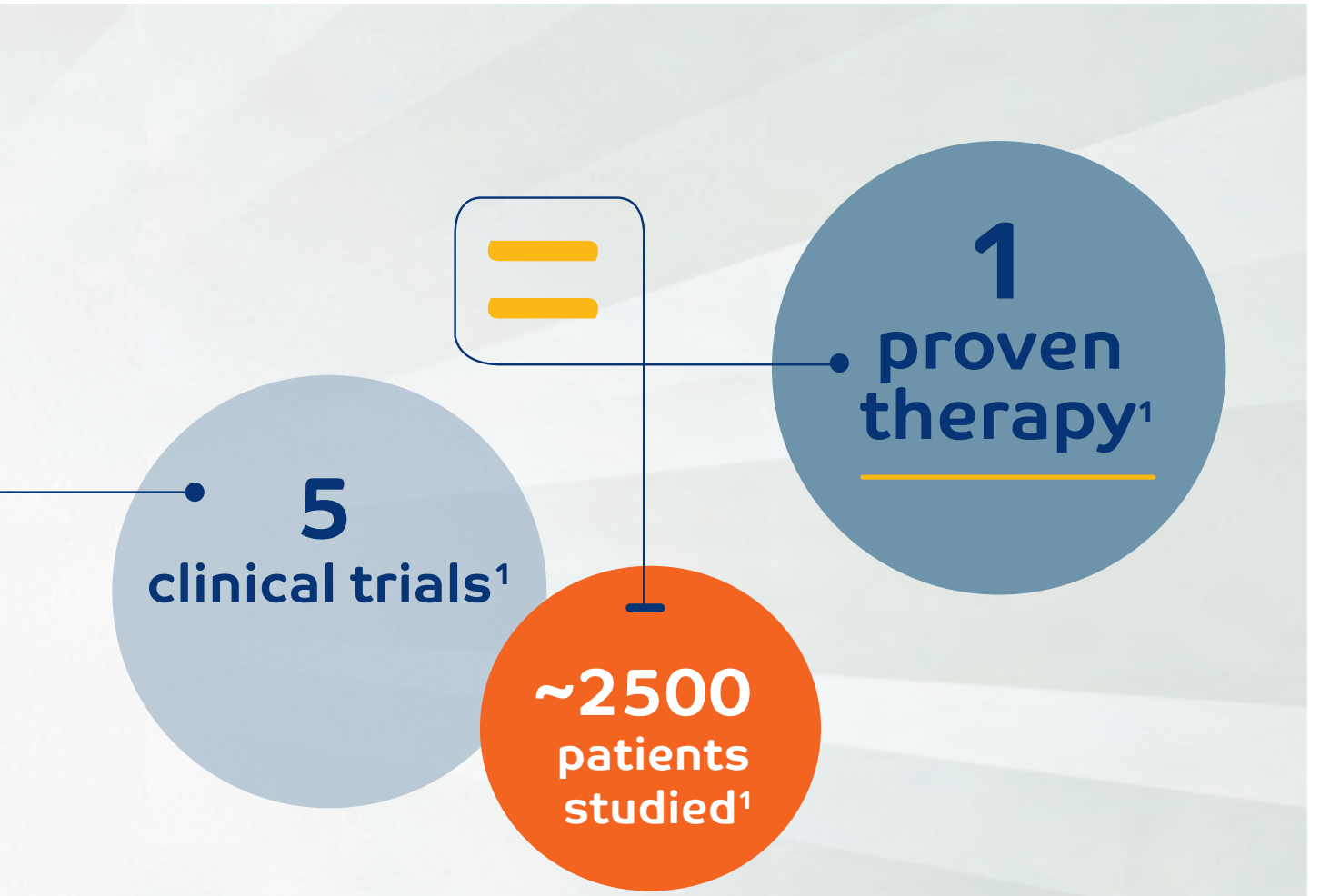

See how the clinical trial data adds up at OFEVhcp.com/experience

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes and Drug-Induced Liver Injury (cont'd)

- In the SSc-ILD study, a maximum ALT and/or AST greater than or equal to 3 times ULN was observed in 4.9% of patients treated with OFEV.
- Patients with low body weight (less than 65 kg), patients who are Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.
- Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Please see additional Important Safety Information on the following pages and accompanying Brief Summary of Prescribing Information.

Continued from previous page

generally higher after the night shift compared to the day shift, and across the 24-hour constant routine the percentage of cells with BRCA1 and g H2AX foci was significantly higher for night shift.

Next steps

The team said that the next step is to conduct the same experiment with real-world shift workers who have been consistently on day or night shifts for many years to determine whether in night workers the unrepaired DNA damage builds up over time, which could ultimately increase the risk for cancer.

Shift work caused significant disturbances in the rhythmicity of gene expression in cancer hallmark pathways.

If what happens in real-world shift workers is consistent with the current findings, this work could eventually be used to develop prevention strategies and drugs that could address the mistiming of DNA repair processes, they suggested.

"Night shift workers face considerable health disparities, ranging from increased risks of metabolic and cardiovascular disease to mental health disorders and cancer,"

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders

Diarrhea

- Events were primarily mild to moderate in intensity and occurred within the first 3 months.
- In IPF studies, diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and less than 1% in placebo patients, respectively.
- In the chronic fibrosing ILDs with a progressive phenotype study, diarrhea was reported in 67% versus 24% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 16% and discontinuation in 6% of OFEV patients, compared to less than 1% of placebo-treated patients, respectively.
- In the SSc-ILD study, diarrhea was the most frequent gastrointestinal event reported in 76% versus 32% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 22% and discontinuation in 7% of OFEV patients versus 1% and 0.3% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider dose reduction or treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting

- In IPF studies, nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- In the chronic fibrosing ILDs with a progressive phenotype study, nausea was reported in 29% versus 9% and vomiting was reported in 18% versus 5% of patients treated with OFEV and placebo, respectively. Nausea led to discontinuation of OFEV in less than 1% of patients, and vomiting led to discontinuation of OFEV in 1% of the patients.
- In the SSc-ILD study, nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- In most patients, events were primarily of mild to moderate intensity. If nausea or vomiting persists despite appropriate supportive care including antiemetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryo-Fetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use highly effective contraception at initiation of treatment, during treatment, and at least 3 months after the last dose of OFEV. Nintedanib does not change the exposure to oral contraceptives containing ethinylestradiol and levonorgestrel in patients with SSc-ILD. However, the efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhea or other conditions where drug absorption may be reduced. Advise women taking oral hormonal contraceptives experiencing these conditions to use alternative highly effective contraception. Verify pregnancy status prior to starting OFEV and during treatment as appropriate.

Arterial Thromboembolic Events

- In IPF studies, arterial thromboembolic events were reported in 2.5% of OFEV and less than 1% of placebo patients, respectively. Myocardial infarction (MI) was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and in less than 1% of placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, arterial thromboembolic events and MI were reported in less than 1% of patients in both treatment arms.
- In the SSc-ILD study, arterial thromboembolic events were reported in 0.7% of patients in both the OFEV-treated and placebo-treated patients. There were 0 cases of MI in OFEV-treated patients compared to 0.7% of placebo-treated patients.
- Use caution when treating patients at higher cardiovascular risk, including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding

- OFEV may increase the risk of bleeding.
- In IPF studies, bleeding events were reported in 10% of OFEV versus 7% of placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, bleeding events were reported in 11% of OFEV versus 13% of placebo patients.
- In the SSc-ILD study, bleeding events were reported in 11% of OFEV versus 8% of placebo patients.
- In clinical trials, epistaxis was the most frequent bleeding event. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation

- OFEV may increase the risk of gastrointestinal perforation.
- In IPF studies, gastrointestinal perforation was reported in less than 1% of OFEV versus in 0% of placebo patients.

co–senior author Hans Van Dongen, PhD, a professor at Washington State University in Pullman and director of the WSU Sleep and Performance Research Center, Spokane, said in a statement. "It is high time that we find diagnosis and treatment solutions for this underserved group of essential workers so that the medical community can address their unique health challenges."

This work could eventually be used to develop prevention strategies and drugs that could address the mistiming of DNA repair processes.

The study was supported by start-up funds from Washington State University and a Center for Human Health and the Environment grant from North Carolina State University, and in part by the United States Army Medical Research and Development Command, the National Institutes of Health, CDMRP (Congressionally Directed Medical Research Programs) Peer Reviewed Cancer Research Program award, and the BRAVE investment.

The authors have disclosed no relevant financial relationships.

A version of this article first appeared on Medscape.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Perforation (cont'd)

- In the chronic fibrosing ILDs with a progressive phenotype study, gastrointestinal perforation was not reported in any treatment arm.
- In the SSc-ILD study, no cases of gastrointestinal perforation were reported in either OFEV or placebo-treated patients.
- In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, have a previous history of diverticular disease, or who are receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Most common adverse reactions reported (greater than or equal to 5%) are diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased and hypertension.
- In IPF studies, the most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and MI (1.5% vs. 0.4%). The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, the most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of OFEV patients and in 5% of placebo patients. No pattern was identified in the adverse events leading to death.
- In the SSc-ILD study, the most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% vs. 1.7%) and pneumonia (2.8% vs. 0.3%). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

CL-OF-100050 10.28.2020

Please see accompanying Brief Summary of Prescribing Information on the following pages.

References: 1. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020. **2.** Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. December 2020.

Boehringer Ingelheim

OFEV® (nintedanib) capsules 150mg

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Pandemic fallout: 1 in 5 clinicians considered quitting

BY DAMIAN MCNAMARA

The COVID-19 pandemic continues to take its toll on the well-being and work satisfaction of health care providers, a new survey of more than 5,000 clinicians at an academic medical center illustrates.

About one in five people reported considering leaving the workforce because of the challenges of working during the COVID-19 pandemic. In addition, 30% reported they are considering cutting back work hours.

"There are a substantial number of employees and trainees who are experiencing major stress and work disruptions because of the pandemic," lead author Rebecca K. Delaney, PhD, said in an interview. "It is particularly alarming that people who have spent 5 or more years in training for their specialty are struggling with their work, so much

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE: 1.1 Idiopathic Pulmonary Fibrosis: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF). **1.2 Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype:** OFEV is indicated for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. **1.3 Systemic Sclerosis-Associated Interstitial Lung Disease:** OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

2 DOSAGE AND ADMINISTRATION: 2.1 Testing Prior to OFEV Administration: Conduct liver function tests in all patients and a pregnancy test in females of reproductive potential prior to initiating treatment with OFEV *[see Warnings and Precautions]*. **2.2 Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food. **2.3 Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV [*see Warnings and Precautions and Adverse Reactions*]. Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions and Adverse Reactions]*. In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

4 CONTRAINDICATIONS: None

5 WARNINGS AND PRECAUTIONS: 5.1 Hepatic Impairment: Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment [*see Use in Specific Populations*]. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV *[see Dosage and Administration]*. **5.2 Elevated Liver Enzymes and Drug-Induced Liver Injury:** Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and postmarketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the postmarketing period. The majority of hepatic events occur within the first three months of treatment. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In IPF studies (Studies 1, 2, and 3), the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), the majority (95%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (94%) of patients with bilirubin elevations had elevations less than 2 times ULN. In the SSc-ILD study (Study 4), a maximum ALT and/or AST greater than or equal to 3 times ULN was observed for 4.9% of patients in the OFEV group and for 0.7% of patients in the placebo group [*see Use in Specific Populations*]. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations. [*see Dosage and Administration*]. **5.3 Gastrointestinal Disorders:** Diarrhea: In clinical trials, diarrhea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. In IPF studies (Studies 1, 2, and 3), diarrhea was reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [*see Adverse Reactions*]. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to less than 1% of placebo-treated patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), diarrhea was reported in 67% versus 24% of patients treated with OFEV and placebo, respectively [*see Adverse Reactions*]. Diarrhea led to permanent dose reduction in 16% of patients treated with OFEV compared to less than 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 6% of the patients compared to less than 1% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 32% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. Diarrhea led to permanent dose reduction in 22% of patients treated with OFEV compared to 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 7% of the patients compared to 0.3% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues [*see Dosage and Administration*]. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV. Nausea and Vomiting: In IPF studies (Studies 1, 2, and 3), nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), nausea was reported in 29% versus 9% and vomiting was reported in 18% versus 5% of patients treated with OFEV and placebo, respectively. In the SSc-ILD study (Study 4), nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, these events were of mild to moderate intensity. In IPF studies (Studies 1, 2, and 3), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), nausea led to discontinuation of OFEV in less than 1% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. In the SSc-ILD study (Study 4), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required [*see Dosage and Administration*]. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **5.4 Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraception at initiation of, during treatment, and at least 3 months after the last dose of OFEV. Nintedanib does not change the exposure to oral contraceptive containing ethinylestradiol and levonorgestrel in patients with SSc-ILD. However, the efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhea or other conditions where the drug absorption may be reduced. Advise women taking oral hormonal contraceptives experiencing these conditions to use alternative highly effective contraception. Verify pregnancy status prior to treatment with OFEV and during treatment as appropriate *[see Use in Specific Populations]*. **5.5 Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In IPF studies (Studies 1, 2, and 3), arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), arterial thromboembolic events were reported in less than 1% of patients in both treatment arms. Myocardial infarction was observed in less than 1% of patients in both treatment arms. In the SSc-ILD study (Study 4), arterial thromboembolic events were reported in 0.7% of patients in both treatment arms. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **5.6 Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In IPF studies (Studies 1, 2, and 3), bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), bleeding events were reported in 11% of patients treated with OFEV and in 13% of patients treated with placebo. In the SSc-ILD study (Study 4), bleeding events were reported in 11% of patients treated with OFEV and in 8% of patients treated with placebo. In the postmarketing period non-serious and serious bleeding events, some of which were fatal, have been observed. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **5.7 Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In IPF studies (Studies 1, 2, and 3), gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), gastrointestinal perforation was not reported in any patients in any treatment arm. In the SSc-ILD study (Study 4), no cases of gastrointestinal perforation were reported in patients treated with OFEV or in placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

6 ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Elevated Liver Enzymes and Drug-Induced Liver Injury [*see Warnings and Precautions*]; Gastrointestinal Disorders *[see Warnings and Precautions]*; Embryo-Fetal Toxicity [*see Warnings and Precautions*]; Arterial Thromboembolic Events [*see Warnings and Precautions*]; Risk of Bleeding *[see Warnings and Precautions]*;

so that they have even considered leaving the workforce or reducing their hours."

"Being a caregiver adds another layer of difficulty for faculty, staff, and trainees who are trying to manage work and child care," added Dr. Delaney, a researcher in the department of population health sciences, University of Utah, Salt Lake City.

The study was published online April 2 in JAMA Network Open (2021. doi: 10.1001/jamanetworkopen.2021.3997).

"This looks like an excellent survey," Carol A Bernstein, MD, said in an interview when asked to comment. "I do not think it provides particularly new information as these challenges in the workplace, especially for women during COVID, have been well documented in the media and the medical literature to date."

"That said, to the extent that data helps drive solutions, I would hope that information such as this would be considered as strong further evidence that health care systems must pay close attention to the well-being of the workforce," added Dr. Bernstein, professor and vice chair of faculty development and well-being, departments of psychiatry and behavioral sciences and obstetrics and gynecology and women's health, Montefiore Medical Center/Albert Einstein College of Medicine, New York.

Continued on following page

Gastrointestinal Perforation [*see Warnings and Precautions*].

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 OFEV was evaluated in over 1000 IPF patients, 332 patients with chronic fibrosing ILDs with a progressive phenotype, and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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

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

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

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

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

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

Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%). The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death. Adverse reactions leading to permanent dose reductions were reported in 33% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (16%). Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%). The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%). Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.

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

[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal [*see Warnings and Precautions*], pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration]*. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [*see Warnings and Precautions*]. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and

Continued from previous page

When the pandemic hits home

A total of 42% of the American workforce rapidly transitioned to working from home at the onset of the COVID-19 pandemic. At the same time, many employees had to provide child care and assistance with schoolwork. This placed a burden on many individuals at academic medical centers, and women in particular.

"Women comprise 74.9% of hospital employees, many of whom are essential clinical workers," the researchers noted. "The extent of the needs and difficulties for these workers during the pandemic remain largely unknown."

To learn more, Dr. Delaney, senior author Angie Fagerlin, PhD, and their colleagues emailed a Qualtrics survey to 27,700 faculty, staff, and trainees at University of Utah Health. The survey was conducted Aug. 5-20, 2020, as part of a quality improvement initiative. All responses were anonymous.

Survey questions included if, because of the pandemic, people had considered leaving the workforce, considered reducing their hours, or experienced reduced productivity. The researchers also asked about career impacts and potential solutions in terms of "work culture adaptations."

Respondents with children under 18 also were asked about child care options. Dr. Delaney and colleagues also inquired about race and ethnicity because they hypothesized that employees from underrepresented groups would likely experience the pandemic differently.

The mean age of the 5,951 (21%) faculty, staff, and trainees who completed the survey was 40 years. A majority of respondents were women, reflecting the higher proportion of women within the health system.

Dr. Bernstein

A majority (86%) identified as White or European American. About two-thirds of respondents (66%) were staff, 16% were faculty, and 13% were trainees.

COVID-19 career concerns

Overall, 1,061 respondents (21%) "moderately or very seriously" considered leaving the workforce and 1,505 (30%) considered reducing hours. Respondents who were younger, married, a member of an underrepresented racial/ethnic group, and worked in a clinical setting were more likely to consider leaving the workforce.

The survey showed 27% felt their productivity increased whereas 39% believed their productivity decreased.

Of the 2,412 survey participants with children aged 18 years or younger, 66% reported that they did not have child care fully available.

Limitations of the study include its generalizability beyond employees of University of Utah Health. Also, respondents included a lower proportion of racial and ethnic groups, compared with national figures, "although this is mostly accounted for by the overall low population of such groups in the state of Utah," the researchers added.

The Jon M. Huntsman Presidential Endowed Chair supported the work with a financial award to Dr. Fagerlin. Dr. Delaney and Dr. Bernstein disclosed no relevant financial relationships.

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miscarriage in clinically recognized pregnancies is 15% to 20%. Data: *Animal Data*: In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **8.2 Lactation:** Risk Summary: There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV. Data: Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. **8.3 Females and Males of Reproductive Potential:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential *[see Use in Specific Populations]*. Counsel patients on pregnancy prevention and planning. Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV and during treatment as appropriate. *[see Dosage and Administration, Warnings and Precautions and Use in Specific Populations]*. Contraception: OFEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception at initiation of, during treatment, and for at least 3 months after taking the last dose of OFEV. Nintedanib does not change the exposure to oral contraceptive containing ethinylestradiol and levonorgestrel in patients with SSc-ILD. However, the efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhea or other conditions where the drug absorption may be reduced. Advise women taking oral hormonal contraceptives experiencing these conditions to use alternative highly effective contraception. Infertility: Based on animal data, OFEV may reduce fertility in females of reproductive potential. **8.4 Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **8.5 Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV in IPF, 60.8% were 65 and over, while 16.3% were 75 and over. In the chronic fibrosing ILDs with a progressive phenotype clinical study (Study 5), 61% were 65 and over, while 19% were 75 and older. In SSc-ILD, 21.4% were 65 and over, while 1.9% were 75 and older. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (greater than 90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily [*see Dosage and Administration*]. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients *[see Dosage and Administration]*. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [*see Warnings and Precautions*]. **8.7 Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (less than 30 mL/min CrCl) and end-stage renal disease. **8.8 Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

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

17 PATIENT COUNSELING INFORMATION: *Advise the patient to read the FDA-approved patient labeling (Patient Information).* Elevated Liver Enzymes and Drug-Induced Liver Injury: Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy, loss of appetite) *[see Warnings and Precautions]*. Gastrointestinal Disorders: Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [*see Warnings and Precautions and Adverse Reactions*]. Embryo-Fetal Toxicity: Counsel patients on pregnancy prevention and planning. Advise females of reproductive potential of the potential risk to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception at initiation of, during treatment, and for at least 3 months after taking the last dose of OFEV. Advise women taking oral hormonal contraceptives who experience vomiting and/or diarrhea or other conditions where the drug absorption may be reduced to contact their doctor to discuss alternative highly effective contraception. Advise female patients to notify their doctor if they become pregnant or suspect they are pregnant during therapy with OFEV *[see Warnings and Precautions and Use in Specific Populations]*. Arterial Thromboembolic Events: Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions]*. Risk of Bleeding: Bleeding events have been reported. Advise patients to report unusual bleeding [*see Warnings and Precautions*]. Gastrointestinal Perforation: Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions]*. Lactation: Advise patients that breastfeeding is not recommended while taking OFEV *[see Use in Specific Populations]*. Smokers: Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV. Administration: Instruct patients to take OFEV with food, to swallow OFEV capsules whole with liquid, and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration]*.

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CHEST Health Policy and Advocacy Conference

BY NEIL FREEDMAN, MD, FCCP
Conference Co-Chair

In keeping with CHEST's commitment to advocating for our patients, we recently hosted a 2-day Health Policy and Advocacy Conference. This event aimed to carry on the tradition of the annual spring meeting held by the National Association for the Medical Direction of Respiratory Care (NAMDRC), which CHEST acquired last year.

In working with my Co-Chair, Katie Sarmiento, MD, MPH, we tried to stay true to what was so valuable from meetings past: convening stakeholders to discuss issues through their particular lens. While there were differences – this year, we gathered around a virtual table – the diversity of perspectives remained intact, bridging the landscape from clinical practice, the patients and caregivers we serve, the businesses that serve the field, and the decision-makers who must be swayed to create the change we desire.


Dr. Freedman

At the same time, we wanted to take the opportunity to do what CHEST does best: provide best-in-class education. We tried to shape a program that would help the entirety of CHEST membership and our partner organizations understand the key components of why and how we advocate, and we dedicated a large portion of the program to exploring our priority issues, such as oxygen access and home mechanical ventilation. Finally, we aimed to address issues that simply cannot be ignored, including health care disparities and the impact of telemedicine on how we practice.

Today, you can access videos from the conference for free through the online CHEST store at Chestnet.org via the e-Learning Library. In the next few *CHEST Physician* issues, you will find reporting and deep dives on some of the key sessions covered at the conference. Ahead at CHEST 2021 in October, there will be opportunities to join in the dialogue through formal sessions and networking opportunities. With thanks to my co-chair, all the faculty, and staff who supported this event, I hope you will listen, read along, and, most importantly, consider lending your lens and perspective to this continuing dialogue.

Under new administration, best time to lobby may be now

BY TED BOSWORTH
MDedge News

REPORTING FROM THE CHEST HEALTH POLICY AND ADVOCACY CONFERENCE ▪ The ambitious infrastructure bill now being debated in the US Congress might be one of the best immediate opportunities to lobby for legislative or policy changes in delivery of health care during the current Biden administration, according to an analysis delivered at the annual health policy and advocacy conference sponsored by the American College of Chest Physicians.


Keith S. Studdard

The infrastructure bill is likely to be pushed forward in the filibuster-proof reconciliation process, which means "that some things might get passed that otherwise would not," explained Keith S. Studdard, Vice President, Jeffrey J. Kimbell & Associates, Washington, DC.

With few exceptions, the key players in the health care team of President Joe Biden's new administration are in place, according to Mr. Studdard, who is a lobbyist and health care expert. By moving quickly to fill key positions, the new administration "got off to a good start" for a health care agenda that Mr. Studdard believes will be a focus of the Biden presidency. There is some degree of urgency.

"The amount of time [the Biden administration has] to get their agenda through is fairly limited," Mr. Studdard reported. The problems include a slim majority of fellow Democrats in the House of Representatives (222 vs 213), no majority of Democrats over Republicans in the Senate (50 vs 50), and midterm elections that are already looming.

"Midterms historically favor the opposition party," Mr. Studdard said. He expects party lines to harden as the midterms approach, dissipating the already limited appetite for bipartisan cooperation.

The midterms provide the basis for trying to affect change in advance of legislative gridlock, but the recently announced $2 trillion infrastructure bill is an even more compelling impetus. Infrastructure in this case is not limited to the construction of bridges and roads. Rather, this bill "is a massive package that will almost certainly touch on health care policy," according to Mr. Studdard.

As the infrastructure bill winds its way through the legislative process, Mr. Studdard expects there will be efforts to include language that favors expansion of services and funding for health care. This includes those related to the Affordable Care Act (ACA) and the temporary modifications permitted under the CARES Act, which was passed during the early months of the COVID-19 pandemic.

For those who think that waivers and exceptions introduced in the CARES Act, such as the expansion of telehealth, should be made permanent, "this will be your main shot on goal," Mr. Studdard said.

The debates around the ambitious infrastructure bill are "all that we will be hearing about from the legislative standpoint for the next few months," Mr. Studdard said. He expects major lobbying efforts in regard to this legislation from a vast array of interest groups, not just those with a stake in health care.

If the bill passes, it will likely be greatly helped by a vote under the reconciliation process. Created in 1974 to allow expedited consideration of spending legislation, the reconciliation process allows bills to be enacted with a simple majority, which is 51 votes in the Senate and 218 votes in the House. Filibustering is not permitted.

Legislation is one of two paths for altering funding and rules regarding health care in the United States. Policy is the other. For reaching decision makers with influence on policy, Mr. Studdard provided a long list of agencies, political appointees, and elected representatives that could be targeted. Many, such as the director of the Centers for Medicare & Medicaid Services (CMS), are well known, but others might be overlooked without a detailed list of the players.

As one example, he pointed to the Center for Medicare and Medicaid Innovation (CMMI), which is a relatively new organization within CMS. Led by Liz Fowler, a former Senate aide involved in writing the ACA, the CMMI has broad authority over several aspects of health policy, such as value-based care.

"The CCMI is something you should put on your radar. It moves with more flexibility than the HHS [Department of Health and Human Services]," Mr. Studdard said.

Mr. Studdard's detailed overview of the intricacies of how to affect change in health policy and the likely trajectory under the Biden administration included frequent comments about the traits, background, and goals of the specific decision makers he identified. The implication is that personal relations matter. Mr. Studdard indicated that knowing who to contact is just the first step.

For the Health Policy and Advocacy Committee, this information is critical. In his outline of the numerous paths for influencing health care policy, Mr. Studdard's comments lead directly to strategies to lobbying goals for CHEST.

"CHEST and its Health Policy and Advocacy Committee are keeping a focus on health care policy to improve access and to improve care for our patients and reduce the burden on our providers," according to the Chair of the Committee, Neil Freedman, MD, FCCP. Dr, Freedman is the Division Head Pulmonary, Critical Care, Allergy, and Immunology, Northshore University HeatlhSystem, Evanston, Illinois.

"We would hope that, in addition to the proposed infrastructure bill subsidizing some additional costs for the ACA and COBRA [Consolidated Omnibus Budget Reconciliation Act] and enhancing Medicaid eligibility, the bill would also provide some additional funding for the provider relief fund," he said.

Mr. Studdard or his lobbying firm represent 62 clients with interests in health care policy.

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CHEST FOUNDATION

NETWORKS

Management of pleural infections. Appendicitis and COVID-19. Screening for PAH. Lung function testing during the pandemic

Interventional chest and diagnostic procedures

Risk stratification and management of pleural infections

Pleural infection carries a significant health care burden with an estimated mortality rate between 10% and 20% in adults. Standard of care for pleural infections has traditionally included antibiotics and tube thoracostomy, with select patients requiring a surgical intervention. The landmark MIST II trial demonstrated that combination intrapleural fibrinolytic and DNase therapy led to reduced length of stay and lower surgical referral rates compared with placebo.[1] While the use of combination intrapleural therapy has become common in the management of these patients, controversies still exist regarding nuances related to the various aspects of this therapy. A recent position paper published in *Lancet Respiratory Medicine*[2] addresses these knowledge gaps and provides recommendations to offer guidance in decision-making. The consensus statement by the authors addresses the topics of intrapleural monotherapy, dosing regimen, sequence of dosing, and cost considerations amongst other things. The authors also summarize evidence and discuss a surgery first vs. intrapleural enzyme therapy first approach based on stage of empyema and presence of surgical expertise and surgical candidacy. However, the debate between early surgical intervention vs early intrapleural enzyme therapy has not been settled yet. A large prospective randomized control trial is currently ongoing to help answer this question [https://doi.org/10.1186/ISRCTN18192121].

Meanwhile, there has been a lack of robust validated prediction methods for selecting high-risk patients at presentation with pleural infection for an early aggressive intervention. Based on previous studies, Rahman et al.[3] had described the RAPID (Renal[urea], Age, fluid Purulence, Infection Source, Dietary [albumin]) score for risk stratification of these patients. Corcoran et al.[4] recently conducted a prospective, observational study and validated that the RAPID risk category (Low-risk [0-2], Medium-risk [3-4], and High-risk [5-7]) can help predict mortality at 3 months. This score may prove to be a useful tool for future research directed at improving outcomes in patients with pleural infections.

Abhinav Agrawal, MD
Samaan Rafeq , MD
NetWork Members

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Pediatric chest medicine

Appendicitis and COVID-19

During the 2020-21 year, there was an unprecedented amount of literature and studies released to the scientific and general public about the severe acute respiratory coronavirus 2 (SARS-CoV-2) syndrome, commonly referred to as COVID-19. The impressive focus on SARS-CoV-2 appeared appropriately featured given the public health concerns with contraction of the disease. While it is important to understand the potential presentations, complications, and treatments in the adult population, clinicians must be aware of the impact of this disease on children. Contrary to reports early in the pandemic, SARS-CoV-2 infection can lead to serious complications in the pediatric population. One complication is a condition called multisystem inflammation syndrome in children (MIS-C) that can mimic Kawasaki disease or toxic

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shock syndrome. In addition to the expected common clinical presentation of respiratory symptoms and fever, gastrointestinal complaints were reported in up to 84% of the infected children. Gastrointestinal symptoms may be the only complaint in this population, typically presenting with nausea, emesis, abdominal pain, and diarrhea. The Pediatric Chest NetWork intends to highlight these gastrointestinal complaints and make clinicians aware of an appendicitis-like syndrome or even true acute appendicitis that seems to occur in association with SARS-CoV-2 infection. There is a handful of case reports and case series that discussed this phenomenon. Due to the overlap of presenting symptoms in SARS-CoV-2 infection and acute appendicitis, clinicians must astutely evaluate patients to prevent worsening complications of a missed diagnosed appendicitis.

Dr. Mull

Eric Mull, DO
NetWork Fellow-in-Training

Pulmonary physiology, function, and rehabilitation

Lung function testing during the COVID-19 pandemic

The COVID-19 pandemic poses unique challenges to caring for patients with established lung disease or new onset respiratory complaints. Although maneuvers differ across individual tests, most involve forced expiration or high ventilatory rates. They also tend to generate cough. Because the SARS-CoV-2 virus is predominantly spread via respiratory droplets, coughing, forced expiration, and high ventilatory rates will increase the risk for transmission.

Respiratory societies across the world have developed recommendations for operating a pulmonary function lab during the pandemic (*Pulmonology*. 2020 Aug 5;S2531-0437[20]30175-6; *Ann Am Thorac Soc.* 2020;17[11]:1343). In general, deferring all nonessential testing and adjusting precautions and testing volume by local infection rates is recommended. Using proper personal protective equipment (PPE), including N95 respirators for staff, enhanced cleaning of rooms and PFT equipment (per manufacturer recommendations), and allowing time for adequate air exchange between tests are recommended practices. Screening for symptoms prior to testing is mandatory, with the recognition that for pulmonary patients, the specificity for COVID-19 will be poor. Finally, testing for SARS-CoV-2, generally within 72 hours, and using negative pressure rooms, has been encouraged by all, though there is variation by institution and resources.

It remains imperative that lung function labs provide a safe environment for patients and staff. However, delays related to deferrals and the increased turnover time required for cleaning and air circulation grow worse over time. As the pandemic persists, the mounting toll on our pulmonary patients looms large – so please, get vaccinated and use proper precautions.

Thomas Decato, MD, FCCP
Vice-Chair
Aaron Holley, MD, FCCP
NetWork Member

Pulmonary vascular disease

I screen, you screen, we all screen for ... PAH

Although rare in the general population, pulmonary arterial hypertension (PAH) occurs more frequently in connective tissue disease, congenital heart disease, HIV, portal hypertension, and in carriers of gene mutations of heritable PAH. Given the high morbidity and mortality, and improved outcomes with earlier diagnosis and treatment, guidelines recommend aggressive assessment and screening for PAH in these high-risk groups (Frost A, et al. *Eur Respir J.* 2019; 53:1801904).

Dr. Mullin

Effective PAH screening algorithms have been developed in systemic sclerosis. The best validated screening tool is the DETECT algorithm (Coghlan JG, et al. *Ann Rheum Dis.* 2014;73:1340), which uses clinical, laboratory, and pulmonary function test parameters in conjunction with echocardiographic findings to recommend right heart catheterization (RHC) for PH diagnosis. Multimodal assessments are more sensitive than echocardiography alone in diagnosing PAH in systemic sclerosis (Hao Y, et al. *Arthritis Res Ther.* 2015;17:7) and should be developed in other at-risk cohorts.

Recently, the DELPHI-2 study prospectively screened 55 asymptomatic adult carriers of a BMPR2 mutation- the most common genetic mutation in heritable PAH- for minimum of 2 years (Montani D, et al. *Eur Respir J.* 2020 Dec 30;2004229. doi: 10.1183/13993003.04229-2020). Using predefined symptomatic, echocardiographic, and cardiopulmonary exercise testing criteria for referral for RHC, the incidence of PAH was 2.3% per year. This study lays the foundation for a multimodal approach to screening carriers of BMPR2 mutations and emphasizes the importance of genetic counseling for idiopathic and familial PAH patients to identify mutation carriers who stand to benefit from appropriate PAH screening.

Christopher J. Mullin, MD, MHS
Steering Committee Member

Message from CHEST 2021 Co-Chair, Chris Carroll, MD, FCCP

A little over a year ago, none of us imagined we'd be where we are right now. The pandemic has deeply affected us all, and there have been so many losses, both professional and personal. I'm proud of how our CHEST community responded to the pandemic. The incredibly rapid pace of knowledge acquisition and the speed at which we disseminated that knowledge took a lot of combined effort, but that's nothing new to our CHEST community.

Throughout the pandemic, CHEST pushed digital education with an array of webinars, podcasts, bite-sized educational modules, and infographics. We held a highly successful, well-received CHEST 2020 online conference with just a few months of planning. I'm so excited to take what we learned about offering high-quality, digital education and turn that into a hybrid meeting for CHEST 2021 that meets the educational needs of every participant!

At CHEST 2021, you will be presented with the latest in pulmonary, critical care, and sleep medicine for clinicians at all levels. Whether you are a trainee or an experienced clinician, there is something to learn at CHEST 2021. We are packing the agenda with experiences from live learning and simulation to high-quality education sessions and smaller problem-based learning classes.

Dr. Carroll

On top of this, you have an amazing opportunity to network and reconnect with colleagues you haven't seen in months! Whether at Experience CHEST, in the gaming area, the Trainee and Transition Lounge, and more, CHEST 2021, as always, is the best at providing top-tier education, team-based learning, and community connections.

This will be the first hybrid meeting put on by CHEST. We came to the decision knowing that while some people are hungry to get back to having an in-person experience, others found that an online conference better fits their needs. I strongly encourage you to join us October 17-20 in Orlando, Florida, to experience the networking and growth opportunities that come from attending in person. We are following strict protocols, as recommended by the CDC, and will be requiring all attendees to attest to being vaccinated. However, if travel isn't possible, join us for livestreamed, immersive digital learning from wherever you are in the world. Regardless of your choice, both options will allow you to engage in fun experiences, learn, and connect.

As Co-Chair of CHEST 2021, I'd like to personally invite you to participate, whether this is your first time or you've lost count how many times you've attended our annual meeting. The community at CHEST is what makes the CHEST conference special, and we are proud to be able to keep you all connected despite geographic restrictions.

Looking forward to seeing you there and connecting on Twitter at #CHEST2021.

Chris Carroll, MD, FCCP
Co-Chair, CHEST 2021

BREZTRI is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

RELEASE THE POWER OF PROTECTION WITH BREZTRI[1]

In Study 1 (52 weeks), BREZTRI significantly reduced the annual rate of moderate or severe COPD exacerbations vs LAMA/LABA (rate ratio=0.76; *P*<0.0001) and ICS/LABA (rate ratio=0.87; *P*=0.0027).[2]
Annual rate estimate: BREZTRI 1.08; LAMA/LABA 1.42; ICS/LABA 1.24.[2]

For your patients with COPD
BREZTRI is now covered without restrictions* for 135 million commercial and Part D patients.†

*"Without Restrictions" is defined as no prior authorizations or step therapy. Quantity limits may apply.
†"Patients" is defined as covered lives (Commercial, EGWP, Employer, Fed Prog, FEHBP, HIX, Medicare MA, Medicare PDP, Medicare SN, Medi-Medi, Municipal Plan, PACE, PBM, Pvt HIX, Union) at Tiers 1-7 in the nation, as calculated by Fingertip Formulary® as of 2/8/2021.

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IMPORTANT SAFETY INFORMATION

- BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients
- BREZTRI is not indicated for treatment of asthma. Long-acting $beta_2$-adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD
- BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting $beta_2$-agonist
- BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation
- Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap
- Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI
- Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy
- Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur
- If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy
- Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy
- Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

Study 1 design[2]: 52-week, Phase 3, randomized 1:1:1:1, double-blind, multicenter, parallel-group trial of 8588 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=2157), BUD/GLY/FORM MDI 160/18/9.6 mcg (n=2137), GLY/FORM MDI 18/9.6 mcg (n=2143), and BUD/FORM MDI 320/9.6 mcg (n=2151), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies, and had a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the annual rate of moderate or severe COPD exacerbations. Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations as those resulting in hospitalization or death.

BREZTRI is administered as 2 inhalations twice daily.

References: 1. BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very severe COPD. *N Engl J Med.* 2020;383(1):35-48.

BREZTRI is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

- Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content
- Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines
- Be alert to hypokalemia or hyperglycemia
- Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.3%) and muscle spasms (3.3%)
- BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system
- BREZTRI should be administered with caution to patients being treated with:
  - Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
  - Adrenergic drugs (may potentiate effects of formoterol fumarate)
  - Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
  - Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
  - Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI
- Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

Please see Brief Summary of Prescribing Information on adjacent pages.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

BREZTRI
AEROSPHERE™
(budesonide 160 mcg, glycopyrrolate 9 mcg and formoterol fumarate 4.8 mcg) Inhalation Aerosol

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BREZTRI AEROSPHERE™

(budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION.
For full Prescribing Information, see package insert.

INDICATIONS AND USAGE
BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Limitations of Use:
BREZTRI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

CONTRAINDICATIONS
BREZTRI AEROSPHERE is contraindicated in patients who have demonstrated hypersensitivity to budesonide, glycopyrrolate, formoterol, or any of the excipients *[see Warnings and Precautions (5.11) and Description (11) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations, Death
The safety and efficacy of BREZTRI AEROSPHERE in patients with asthma have not been established. BREZTRI AEROSPHERE is not indicated for the treatment of asthma.

Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

Deterioration of Disease and Acute Episodes
BREZTRI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BREZTRI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BREZTRI AEROSPHERE in this setting is not appropriate.

BREZTRI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREZTRI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREZTRI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting $beta_2$-agonist becomes less effective or the patient needs more inhalations of short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of BREZTRI AEROSPHERE should not be increased beyond the recommended dose.

Avoid Excessive Use of BREZTRI AEROSPHERE and Avoid Use with other Long-Acting $Beta_2$-Agonists
As with other inhaled drugs containing $beta_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Patients using BREZTRI AEROSPHERE should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Oropharyngeal Candidiasis
BREZTRI AEROSPHERE contains budesonide, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products containing budesonide. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREZTRI AEROSPHERE continues. In some cases, therapy with BREZTRI AEROSPHERE may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of BREZTRI AEROSPHERE to help reduce the risk of oropharyngeal candidiasis.

Pneumonia
Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

In a 52-week trial of subjects with COPD (n = 8,529), the incidence of confirmed pneumonia was 4.2% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 2144), 3.5% for budesonide, glycopyrrolate and formoterol fumarate [BGF MDI 160 mcg/18 mcg/9.6 mcg] (n = 2124), 2.3% for GFF MDI 18 mcg/9.6 mcg (n = 2125) and 4.5% for BFF MDI 320 mcg/9.6 mcg (n = 2136).

Fatal cases of pneumonia occurred in 2 subjects receiving BGF MDI 160 mcg/18 mcg/9.6 mcg, 3 subjects receiving GFF MDI 18 mcg/9.6 mcg, and no subjects receiving BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg.

In a 24-week trial of subjects with COPD (n = 1,896), the incidence of confirmed pneumonia was 1.9% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 639), 1.6% for glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg] (n = 625) and 1.9% for budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg] (n = 320). There were no fatal cases of pneumonia in the study.

Immunosuppression and Risk of Infections
Patients who are using drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREZTRI AEROSPHERE may provide control of COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare practitioner for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREZTRI AEROSPHERE. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREZTRI AEROSPHERE. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to BREZTRI AEROSPHERE may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression
Inhaled budesonide is absorbed into the circulation and can be systemically active. Effects of budesonide on the HPA axis are not observed with the therapeutic doses of budesonide in BREZTRI AEROSPHERE. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9) and Drug Interactions (7.1) in the full Prescribing Information]*.

Because of the possibility of significant systemic absorption of ICS, patients treated with BREZTRI AEROSPHERE should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be initiated as needed.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of BREZTRI AEROSPHERE with long-term ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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

Hypersensitivity Reactions including Anaphylaxis
Immediate hypersensitivity reactions have been reported after administration of budesonide, glycopyrrolate or formoterol fumarate, the components of BREZTRI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips, and face), urticaria, or skin rash, BREZTRI AEROSPHERE should be stopped at once and alternative treatment should be considered *[see Contraindications (4) in the full Prescribing Information]*.

Cardiovascular Effects
Formoterol fumarate, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

If such effects occur, BREZTRI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, BREZTRI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

In a subset of COPD patients in a 24-week trial with a 28-week safety extension that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg and GFF MDI 18/9.6 mcg, the effects on BMD endpoints were evaluated. BMD evaluations were performed at baseline and 52-weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean percent changes in BMD from baseline was -0.1% for BREZTRI AEROSPHERE 320/18/9.6 mcg and 0.4% for GFF MDI 18/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma
Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. BREZTRI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI AEROSPHERE long term.

In a 52-week trial that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg, GFF MDI 18/9.6 mcg, and BFF MDI 320/9.6 mcg in subjects with COPD, the incidence of cataracts ranged from 0.7% to 1.0% across groups.

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist therapies may produce transient hyperglycemia in some patients.

ADVERSE REACTIONS

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

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression and risk of infections *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10) in the full Prescribing Information]*
- Hypersensitivity reactions including anaphylaxis *[see Contraindications (4) and Warnings and Precautions (5.11) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma and cataracts *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

Clinical Trials Experience

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

The safety of BREZTRI AEROSPHERE is based on the safety data from one 52-week exacerbation trial (Trial 1) and one 24-week lung function trial with a 28-week safety extension study, resulting in up to 52 weeks of treatment (Trial 2). In Trials 1 and 2, a total of 2783 subjects have received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trials 1 and 2, subjects received one of the following treatments: BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg], or budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg]. Each treatment was administered twice daily.

In Trial 1, a 52-week, randomized, double-blind clinical trial, a total of 2144 subjects with COPD received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 64.7 years, 84.9% Caucasian, 59.7% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trial 2, a 24-week, randomized, double-blind clinical trial, with a 28-week long-term safety extension resulting in up to 52 weeks of treatment, a total of 639 subjects received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 65.2 years, 50.1% Caucasian, 71.2% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

The incidence of adverse reactions from the 52-week trial (Trial 1) is presented in Table 1 for subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, GFF MDI 18 mcg/9.6 mcg, or BFF MDI 320 mcg/9.6 mcg.

Table 1: Adverse reactions occurring at an incidence of ≥ 2% of subjects and more common in BREZTRI AEROSPHERE compared to GFF MDI and BFF MDI (Trial 1)

Adverse Reaction	BREZTRI AEROSPHERE[1] 320 mcg/18 mcg/9.6 mcg N=2144 (%)	GFF MDI[1] 18 mcg/9.6 mcg N=2125 (%)	BFF MDI[1] 320 mcg/9.6 mcg N=2136 (%)
Upper Respiratory Tract Infection	123 (5.7)	102 (4.8)	115 (5.4)
Pneumonia	98 (4.6)	61 (2.9)	107 (5.0)
Back pain	67 (3.1)	55 (2.6)	64 (3.0)
Oral candidiasis	65 (3.0)	24 (1.1)	57 (2.7)
Influenza	63 (2.9)	42 (2.0)	61 (2.9)
Muscle spasms	60 (2.8)	19 (0.9)	53 (2.5)
Urinary tract infection	58 (2.7)	60 (2.8)	41 (1.9)
Cough	58 (2.7)	50 (2.4)	51 (2.4)
Sinusitis	56 (2.6)	47 (2.2)	55 (2.6)
Diarrhea	44 (2.1)	37 (1.7)	38 (1.8)

[1] BREZTRI AEROSPHERE = budesonide/glycopyrrolate/formoterol fumarate 320 mcg/18 mcg/9.6 mcg; GFF MDI = glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; BFF MDI = budesonide/formoterol fumarate 320 mcg/9.6 mcg; all treatments were administered twice daily.

In 24-week data from Trial 2, adverse reactions that occurred in subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n=639) at an incidence of ≥ 2% included dysphonia (3.3%) and muscle spasms (3.3%).

Additional Adverse Reactions

Other adverse reactions that have been associated with one or more of the individual components of BREZTRI AEROSPHERE include: hyperglycemia, anxiety, insomnia, headache, palpitations, nausea, hypersensitivity, depression, agitation, restlessness, nervousness, tremor, dizziness, angina pectoris, tachycardia, cardiac arrhythmias (e.g., atrial fibrillation, supraventricular tachycardia, and extrasystoles), throat irritation, bronchospasm, dry mouth, bruising, urinary retention, chest pain, sign or symptoms of systemic glucocorticoid steroid effects (e.g., hypofunctional adrenal gland), and abnormal behavior.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BREZTRI AEROSPHERE.

Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of BREZTRI AEROSPHERE, is via cytochrome P450 isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of a CYP3A4 inhibitor may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of BREZTRI AEROSPHERE with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BREZTRI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of beta$_2$-adrenergic agonists such as formoterol, a component of BREZTRI AEROSPHERE.

Non-Potassium Sparing Diuretics

The hypokalemia and/or ECG changes that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta$_2$-agonists, especially when the recommended dose of the beta$_2$-agonist is exceeded.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BREZTRI AEROSPHERE, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and BREZTRI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta$_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

OVERDOSAGE

No cases of overdose have been reported with BREZTRI AEROSPHERE. BREZTRI AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BREZTRI AEROSPHERE. Treatment of overdosage consists of discontinuation of BREZTRI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Budesonide

If used at excessive doses for prolonged periods, systemic corticosteroid effects, such as hypercorticism may occur *[see Warnings and Precautions (5.8) in the full Prescribing Information]*.

Glycopyrrolate

High doses of glycopyrrolate, a component of BREZTRI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation, or difficulties in voiding.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest, and even death may be associated with overdosage of formoterol fumarate.

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SLEEP STRATEGIES

Obstructive sleep apnea and COVID-19

BY ASHIMA S SAHNI, MD; AND MICHELLE CAO, DO, FCCP

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by the novel coronavirus of the year 2019 (COVID-19) has had a major impact on global health and economy. United States reported a total caseload of 28,998,834 patients and total mortality of 525,031 as of March 2021 (NPR.org; worldometer. Accessed March 8, 2021). The beginning of 2021 ushered positivity with the development of multiple highly effective SARS-CoV-2 vaccines. Although the medical world has gained much knowledge about this deadly disease, there are many unknowns and still much to be learned.

SARS-CoV-2 triggers a severe inflammatory response involving type-II pneumocytes and angiotensin-converting enzyme 2 pathway.

Two early landmark studies from Italy (Lombardy) and United States (New York City area) provided initial insight on comorbid conditions associated with increased risk of severe COVID-19 infection (Richardson S, et al. *JAMA*. 2020;323[20]:2052; Grasselli G, et al. *JAMA Intern Med*. 2020;180[10]:1345). In the United States cohort, hypertension (HTN), obesity, and diabetes (DM) were independent risk factors for severe disease, while in the Italy cohort, older age, male, COPD, hypercholesterolemia, and diabetes were independent risk factors for increased mortality. Obstructive sleep apnea (OSA) was not mentioned as a comorbid risk factor.

Dr. Sahni

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There is much speculation regarding OSA as an independent risk factor for severe COVID-19 infection. OSA is a common sleep-related breathing disorder with increased prevalence in men, older age, and higher body mass index (BMI); and OSA is associated with hypertension, obesity, and diabetes, all of which are risk factors for severe COVID-19. Because of the shared similarities in pathophysiology between OSA and COVID-19 (Tufik S, et al. J *Clin Sleep Med*. 2020;16[8]:1425), and shared comorbid conditions associated with increased risk of severe COVID-19 disease, OSA has been suggested as an independent risk factor for unfavorable COVID-19-related outcomes.

SARS-CoV-2 triggers a severe inflammatory response involving type-II pneumocytes and angiotensin-converting enzyme 2 pathway. OSA is characterized by intermittent hypoxia and sleep fragmentation, leading to a cascade of systemic inflammatory response involving oxidative stress, pro-inflammatory cytokines, endothelial dysfunction, and consequent cardiovascular injury (Jose RJ, et al. *Lancet Respir Med*. 2020;8[6]:e46; Saxena K, et al. *Sleep Med*. 2021;79:223). In this regard, OSA may contribute to COVID-19 "cytokine storm" by causing or exacerbating endothelial dysfunction, inflammation, and oxidative stress.

Multiple studies have recently been published on the impact of OSA on COVID-19 outcomes. The Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study was one of the initial studies that analyzed the relationship between OSA and COVID-19-related outcomes. This was a multicenter observational study involving diabetic patients hospitalized with COVID-19. The primary outcome was mechanical ventilation and/or death within 7 days of admission. Multivariate adjustment showed that age, BMI, and OSA, among other factors, were independently associated with risk of death on day 7 (Cariou B, et al. *Diabetologia*. 2020;63[8]:1500). Strausz and colleagues also evaluated OSA as an independent risk factor for severe COVID-19 in a large registry of hospital discharge patients (FinnGen study). The authors reported that although the risk of contracting COVID-19 was the same for patients with or without OSA, after adjusting for age, sex, and BMI, OSA was associated with higher risk of hospitalization (Strausz S, et al. *BMJ Open Resp Res*. 2021;8:e000845). Similar findings were confirmed by the Maas et al. study, which utilized a large socioeconomically diverse database composed of 10 hospital systems. Diagnoses and outcomes were identified by ICD-10 coding and medical record data. After adjustments for diabetes, HTN, and BMI, OSA conferred an eight-fold risk for COVID-19 infection, was associated with increased risk of hospitalization, and doubled the risk of developing respiratory failure (Maas MB, et al. *Sleep Breath*. 2020 Sep; 29:1-3. doi: 10.1007/s11325-020-02203-0).

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Peker and colleagues conducted a prospective multicenter observational study comparing clinical outcomes of severe COVID-19 infection in patients with low vs high pretest probability of having OSA based on the Berlin questionnaire. The authors reported a clinically significant risk of poorer clinical outcomes in the high pretest probability OSA group after adjustments for age, sex, and comorbidities (Peker Y, et al. *Ann Am Thorac Soc*. 2021. Feb 17. doi: 10.1513/AnnalsATS.202011-1409OC). A timely meta-analysis including 21 studies (19 with retrospective design) with 54,276 COVID-19 patients and 4,640 OSA patients concluded poor composite outcomes including severe COVID-19, intensive care unit admission, mechanical ventilatory support, and death in association with OSA (OR – 1.72 95% CI 1.55-1.91, $P < .00001$). In patients with obesity, OSA is a highly prevalent co-morbid condition. BMI, however, was not adjusted in this model (Hariyanto TI, et al. *Sleep Med*. 2021. doi: 10.1016/j.sleep.2021.03.029).

Other studies have concluded the opposite with OSA not being an independent risk factor for severe COVID-19 infection. Cade and

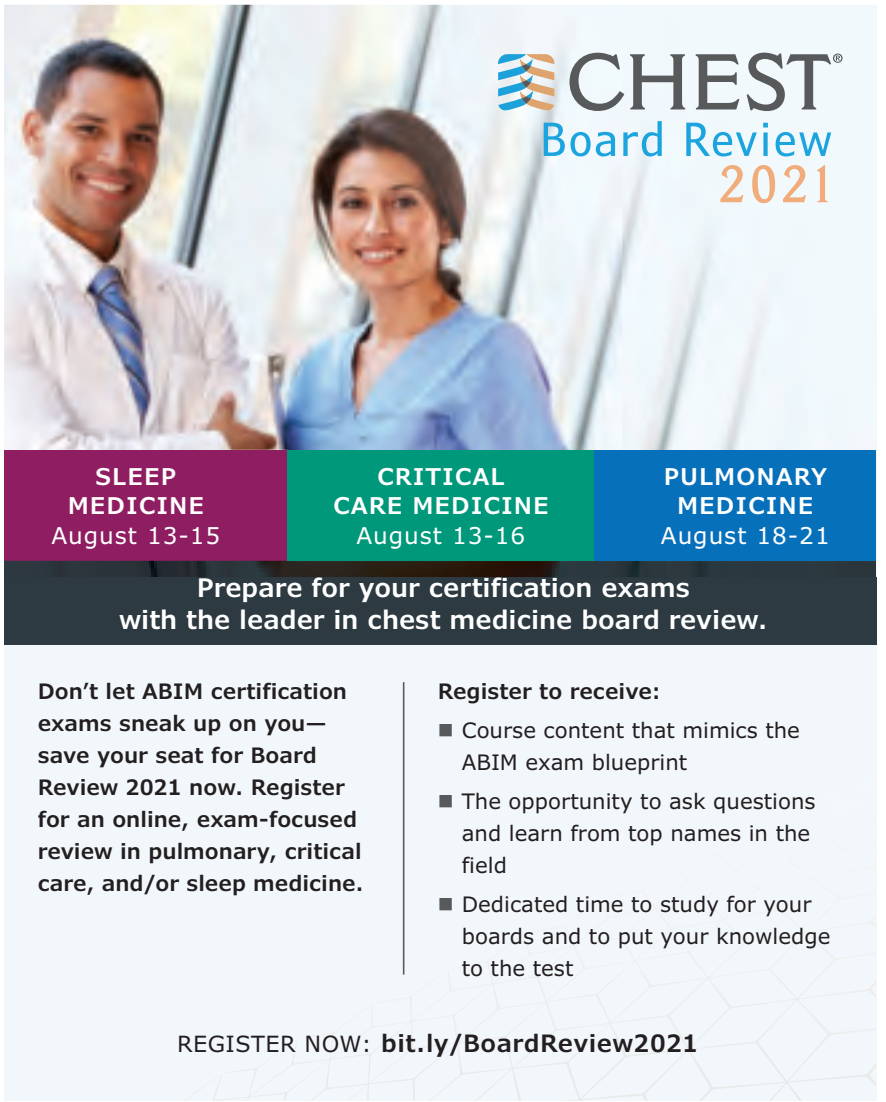
colleagues conducted a retrospective analysis from a comprehensive electronic health dataset using ICD codes to identify OSA patients with severe COVID-19 infection. A significant association between OSA and COVID-19 death was noted after adjustment for demographics (ethnicity, age, sex). However, when fully adjusted for demographics, BMI, asthma, COPD, HTN, or DM, OSA was not an independent risk factor for COVID-19-related mortality and hospitalization (Cade BE, et al. *Am J Respir Crit Care Med.* 2020;202[10]:1462). The FinnGen study (Strausz S et al. *BMJ Open Resp* Res. 2021;8:e000845). was part of a meta-analysis examining the association between OSA and severe COVID-19 with and without adjustments for BMI. This meta-analysis consisted of 15,835 COVID-19 patients including 1,294 with OSA. The authors found that OSA was a risk factor with a two-fold increased risk of severe COVID-19 infection (OR = 2.37, *P* = .021). However, after adjustments were made for BMI, this finding lost statistical significance (OR=1.55, P=.13) (Strausz S, et al. *BMJ Open Resp Res.* 2021;8:e000845).

It is worth noting that a majority of studies identified OSA by indirect and imperfect methods through chart review, ICD codes, and databases. Confirmed OSA based on formal testing with a sleep study in COVID-19 patients remains a challenge. Perhaps well performed screening questionnaires, such as STOP-Bang, Berlin, or NoSAS, can be utilized as was the case in one study. It is also unclear if outcomes of COVID-19 infection differ in patients with treated or untreated OSA, as raised by the CORONADO study. A recent cross-sectional telephone interview survey of patients with confirmed OSA in Iran alluded to higher prevalence of COVID-19 in patients with severe OSA with suggestion of lower prevalence in patients who were currently receiving OSA treatment with positive airway pressure (PAP) therapy (Najafi A, et al. *Sleep Health*. 2021 Feb;7[1]:14). This is a crucial question as PAP therapy is considered an aerosol-generating procedure (Lance CG. *Cleve Clin J Med*. 2020 May 5. doi: 10.3949/ccjm.87a.ccc003). Studies have suggested continued use of PAP therapy with additional measures to mitigate the spread of virus, since failure to use PAP could be deleterious to the patient's quality of life. Interestingly, PAP adherence seemed to have improved during the pandemic as evidenced by a telephonic survey done in New York City that showed 88% of patients with OSA used a PAP device consistently (Attias D, et al. *Eur Respir J.* 2020 Jul 30;56[1]:2001607. doi: 10.1183/13993003.01607-2020).

The jury is still out on whether OSA is a facilitator for viral replication, or an independent risk factor for poor prognosis related to COVID-19 infection, or has no clinical relevance to COVID-19.

In summary, the jury is still out on whether OSA is a facilitator for viral replication, or an independent risk factor for poor prognosis related to COVID-19 infection, or has no clinical relevance to COVID-19. COVID-19 and OSA share comorbidities and pathways leading to a systemic inflammatory cascade. Theoretically, it would make sense that OSA is a risk factor for severe COVID-19 infection; however, it remains to be proven. The recent studies are limited by retrospective and observational nature, imprecise OSA classification/diagnostic criteria, and confounded by difficult to control variables. Further research is needed to expand our understanding of OSA-induced intermittent hypoxemia, inflammation, and endothelial dysfunction that may play a role in COVID-19 morbidity and mortality. Until we have more clarity, close monitoring of OSA patients infected with COVID-19 is recommended along with implementation of safe protocols for continuation of PAP usage during the infectious phase. Identifying underlying comorbid conditions that contribute to worsening of a COVID-19 infectious course is a crucial step in improving clinical outcomes.

Dr. Sahni is Assistant Professor of Clinical Medicine, Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago. Dr. Cao is Clinical Associate Professor, Division of Sleep Medicine and Division of Neuromuscular Medicine, Department of Psychiatry and Department of Neurology, Stanford (Calif.) University.



ABIM extends MOC requirement deadlines: Prepares to launch the longitudinal knowledge assessment

BY LISA FINNEGAN
ABIM Program Manager, Physician Communications

Recognizing that caring for patients with COVID continues to be the focus of many physicians, in March, the American Board of Internal Medicine (ABIM) announced that it extended all MOC requirement deadlines until 12/31/22. For those ABIM Board Certified in Critical Care Medicine, Hospital Medicine, Infectious Disease, or Pulmonary Disease, MOC requirements have been extended until the end of 2023.

In a letter to the internal medicine community, Richard J. Baron, MD, MACP, ABIM President and CEO; and Marianne M. Green, MD, Chair of the ABIM Board of Directors, said, "We know internists and internal medicine subspecialists have been on the front lines meeting the country's needs, many experiencing the tragedy of COVID in deeply personal ways… We also recognize the high levels of stress you may have faced over the last 12 months, and that it will likely be some time until it subsides…We hope this gives you one less thing to worry about."

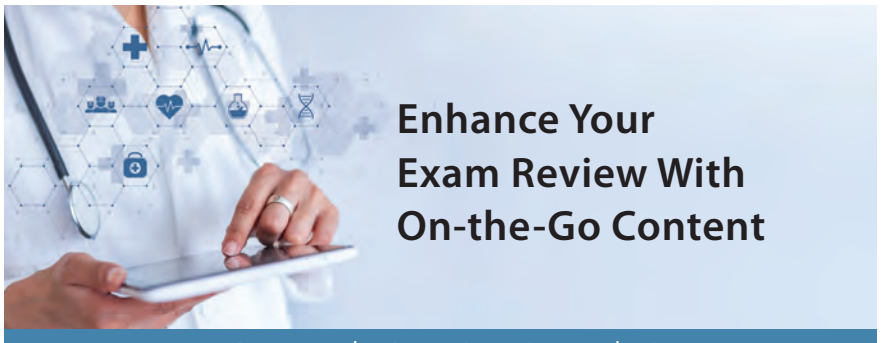
The decision means that nobody will lose ABIM certification if they are unable to complete MOC requirements this year. Recognizing every physician's situation is different, all ABIM MOC exams will be administered as scheduled in 2021 for those who wish to take one.

In January 2022, ABIM will launch a new Longitudinal Knowledge Assessment (LKA™) (www.abim.org/lka/), a more flexible and convenient way to maintain certification. Physicians who decide to delay their 2021 assessment will be able to enroll in the LKA when it rolls out (pending availability) (LKA Rollout Schedule: https://tinyurl.com/rttdd26y), or can choose to take the traditional, 10-year MOC exam if they prefer.

The LKA for Critical Care, Hospital Medicine, Infectious Disease, and Pulmonary Disease will launch in January 2023. As these were among the disciplines most impacted by COVID, additional time is needed to create the requisite content for a high-quality assessment and is why MOC requirement deadlines for these specialties is extended an additional year to provide a transition pathway to the LKA.

Through the LKA, questions can be answered on almost any internet-connected device at any time, and physicians can access all the resources used in practice (except another person). ABIM will release 30 questions each quarter that can be answered a few at a time, or all at once. Immediate feedback with rationale and reference will be provided. As long as at least 500 of the 600 questions are answered over the 5-year cycle, the LKA Participation Requirement will be met (https://tinyurl.com/ym6jdvk6).

ABIM is in the process of updating the Physician Portal in light of the MOC requirements deadline extension. If you have any questions about your requirements, call 1-800-441-ABIM or email request@abim.org. For further information about the LKA, visit abim.org/lka/.



CHEST Foundation reimagines events during the pandemic

Feeling lonely is one of the biggest challenges that we are faced with during this pandemic. It doesn't matter who you are – a patient, a caregiver, or a physician – it affects us all.

Social distancing practices make it almost impossible to host in-person gatherings, which is hard on everyone, but as a philanthropic organization that focuses on community events, it's down-right devastating. Not only does the CHEST Foundation look to events to help form a sense of camaraderie among our donors, we rely on them to help fund our projects.

That's why we had to get creative last year and quickly reimagine our events in a totally new space ... cyberspace to be exact.

New takes on old favorites

We're proud to say that we hosted seven online events in 2020, including Irv Feldman's Poker Tournament, one of our most popular fundraisers. "We wanted to continue our traditions but knew we had to do it in a different format. We learned to pivot quickly and get everything online, but we then had to cross our fingers that our donors would get onboard," said Angela Perillo, Director, Development & Foundation Operations. To the foundation's delight, the events not only piqued people's interest, they brought in more than $150,000!

The impact of your ticket purchase

The foundation has a new motto in 2021: "When you attend an event, you tend to our mission." In other words, every event we host raises funds for our initiatives. "We want our donors to know that while they're having a great time, they're also doing their part in helping the foundation enable more people to get access to the resources they need. A ticket sale today might help a patient get better care tomorrow, " said Perillo.

Now's the time to attend

Several events have been planned for this spring and summer. We hope you'll join us by registering at chestfoundation.org and following #CHESTFoundation25 on social media:

- Irv's Spring Splash Poker Tournament: Thursday, May 20 at 7 pm CT
- Belmont Stakes Reception & Auction: June 5 at 5 pm CT
- Irv's Spring Splash Poker Tournament: June 18 at 7 pm CT
- Wine Tasting: June 24 at 7 pm CT
- Trivia Night: July 21 at 7 pm CT

Chestfoundation.org

CPT® and COVID-19 vaccination

BY MICHAEL E. NELSON, MD, FCCP
CHEST Physician Editorial Board Member

COVID-19 vaccination efforts were initially restricted to health department control, and physician practices were not often included as vaccination sites. However, as vaccine availability improves, physician offices will become a place where vaccines can be delivered conveniently and efficiently. It is important to understand the current and future coding and billing requirements for COVID-19 vaccination so that one's practice may be appropriately reimbursed.

The provision of COVID-19 vaccination in an office setting is not as simple as influenza or pneumonia vaccination. One can find useful information about all vaccines and specifically about COVID-19 vaccines at https://www.cdc.gov/vaccines/ed/index.html. This site includes video training modules and downloadable resources for clinical use, as well as patient education. This information is important as providing vaccinations may require a change in infrastructure, equipment, and clinical flow. It may not be financially advantageous for one's practice to provide COVID-19 vaccination.


Dr. Nelson

If the decision is made to provide COVID-19 vaccinations, there are specific CPT codes for each vaccine and its administration (Table 1). These codes are valid for the vaccines with emergency use authorization (Pfizer, Moderna, Janssen) but not yet for as yet unauthorized vaccines (AstraZeneca). Should additional vaccines be authorized, it is expected that new CPT codes will be added.

Vaccine	CPT code	Administration code	Dose schedule	Remarks
Pfizer	91300			16 years and older
		0001A (1st dose)	Day 1	
		0002A (2nd dose)	Day 21	
Moderna	91301			18 years and older
		0011A (1st dose)	Day 1	
		0012A (2nd dose)	Day 28	
AstraZeneca	91302			Not yet authorized
		0021A (1st dose)	Day 1	
		0022A (2nd dose)	Day 28	
Janssen	91303			18 years and older
		0031A (single dose)		

When a patient is vaccinated, only the administration code is used at this time. The CPT codes for the vaccine (**91300-3**) should not be used because the cost of the vaccine is currently born by the federal government. When the vaccines are available for purchase by a practice, it will then be appropriate to use the vaccine CPT code. If an evaluation and management (E/M) service is performed, the appropriate E/M service code should be reported in addition to the vaccine administration code.

For payment of the vaccine administration by Medicare, either a single claim or roster claim can be submitted. When five or more patients are vaccinated using the same vaccine on the same day, one may submit a roster claim. Instructions on how to appropriately bill the various Medicare plans can be found at https://tinyurl.com/hfya8888. Guidelines for payment by private insurers should also be reviewed as well, as they will have their own requirements. If a vaccine is given to an individual who does not have any insurance coverage, reimbursement may be available through the Provider Relief Fund. These funds were made available by legislation, including the CARES act and information about claim submittal for the uninsured can be found at https://www.hrsa.gov/CovidUninsuredClaim.

This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP
Editor in Chief

Clinical outcomes and healthcare resource utilization associated with reslizumab treatment in adults with severe eosinophilic asthma in real-world practice.
By Dr. M. Wechsler et al.

Corticosteroid therapy is associated with improved outcome in critically ill COVID-19 patients with hyperinflammatory phenotype.
By Dr. H. Qiu, et al.

Quantitative emphysema on low-dose computed tomography of the chest and risk of lung cancer and airflow obstruction: An analysis of the National Lung Screening Trial.
By Dr. M. Han, et al.

How I Do It: Endobronchial valves for the treatment of advanced emphysema.
By Dr. D-J. Slebos, et al.

Prolonged hospitalization following acute respiratory failure.
By Dr. M. Marmor, et al.

How I Do It: Assessing patients for air travel.
By Dr. J. Mandel, et al.

Development and validation of algorithms to identify pulmonary arterial hypertension in administrative data.
By Dr. K. Gillmeyer, et al.

Sleep apnea and insomnia: Emerging evidence for effective clinical management.
By Dr. J. Ong, et al.

Shades of gray: Subsolid nodule considerations and management.
By Dr. L. Azour, et al.

In memoriam

CHEST has been informed of the following deaths of CHEST members.

We extend our sincere condolences.

Noe Zamel, MD (2020)
Stuart Craig Lennox, MD (2018)
Teruo Hirose, MD, PhD, FCCP
Priscilla S. A Sarinas, MD, FCCP
Stephen Jenkinson, MD, FCCP (2021)

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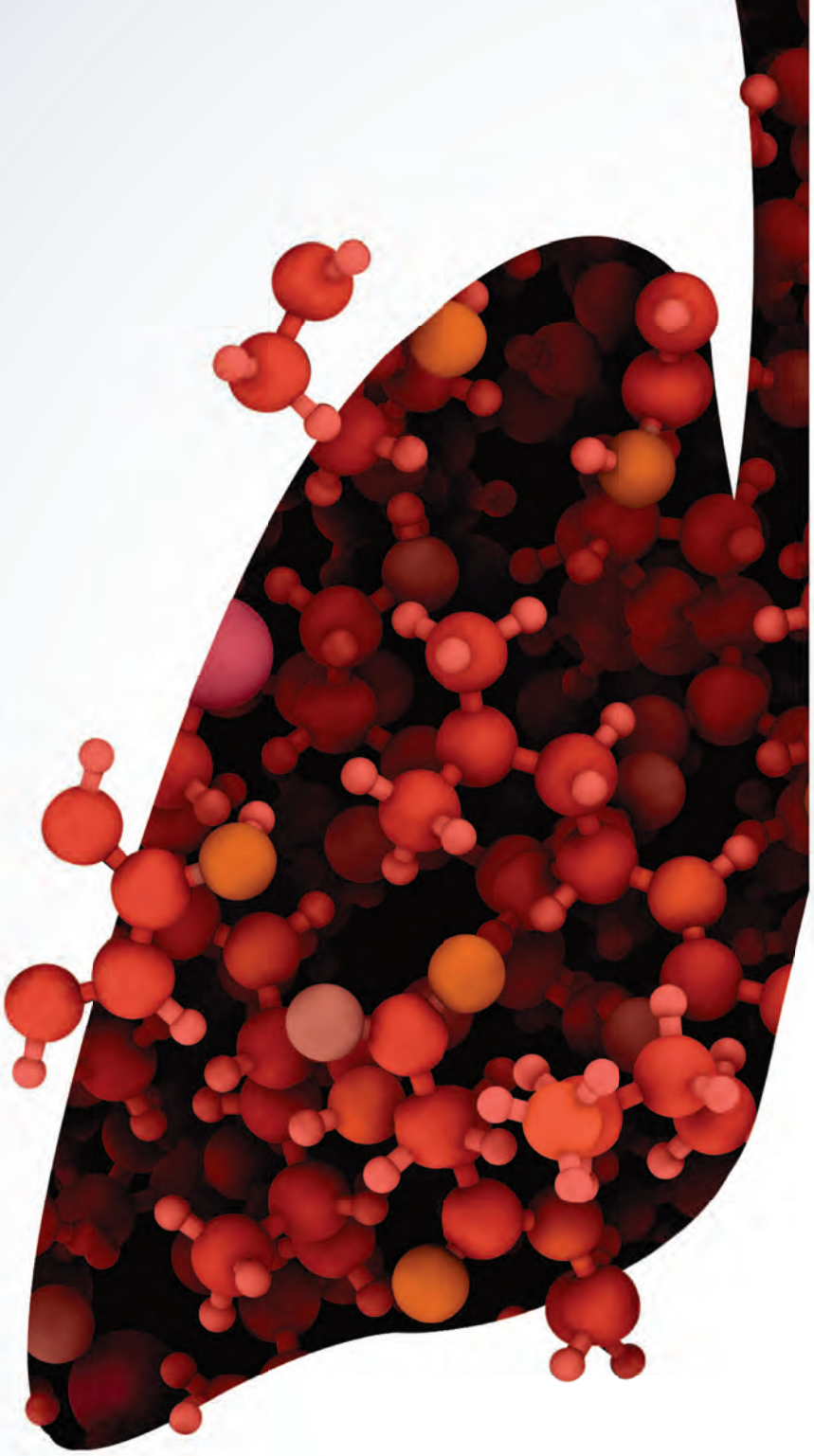

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