Go to **MDedge.com/CHESTPhysician** for the latest news on the coronavirus pandemic.

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CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Dr. Adam Gaffney

Underinsurance impedes access to care for patients with COPD, asthma

BY THOMAS R. COLLINS
MDedge News

FROM THE JOURNAL CHEST ▪ Over the past 20 years, patients with asthma and chronic obstructive pulmonary disease (COPD) have seen next to no improvement in problems of delayed care because of cost or unaffordable medications, despite wider insurance coverage since the passage of the Affordable Care Act, a new analysis shows.

The long-view analysis illuminates the ongoing problem for people with these chronic diseases despite health care legislation that was considered historic.

"That long-term scope puts recent improvements in better context – whereas we have made improvements in coverage in recent years due to the Affordable Care Act, the longer-term picture is that people with asthma and COPD are struggling to obtain needed medical care and medications despite a substantial reduction in the uninsurance rate," said Adam Gaffney, MD, MPH, assistant professor of medicine at Harvard Medical School, Boston, in an interview. Dr. Gaffney authored the paper with David Himmelstein, MD, professor of public health at City University of New York–Hunter College. The findings were published in Chest (2021 Jan 23. doi: 10.1016/j.chest.2021.01.035).

Researchers examined data from 1997 to

COPD // *continued on page 4*

Physician burnout may start with the workload

BY CALEB RANS, PHARMD
MDedge News

Workload, not personal vulnerability, may be at the root of the current physician burnout crisis, a recent study has concluded.

The cutting-edge research utilized cognitive theory and workload analysis to get at the source of burnout among practitioners. The findings indicate that, although some institutions continue to emphasize personal responsibility of physicians to address the issue, it may be the amount and structure of the work itself that trigger burnout in doctors.


Dr. Harry

"We evaluated the cognitive load of a clinical workday in a national sample of U.S. physicians and its relationship with burnout and professional satisfaction," wrote Elizabeth Harry, MD, of the University of Colorado at Denver, Aurora, and

WORKLOAD // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

President's report

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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

Patients with asthma and COPD delay care because of cost // continued from page 1

2018 for 76,843 adults with asthma and 30,548 adults with COPD, from the National Health Interview Survey, an annual survey by the Centers for Disease Control and Prevention that is based on in-person interviews and health questionnaires completed by an adult in each family.

Insurance coverage up, patients losing ground

During 1997 and 2018, there was an overall 9.3% decrease in the rate of adults with asthma who were uninsured, a significant improvement ($P < .001$). Between the pre- and post-ACA years, there was modest improvement in those putting off care because of cost, a drop of 3.8%, or going without prescriptions, a drop of 4.0%. But those improvements didn't correspond to the 7.2% drop in the uninsured rate after the ACA, contributing to the finding that there was no significant improvement over the 20 years.

For adults with COPD, it was a

slightly different story. Over those 2 decades, the uninsured rate dropped by 9.5%. But the number of patients foregoing care because of cost actually rose by 3.4%, which wasn't statistically significant, but the rate of those unable to afford needed medications rose significantly by 7.8%.

Researchers found there was improvement between the pre- and post-ACA years among COPD patients putting off care and going without medications (decreases of 6.9% and 4.5%, respectively). That adhered fairly closely with the improvement in the uninsured rate, which fell by 7.1%. But over the 20-year study period, the percentage of those needing medications they couldn't afford increased significantly by 7.8%. The rate of those delaying or foregoing care also increased, though this amount was not statistically significant.

After the ACA was created, Blacks and Hispanics with asthma had greater improvement in obtaining insurance, compared with other racial and ethnic groups. But over the 20 years, like all racial and ethnic groups, they saw no statistically significant improvement in rates of "inadequate coverage," defined in this study as either being uninsured, having to delay care because of cost, or being unable to afford needed medications.

For those with COPD, only Whites had statistically significant improvement in the number of patients with inadequate coverage after the ACA, researchers found.


Dr. Ouellette

So despite obtaining insurance, patients lost ground in managing their disease because of the growing cost of care and medication.

"Medication affordability has actually worsened for those with COPD – a worrisome development given that medication nonadherence worsens outcomes for these vulnerable patients," Dr. Gaffney said. "Policy makers should return to the issue of national health care reform. Both uninsurance and underinsurance undermine pulmonologists' ability to care for their patients with chronic disease. A health care system without financial barriers, in contrast, might well improve these patients' outcomes, and advance health equity."

Insurance is no guarantee to access

Daniel Ouellette, MD, FCCP, a pulmonary and critical care specialist at Henry Ford Health System in Detroit, said it's not surprising that access to care remains a problem despite the Affordable Care Act.

"It covers the hospitalizations and ER visits – patients in this segment of society were getting cared for there anyway," he said. "And what the ACA didn't always do was provide adequate prescription coverage or cover these outpatient gaps. So even though the patients have the ACA they still have unaffordable prescriptions, they still can't buy them, and they still can't pay for their outpatient clinic if they have a $500 or $1,000 deductible." These patients also continue to struggle with more fundamental issues that affect access to care, such as lack of transportation and poor health literacy.

At Henry Ford, pharmacists work with patients to identify medications

Continued on following page

COVID cases severely undercounted

BY CAROLYN CRIST

Large numbers of COVID-19 cases have been undetected and unreported, which has resulted in severe undercounting of the total number of people who have been infected during the pandemic, according to a new study published in the journal *PLOS ONE* (2021 Feb 8. doi: 10.1371/journal.pone.0246772).

In the United States, the number of COVID-19 cases is likely three times that of reported cases. According to the study, more than 71 million Americans have contracted the virus during the pandemic, and 7 million were infected or potentially contagious last week.

Public health officials rely on case counts to guide decisions, so the undercounting should be considered while trying to end the pandemic.

"The estimates of actual infections reveal for the first time the true severity of COVID-19 across the U.S. and in countries worldwide," Jungsik Noh, PhD, a bioinformatics professor at the University of Texas Southwestern Medical Center, said in a statement.

Dr. Noh and colleague Gaudenz Danuser, PhD, created a computational model that uses machine-learning strategies to estimate the actual number of daily cases in the United States and the 50 most-infected countries.

The model pulls data from the Johns Hopkins University database and the COVID Tracking Project, as well as large-scale surveys conducted by the Centers for Disease Control and Prevention and several states. The algorithm uses the number of reported deaths, which is thought to be more accurate than the number of lab-confirmed cases, as the basis for calculations.

In 25 of the 50 countries, the "actual" cumulative cases were estimated to be 5-20 times greater than the confirmed cases. In the United States, Belgium, and Brazil, about 10% of the population has contracted the coronavirus, according to the model. At the beginning of February, about 11% of the population in Pennsylvania had current infections, which was the highest rate of any state.

"Knowing the true severity in different regions will help us effectively fight against the virus spreading," Dr. Noh said. "The currently infected population is the cause of future infections and deaths. Its actual size in a region is a crucial variable required when determining the severity of COVID-19 and building strategies against regional outbreaks.

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

Continued from previous page

covered by their insurance and work to find discounts and coupons, he said. As for the ACA, "it's a good first start, but we really need to identify what its limitations are." Locally driven, less expensive solutions might be a better way forward than costly federal initiatives.

Dr. Seay

Brandon M. Seay, MD, a pediatric pulmonologist and sleep specialist at Children's Healthcare of Atlanta, said the findings dovetail with what he has seen in the pediatric population.

"From my experience, the ACA has helped patients get their foot in the door and has helped patients decrease the possibility of serious financial burden in emergency situations, but the ability to afford medications has not changed very much," he said. When patients struggle with sufficient prescription coverage, he helps patients fight for coverage and connects them with prescription assistance programs such as GoodRx.

"Instead of focusing on the access of insurance to patients, the goal of the system should be to make care as affordable as possible," Dr. Seay said. "Access does not meet the needs of a patient if they cannot afford what they have access to. Transition to a nationalized health system where there is no question of access could help to drive down prescription drug prices by allowing the government to negotiate with pharmaceutical companies more adequately by removing the 'middle man' of the private insurance industry."

The investigators reported no financial conflicts. Dr. Ouellette and Dr. Seay reported no financial conflicts.

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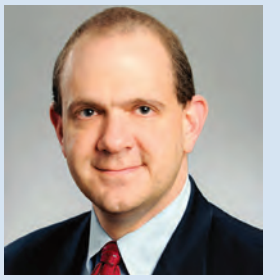

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Specialties with higher workload had higher rates of burnout

// continued from page 1

coauthors. The results were reported in the Joint Commission Journal on Quality and Patient Safety (2021 Feb. doi: 10.1016/j.jcjq.2020.09.011).

The researchers investigated whether task load correlated with burnout scores in a large national study of U.S. physicians from October 2017 to March 2018.

As the delivery of health care becomes more complex, physicians are charged with ever-increasing amount of administrative and cognitive tasks. Recent evidence indicates that this growing complexity of work is tied to a greater risk of burnout in physicians, compared with workers in other fields. Cognitive-load theory, pioneered by psychologist Jonathan Sweller, identified limitations in working memory that humans depend on to carry out cognitive tasks. Cognitive load refers to the amount of working memory used, which can be reduced in the presence of external emotional or physiological stressors. While a potential link between cognitive load and burnout may seem self-evident, the correlation between the cognitive load of physicians and burnout has not been evaluated in a large-scale study until recently.

Physician task load (PTL) was measured using the National Aeronautics and Space Administration Task Load Index (NASA-TLX), a validated questionnaire frequently used to evaluate the cognitive load of work environments, including health care environments. Four domains (perception of effort and mental, physical, and temporal demands) were used to calculate the total PTL score.

Burnout was evaluated using the Emotional Exhaustion and Depersonalization scales of the Maslach Burnout Inventory, a validated tool considered the gold standard for measurement.

The survey sample consisted of physicians of all specialties and was assembled using the American Medical Association Physician Masterfile, a record of all nearly U.S. physicians independent of AMA membership. All responses were anonymous and participation was voluntary.

Results

Among 30,456 physicians who received the survey, 5,197 (17.1%) responded. In total, 5,276 physicians were included in the analysis.

The median age of respondents was 53 years, and 61.8% self-identified as male. Twenty-four specialties were identified: 23.8% were from a primary care discipline and internal medicine represented the largest respondent group (12.1%).

Almost half of respondents (49.7%) worked in private practice, and 44.8% had been in practice for 21 years or longer.

Overall, 44.0% had at least one symptom of burnout, 38.8% of participants scored in the high range for emotional exhaustion, and 27.4% scored in the high range for depersonalization. The mean score in task-load dimension varied by specialty.

The mean PTL score was 260.9 (standard deviation, 71.4). The specialties with the highest PTL score were emergency medicine (369.8), urology (353.7), general surgery subspecialties (343.9), internal medicine subspecialties (342.2), and radiology (341.6).

Aside from specialty, PTL scores also varied by practice setting, gender, age, number of hours worked per week, number of nights on call per week, and years in practice.

The researchers observed a dose-response relationship between PTL and risk of burnout. For every 40-point (10%) reduction in PTL, there was 33% lower odds of experiencing burnout (odds ratio, 0.67; 95% confidence interval, 0.65-0.70; $P < .0001$). Multivariable analyses also indicated that PTL was a significant predictor of burnout, independent of practice setting, specialty, age, gender, and hours worked.

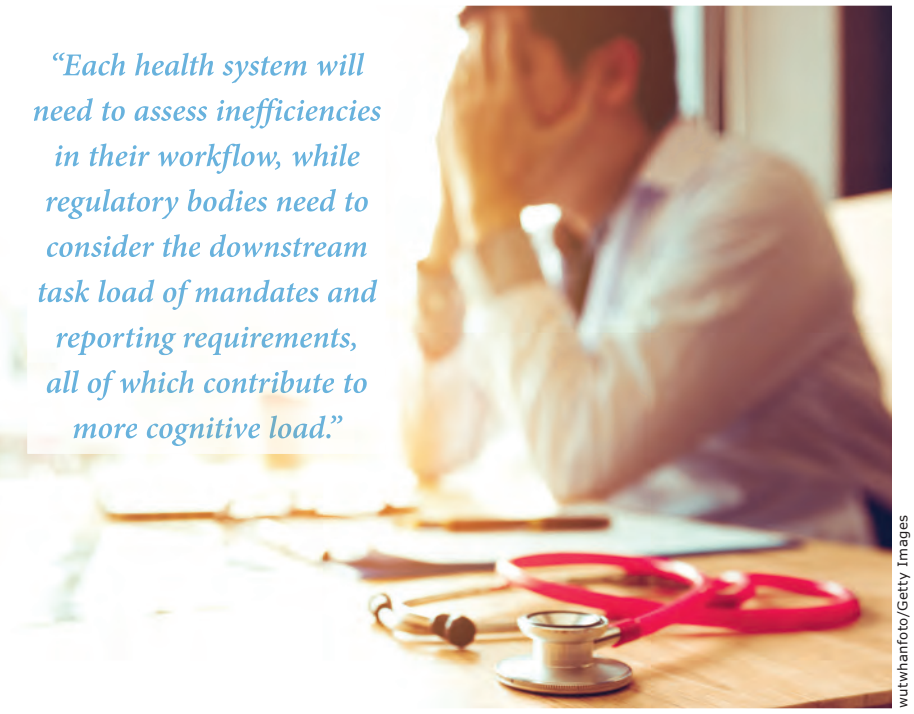
Dr. Shanafelt

Organizational strategies to reduce physician burnout

Coauthors of the study, Tait D. Shanafelt, MD, professor of medicine at Stanford (Calif.) University and Colin P. West, MD, PhD, of the Mayo Clinic in Rochester, Minn., are both experts on physician well-being and are passionate about finding new ways to reduce physician distress and improving health care delivery.

"Authentic efforts to address this problem must move beyond personal resilience," Dr. Shanafelt said in an interview. "Organizations that fail to get serious about this issue are going to be left behind and struggle in the war for talent.

"Much like our efforts to improve quality, advancing clinician well-being requires organizations to make it a priority and establish the structure, process, and leadership to promote the desired outcomes," said Dr. Shanafelt.



"Each health system will need to assess inefficiencies in their workflow, while regulatory bodies need to consider the downstream task load of mandates and reporting requirements, all of which contribute to more cognitive load."

wutwhanfoto/Getty Images

One potential strategy for improvement is appointing a chief wellness officer, a dedicated individual within the health care system that leads the organizational effort, explained Dr. Shanafelt. "Over 30 vanguard institutions across the United States have already taken this step."

Dr. West explained that conducting an analysis of PTL is fairly straightforward for hospitals and individual institutions. "The NASA-TLX tool is widely available, free to use, and not overly complex, and it could be used to provide insight into physician effort and mental, physical, and temporal demand levels," he said in an interview.

"Deeper evaluations could follow to identify specific potential solutions, particularly system-level approaches to alleviate PTL," Dr. West explained. "In the short term, such analyses and solutions would have costs, but helping physicians work more optimally and with less chronic strain from excessive task load would save far more than these costs overall."

Dr. West also noted that physician burnout is very expensive to a health care system, and strategies to promote physician well-being would be a prudent financial decision long term for health care organizations.

Dr. Harry, lead author of the study, agreed with Dr. West, noting that "quality improvement literature has demonstrated that improvements in inefficiencies that lead to increased demand in the workplace often have the benefit of reduced cost.

"Many studies have demonstrated the risk of turnover due to burnout and the significant cost of physician turnover," she said in an interview. "This cost avoidance is well worth the investment in improved operations to minimize unnecessary task load."

Dr. Harry also recommended the NASA-TLX tool as a free resource for health systems and organizations. She noted that future studies will further validate the reliability of the tool.

"At the core, we need to focus on system redesign at both the micro and the macro level," Dr. Harry said. "Each health system will need to assess inefficiencies in their workflow, while regulatory bodies need to consider the downstream task load of mandates and reporting requirements, all of which contribute to more cognitive load."

The study was supported by funding from the Stanford Medicine WellMD Center, the American Medical Association, and the Mayo Clinic department of medicine program on physician well-being. Coauthors Lotte N. Dyrbye, MD, and Dr. Shanafelt are coinventors of the Physician Well-Being Index, Medical Student Well-Being Index, Nurse Well-Being, and Well-Being Index. Mayo Clinic holds the copyright to these instruments and has licensed them for external use. Dr. Dyrbye and Dr. Shanafelt receive a portion of any royalties paid to Mayo Clinic. All other authors reported no conflicts of interest.

chestphysician@chestnet.org

COVID-19: Peginterferon lambda may prevent clinical deterioration, shorten viral shedding

BY WALTER ALEXANDER
MDedge News

In outpatients with COVID-19, peginterferon lambda has the potential to prevent clinical deterioration and shorten the duration of viral shedding, according to results of a double-blind, placebo-controlled trial (NCT04354259).

Reductions in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA were greater with peginterferon lambda than with placebo from day 3 onward in the phase 2 study led by Jordan J. Feld, MD, of the Toronto Centre for Liver Disease. The findings were reported in The Lancet Respiratory Medicine (2021 Feb 5. doi: 10.1016/S2213-2600[20]30566-X).

Fewer side effects

To date in randomized clinical trials, efficacy in treatment of COVID-19 has been shown only for remdesivir and dexamethasone in hospitalized patients, and in an interim analysis of accelerated viral clearance for a monoclonal antibody infusion in outpatients.

Activity against respiratory pathogens has been demonstrated for interferon lambda-1, a type III interferon shown to be involved in innate antiviral responses. Interferons, Dr. Feld and coauthors stated, drive induction of genes with antiviral, antiproliferative, and immunoregulatory properties, and early treatment with interferons might halt clinical progression and shorten the duration of viral shedding with reduced onward transmission. In addition, interferon lambdas (type III) use a distinct receptor complex with high expression levels limited to epithelial cells in the lung, liver, and intestine, leading to fewer side effects than other interferons, including avoiding risk of promoting cytokine storm syndrome.

The researchers investigated peginterferon lambda safety and efficacy in treatment of patients with laboratory-confirmed, mild to moderate COVID-19. Sixty patients (median age 46 years, about 60% female, about 50% White) were recruited from outpatient testing centers at six institutions in Toronto, and referred to a single ambulatory site. Patients were randomly assigned 1:1 to a single subcutaneous injection of peginterferon lambda 180 mcg or placebo within 7 days of symptom onset or, if asymptomatic, of their first positive swab. Mean time from symptom onset to injection was about 4.5 days, and about 18.5% were asymptomatic. The primary outcome was the proportion of patients negative for SARS-CoV-2 RNA on day 7 after the injection.

Benefit greater for higher baseline load

A higher baseline SARS-CoV-2 RNA concentration found in the peginterferon-lambda group was found to be significantly associated with day 7 clearance (odds ratio, 0.69 ; 95% confidence interval, 0.51-0.87; P = ·001). In the peginterferon-lambda group, also, the mean decline in SARS-CoV-2 RNA was significantly larger than in the placebo group across all time points (days 3, 5, 7, and 14). While viral load decline was 0.81-log greater in the treatment group (P = .14) by day 3, viral-load decline increased to 1.67-log copies per mL by day 5 (P = .013) and 2.42-log copies per mL by day 7 (P = .0041). At day 14, the viral decline was 1.77-log copies per mL larger in the peginterferon-lambda group (P = .048). The investigators pointed out that the difference in viral-load decline between groups was greater in patients with high baseline viral load (at or above 10^6 copies per mL). In the peginterferon-lambda high–baseline viral load group, the reduction was 7.17-log copies per mL, versus 4.92-log copies per mL in the placebo group (P = .004).

More patients SARS-CoV-2–RNA negative

By day 7, 80% of patients in the peginterferon-lambda group were negative for SARS-CoV-2 RNA, compared with 63% in the placebo group (P = .15). After baseline load adjustment, however, the peginterferon-lambda treatment was significantly associated with day 7 clearance (OR, 4.12; 95% CI, 1.15-16.73; P = .029).

Respiratory symptoms improved faster

Most symptoms in both groups were mild to moderate, without difference in frequency or severity. While symptom improvement was generally similar over time for both groups, respiratory symptoms improved faster with peginterferon lambda, with the effect more pronounced in the high–baseline viral load group (OR, 5·88; 95% CI, 0.81-42.46; P =. 079).

"Peginterferon lambda has potential to prevent clinical deterioration and shorten duration of viral shedding," the investigators concluded.

"This clinical trial is important" because it suggests that a single intravenous dose of peginterferon lambda administered to outpatients with a positive SARS-CoV-2 nasopharyngeal swab speeds reduction of SARS-CoV-2 viral load, David L. Bowton, MD, FCCP, professor emeritus, Wake Forest Baptist Health, Winston-Salem, N.C., said in an interview. He observed that the smaller viral load difference observed at day 14 likely reflects host immune responses. Dr. Bowton also noted that two placebo-group baseline characteristics (five placebo-group patients with anti–SARS-CoV-2 S protein IgG antibodies; two times more undetectable SARS-CoV-2 RNA at baseline assessment) would tend to reduce differences between the peginterferon-lambda and placebo groups. He added that the study findings were concordant with another phase 2 trial of hospitalized COVID-19 patients receiving inhaled interferon beta-1a (Lancet Respir Med. 2021;9[2]:196-206).


Dr. Bowton

"Thus, interferons may find a place in the treatment of COVID-19 and perhaps other severe viral illnesses," Dr. Bowton said.

The study was funded by the Toronto COVID-19 Action Initiative, University of Toronto, and the Ontario First COVID-19 Rapid Research Fund, Toronto General & Western Hospital Foundation.

Dr. Bowton had no disclosures. Disclosures for Dr. Feld and coauthors are listed on the Lancet Respiratory Medicine website (doi: 10.1016/S2213-2600[20]30566-X).

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ColCORONA: More questions than answers

BY PATRICE WENDLING

Science by press release and preprint has cooled clinician enthusiasm for the use of colchicine in nonhospitalized patients with COVID-19, despite a pressing need for early treatments.

As previously reported by this news organization, a Jan. 22 press release announced that the massive ColCORONA study missed its primary endpoint of hospitalization or death among 4,488 newly diagnosed patients at increased risk for hospitalization.

It also touted that use of the anti-inflammatory drug significantly reduced the primary endpoint in 4,159 of those patients with polymerase chain reaction–confirmed COVID and led to reductions of 25%, 50%, and 44%, respectively, for hospitalizations, ventilations, and death.

Dr. Tardif

Dr. Glatt

Lead investigator Jean-Claude Tardif, MD, director of the Montreal Heart Institute Research Centre, deemed the findings a "medical breakthrough."

When the preprint released a few days later (MedRxiv. 2021 Jan 27. doi: 10.1101/2021.01.26.21250494), however, newly revealed confidence intervals showed colchicine did not meaningfully reduce the need for mechanical ventilation (odds ratio, 0.50; 95% confidence interval, 0.23-1.07) or death alone (OR, 0.56; 95% CI, 0.19-1.66).

Further, the significant benefit on the primary outcome came at the cost of a fivefold increase in pulmonary embolism (11 vs. 2; $P = .01$), which was not mentioned in the press release.

"Whether this represents a real phenomenon or simply the play of chance is not known," Dr. Tardif and colleagues noted later in the preprint.

"I read the preprint on colchicine and I have so many questions," Aaron E. Glatt, MD, spokesperson for the Infectious Diseases Society of America and chief of infectious diseases, Mount Sinai South Nassau, Hewlett, N.Y., said in an interview. "I've been burned too many times with COVID and prefer to see better data.

"People sometimes say if you wait for perfect data, people are going to die," he said. "Yeah, but we have no idea if people are going to die from getting this drug more than not getting it. That's what concerns me. How many pulmonary emboli are going to be fatal versus the slight benefit that the study showed?"

The pushback to the non–peer-reviewed data on social media and via emails was so strong that Dr. Tardif posted a nearly 2,000-word letter responding to the many questions.

Chief among them was why the trial, originally planned for 6,000 patients, was stopped early by the investigators without consultation with the data safety monitoring board (DSMB).

The explanation in the letter that logistical issues like running the study call center, budget constraints, and a perceived need to quickly communicate the results left some calling foul that the study wasn't allowed to finish and come to a more definitive conclusion.

"The press release really didn't help things because it very much oversold the effect. That, I think, poisoned the well," said David Boulware, MD, MPH, professor of medicine in infectious diseases at the University of Minnesota, Minneapolis.

"The question I'm left with is not whether colchicine works, but who does it work in," he said. "That's really the fundamental question because it does seem that there are probably high-risk groups in their trial and others where they benefit, whereas other groups don't benefit. In the subgroup analysis, there was absolutely no beneficial effect in women."

According to the authors, the number needed to treat to prevent one death or hospitalization was 71 overall, but 29 for patients with diabetes, 31 for those aged 70 years and older, 53 for patients with respiratory disease, and 25 for those with coronary disease or heart failure.

Men are at higher risk overall for poor outcomes. But "the authors didn't present a multivariable analysis, so it is unclear if another factor, such as a differential prevalence of smoking or cardiovascular risk factors, contributed to the differential benefit," Rachel Bender Ignacio, MD, MPH, infectious disease specialist, University of Washington, Seattle, said in an interview.

Importantly, in this pragmatic study, duration and severity of symptoms were not reported, observed Dr. Bender Ignacio, who is also a STOP-COVID-2 investigator. "We don't yet have data as to whether colchicine shortens duration or severity of symptoms or prevents long COVID, so we need more data on that."

The overall risk for serious adverse events was lower in the colchicine group, but the difference in pulmonary embolism (PE) was striking, she said. This could be caused by a real biologic effect, or it's possible that persons with shortness of breath and hypoxia, without evident viral pneumonia on chest x-ray after a positive COVID-19 test, were more likely to receive a CT-PE study.

The press release also failed to include information, later noted in the preprint, that the MHI has submitted two patents related to colchicine: "Methods of treating a coronavirus infection using colchicine" and "Early administration of low-dose colchicine after myocardial infarction."

Reached for clarification, MHI communications adviser Camille Turbide said in an interview that the first patent "simply refers to the novel concept of preventing complications of COVID-19, such as admission to the hospital, with colchicine as tested in the ColCORONA study."

The second patent, she said, refers to the "novel concept that administering colchicine early after a major adverse cardiovascular event is better than waiting several days," as supported by the COLCOT study, which Dr. Tardif also led.

The patents are being reviewed by authorities, and "Dr. Tardif has waived his rights in these patents and does not stand to benefit financially at all if colchicine becomes used as a treatment for COVID-19," Ms. Turbide said.

Dr. Tardif did not respond to interview requests for this story. Dr. Glatt said conflicts of interest must be assessed and are "something that is of great concern in any scientific study."

Cardiologist Steve Nissen, MD, of the Cleveland Clinic said in an interview that, "despite the negative results, the study does suggest that colchicine might have a benefit and should be studied in future trials. These findings are not sufficient evidence to suggest use of the drug in patients infected with COVID-19."

"Stopping the trial for administrative reasons is puzzling and undermined the ability of the trial to give a reliable answer," Dr. Nissen said. "This is a reasonable pilot study that should be viewed as hypothesis generating but inconclusive."

Several sources said a new trial is unlikely, particularly given the cost and 28 trials already evaluating colchicine. Among these are RECOVERY and COLCOVID, testing whether colchicine can reduce the duration of hospitalization or death in hospitalized patients with COVID-19.

"We have already learned the lesson in the pandemic that early adoption of potentially promising therapies can negatively impact our ability to study and develop other promising treatments," she said.

The trial was coordinated by the Montreal Heart Institute and funded by the government of Quebec; the National Heart, Lung, and Blood Institute of the National Institutes of Health; Montreal philanthropist Sophie Desmarais; and the COVID-19 Therapeutics Accelerator launched by the Bill & Melinda Gates Foundation, Wellcome, and Mastercard. CGI, Dacima, and Pharmascience of Montreal were also collaborators. Dr. Glatt reported no conflicts of interest.

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

ColCORONA: Composite of death or hospitalization in 30 days

	Colchicine (%)	Placebo (%)	Odds ratio	95% CI
Overall cohort	4.7	5.8	0.79	0.61-1.03
PCR-confirmed patients	4.6	6.0	0.75	0.57-0.99
Men	5.8	8.4	0.67	0.48-0.95
Women	3.7	3.5	1.07	0.70-1.65

MDedge News

Note: Based on data for 4,488 newly diagnosed patients at increased risk for hospitalization.

Source: medRxiv. 2021 Jan 27. doi: 10.1101/2021.01.26.21250494

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

AstraZeneca

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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Loss of smell lingers post COVID-19

BY PAULINE ANDERSON

More than 50% of health care workers infected with SARS-CoV-2 report that their sense of smell has not returned to normal an average of 5 months post infection, new research shows.

The findings illustrate that olfactory problems are common not only during the acute COVID-19 phase but also "in the long run" and that these problems should be "taken into consideration" when following up these patients, study investigator Johannes Frasnelli, MD, professor, department of anatomy, Université du Québec à Trois-Rivières, said in an interview.

Loss of the sense of smell can affect quality of life because it affects eating and drinking, and may even be dangerous, said Dr. Frasnelli. "If your sense of smell is impaired, you may unknowingly eat spoiled food, or you may not smell smoke or gas in your home," he said. In addition, Dr. Frasnelli noted that an impaired sense of smell is associated with higher rates of depression. The findings will be presented at the annual meeting of the American Academy of Neurology in April.

'Striking' finding

Research shows that about 60% of patients with COVID-19 lose their sense of smell to some degree during the acute phase of the disease. "But we wanted to go further and look at the longer-term effects of loss of smell and taste," said Dr. Frasnelli.

The analysis included 813 health care workers in the province of Quebec. For all the patients, SARS-CoV-2 infection was confirmed through testing with a nasopharyngeal viral swab.

Participants completed a 64-item online questionnaire that asked about three senses: olfactory; gustatory, which includes tastes such as sweet, sour, bitter, salty, savory, and umami; and trigeminal, which includes sensations such as spiciness of hot peppers and "coolness" of mint.

They were asked to rate these on a scale of 0 (no perception) to 10 (very strong perception) before the infection, during the infection, and currently. They were also asked about other symptoms, including fatigue.

Most respondents had been infected in the first wave of the virus in March and April of 2020 and responded to the questionnaire an average of 5 months later.

The vast majority of respondents (84.1%) were women, which Dr. Frasnelli said was not surprising because women predominate in the health care field.

The analysis showed that average smell ratings were 8.98 before infection, 2.85 during the acute phase, and 7.41 when respondents answered the questionnaire. The sense of taste was less affected and recovered faster than did the sense of smell. Results for taste were 9.20 before infection, 3.59 during the acute phase, and 8.05 after COVID-19.

Among 580 respondents who indicated a compromised sense of smell during the acute phase, the average smell rating when answering the questionnaire was 6.89, compared to 9.03 before the infection. More than half (51.2%) reported not regaining full olfactory function.

The fact that the sense of smell had not returned to normal for half the participants so long after being infected is "novel and quite striking," said Dr. Frasnelli.

However, he noted, this doesn't necessarily mean all those with a compromised sense of smell "have huge problems." In some cases, he said, the problem "is more subtle."

Further study

Respondents also completed a chemosensory dysfunction home test (CD-HT). They were asked to prepare common household food items, such as peanut butter, sugar, salt, and vinegar, in a particular way – for example, to add sugar or salt to water – and provide feedback on how they smell and taste.

"From the questionnaires, roughly 50% said their sense of smell is still not back to normal, and when we look at the [chemosensory dysfunction] home test, we see that almost 20% of subjects indeed have pretty strong impairment of their sense of smell,"

For this CD-HT analysis, 18.4% of respondents reported having persistent loss of smell. This, Dr. Frasnelli said, adds to evidence from self-reported responses and suggests that in some cases the problem is more than senses not returning to normal.

"From the questionnaires, roughly 50% said their sense of smell is still not back to normal, and when we look at the CD home test, we see that almost 20% of subjects indeed have pretty strong impairment of their sense of smell," he said.

The results showed no sex differences, although Dr. Frasnelli noted that most of the sample were women. "It's tricky to look at the data with regard to sex because it's a bit skewed," he said.

Male respondents were older than female participants, but there was no difference in impairment between age groups. Dr. Frasnelli said this was "quite interesting," inasmuch as older people usually lose some sense of smell.

The researchers have not yet examined whether the results differ by type of health care worker.

They also have not examined in detail whether infection severity affects the risk for extended olfactory impairment. Although some research suggests that the problem with smell is more common in less severe cases, Dr. Frasnelli noted this could be because loss of smell is not a huge problem for patients battling grave health problems.

As for other symptoms, many respondents reported lingering fatigue; some reported debilitating fatigue, said Dr. Frasnelli. However, he cautioned that this is difficult to interpret, because the participants were health care workers, many of whom returned to work during the pandemic and perhaps had not fully rested.

He also noted that he and his colleagues have not "made the link" between impaired smell and the degree of fatigue.

The COVID-19 virus appears to attack supporting sustentacular cells in the olfactory epithelium, not nerve cells.

"Right now, it seems that the smell problem is not a central nervous system problem but a peripheral problem," said Dr. Frasnelli. "But we don't know for sure; it may be that the virus somehow gets into the brain and some symptoms are caused by the effects of the infection on the brain."

The researchers will extend their research with another questionnaire to assess senses 10-12 months after COVID-19.

Limitations of the study include the subjective nature of the smell and taste ratings and the single time point at which data were collected.

Confirmatory findings

Commenting on the research in an interview, Thomas Hummel, MD, professor, smell and taste clinic, department of otorhinolaryngology, Technische Universität Dresden (Germany), said the new results regarding loss of smell after COVID-19 are "very congruent" with what he and his colleagues have observed.

Research shows that up to one in five of those infected with SARS-CoV-2 experience olfactory loss. "While the numbers may vary a bit from study to study or lab to lab, I think 5%-20% of post–COVID-19 patients exhibit long-term olfactory loss," Dr. Hummel said.

His group has observed that "many more are not back to normal," which conforms with what Dr. Frasnelli's study reveals, said Dr. Hummel.

Also commenting on the research, Kenneth L. Tyler, MD, professor of neurology, University of Colorado at Denver, Aurora, and a fellow of the American Academy of Neurology, said the study was relatively large and the results "interesting."

Although it "provides more evidence there's a subset of patients with symptoms even well past the acute phase" of COVID-19, the results are "mostly confirmatory" and include "nothing super surprising," Dr. Tyler said in an interview.

However, the investigators did attempt to make the study "a little more quantitative" and "to confirm the self-reporting with their validated CD home test," he said.

Dr. Tyler wondered how representative the sample was and whether the study drew more participants with impaired senses. "If I had a loss of smell or taste, maybe I would be more likely to respond to such a survey," he said.

He also noted the difficulty of separating loss of smell from loss of taste.

"If you lose your sense of smell, things don't taste right, so it can be confounding as to how to separate out those two," he noted. The study was supported by the Foundation of the Université du Québec à Trois-Rivières and the Province of Quebec. Dr. Frasnelli has received royalties from Styriabooks in Austria for a book on olfaction published in 2019 and has received honoraria for speaking engagements. Dr. Hummel and Dr. Tyler have disclosed no relevant financial relationships.

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

Health care workers not immune to vaccine hesitancy

BY DOUG BRUNK

Nearly 60% of those working in a large health care system expressed their intent to roll up their sleeves to receive the COVID-19 vaccine, but about one-third were unsure of doing so.

Moreover, 54% of direct care providers indicated that they would take the vaccine if offered, compared with 60% of non–care providers.

The findings come from what is believed to be the largest survey of health care provider attitudes toward COVID-19 vaccination, published online Jan. 25 in Clinical Infectious Diseases (2021. ciab054. doi: 10.1093/cid/ciab054).

"We have shown that self-reported willingness to receive vaccination against COVID-19 differs by age, gender, race, and hospital role, with physicians and research scientists showing the highest acceptance," Jana Shaw, MD, MPH, State University of New York, Syracuse, the study's corresponding author, told this news organization. "Building trust in authorities and confidence in vaccines is a complex and time-consuming process that requires commitment and resources. We have to make those investments as hesitancy can severely undermine vaccination coverage. Because health care providers are members of our communities, it is possible that their views are shared by the public at large."

For the study, Dr. Shaw and her colleagues emailed an anonymous survey to 9,565 employees of State University of New York Upstate Medical University, Syracuse, an academic medical center that cares for an estimated 1.8 million people. The survey, which contained questions intended to evaluate attitudes, belief, and willingness to get vaccinated, took place between Nov. 23 and Dec. 5, 2020, about a week before the U.S. Food and Drug Administration granted the first emergency use authorization for the Pfizer-BioNTech BNT162b2 mRNA vaccine.

Survey recipients included physicians, nurse practitioners, physician assistants, nurses, pharmacists, medical and nursing students, allied health professionals, and nonclinical ancillary staff.

Of the 9,565 surveys sent, 5,287 responses were collected and used in the final analysis, for a response rate of 55%. The mean age of respondents was 43, 73% were female, 85% were White, 6% were Asian, 5% were Black/African American, and the rest were Native American, or Native Hawaiian/Pacific Islander, or from other races. More than half of respondents (59%) reported that they provided direct patient care, and 32% said they provided care for patients with COVID-19.

Of all survey respondents, 58% expressed their intent to receive a COVID-19 vaccine, but this varied by their role in the health care system. For example, in response to the statement, "If a vaccine were offered free of charge, I would take it," 80% of scientists and physicians agreed that they would, while colleagues in other roles were unsure whether they would take the vaccine, including 34% of registered nurses, 32% of allied health professionals, and 32% of master's-level clinicians. These differences across roles were significant (*P* less than .001).

The researchers also found that direct patient care or care for COVID-19 patients was associated with lower vaccination intent. For example, 54% of direct care providers and 62% of non–care providers indicated they would take the vaccine if offered, compared with 52% of those who had provided care for COVID-19 patients vs. 61% of those who had not (*P* less than .001).

"This was a really surprising finding," said Dr. Shaw, who is a pediatric infectious diseases physician at SUNY Upstate. "In general, one would expect that perceived severity of disease would lead to a greater desire to get vaccinated. Because our question did not address severity of disease, it is possible that we oversampled respondents who took care of patients with mild disease (i.e., in an outpatient setting). This could have led to an underestimation of disease severity and resulted in lower vaccination intent."

The authors have disclosed no relevant financial relationships. Dr. Milstone disclosed that he has received a research grant from Merck, but it is not related to vaccines.

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

Short sleep predicts dementia and all-cause mortality

BY HEIDI SPLETE
MDedge News


amenic181/Getty Images

More evidence has emerged linking sleep deficiency, dementia, and mortality.

"Sleep disturbance and insufficiency have been shown to be associated with both the development and progression of Alzheimer's disease and with all-cause mortality," wrote Rebecca S. Robbins, PhD, of Brigham and Women's Hospital, Boston, and colleagues. However, research on this topic has yielded conflicting results, and "few studies have included a comprehensive set of sleep characteristics in a single examination of incident dementia and all-cause mortality."

In a study published in Aging (2021 Feb 11;13[3]:3254-68. doi: 10.18632/aging.202591), the researchers identified 2,812 adults aged 65 years and older from the National Health and Aging Trends Study (NHATS), a nationally representative longitudinal study of Medicare beneficiaries aged 65 years and older in the United States.

Participants completed surveys about sleep disturbance and duration in 2013 (1,575 individuals) and in 2014 (1,237 individuals), and the researchers examined the relationship between sleep disturbance and deficiency and incident dementia and all-cause mortality over the next 5 years. The average age of the study participants was 76.9 years, 60% were women, and 72% were White.

Overall, approximately 60% of the participants reported never or rarely having problems with alertness, approximately half said that they rarely or never napped, and more than half said they fell asleep in 15 minutes or less. Approximately 70% rated their sleep quality as good or very good, and more than 90% said they rarely or never snored.

"Short sleep duration was a strong predictor of both incident dementia and all-cause mortality, suggesting this may be a sleep characteristic that is important – over and above the other predictors – of adverse outcomes among older adults."

The researchers examined the relationships between sleep characteristics and the development of incident dementia over 5 years. In a fully adjusted Cox multivariate analysis, individuals who slept 5 hours or less per night had approximately twice the risk for incident dementia as those who slept longer (hazard ratio, 2.04); risk of dementia also was higher among those who took 30 minutes or longer to fall asleep (HR, 1.45).

In addition, the risk of all-cause mortality was significantly higher among individuals who reported difficulty maintaining alertness some days or most days/every day (HR, 1.49 and HR, 1.65, respectively), routinely napping some days or most days/every day (HR, 1.38 and HR, 1.73, respectively), poor or very poor sleep quality (HR, 1.75), and sleeping 5 hours or less each night (HR, 2.38).

The study findings were limited by several factors including a population representing only one-quarter of the NHATS cohort, which prevented nationally representative estimates, the availability of only 2 years of sleep data, and small sample size for certain response categories, the researchers noted.

However, "our study offers a contribution to the literature on sleep among aging populations in its assessment of incident dementia and all-cause mortality and a range of sleep characteristics among older adults," they said. In particular, "short sleep duration was a strong predictor of both incident dementia and all-cause mortality, suggesting this may be a sleep characteristic that is important – over and above the other predictors – of adverse outcomes among older adults," and future areas for research include the development of novel behavioral interventions to improve sleep in this population.

The study was supported in part by the National Institute for Occupational Safety and Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; and the Brigham Research Institute Fund to Sustain Research Excellence. Lead author Dr. Robbins disclosed fees from Denihan Hospitality, Rituals Cosmetics, Dagmejan, Asystem, and SleepCycle. Several coauthors disclosed relationships with multiple pharmaceutical companies, and support from various philanthropic organizations.

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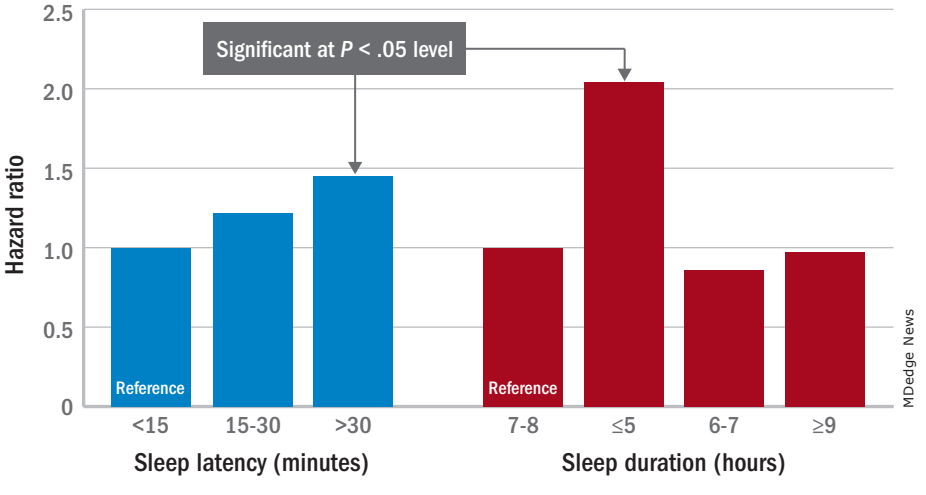
Association between sleep disturbance and incident dementia



Note: Based on data for 2,812 Medicare beneficiaries included in the 2013 and 2014 National Health and Aging Trends Study surveys.

Source: Aging. 2021 Feb 11;13(3):3254-68. doi: 10.18632/aging.202591

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

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President's report

BY STEVEN Q. SIMPSON, MD, FCCP

As I write, it is 1 degree Fahrenheit and dreary in Kansas City, where I live. That's minus 17 degrees Celsius for many of you. I hope that it is cheerier and bordering on springtime when you're reading. You'll understand, though, why I say Happy 2021! 2020 was a humdinger in many ways.

One of those ways, of course, was the COVID-19 pandemic, which wrought so many things – face masks, social distancing, steep learning curves, over 300,000 excess deaths, and new vaccines. For CHEST, it meant that two of our most important educational opportunities of the year, board review and the annual meeting, were held virtually. Dr. Levine has already written about the board reviews, so I'll focus on the annual meeting, held in late October.

In many ways, the meeting was a success. We had over 6,800 attendees. There were 88 live online sessions, 22 that were semi-live, and 160 prerecorded sessions. For presenters, this was simultaneously both easy and difficult. They had to ensure that their recording equipment and their Internet access were of sufficient quality, and if prerecorded, the sessions had to be finished weeks ahead of time. But the presentations could be given from presenters' homes or from their normal work offices. For attendees, the ability for nonsimultaneous playback allowed for fitting the meeting into a work-life schedule. In fact, at least one friend related that he watched sessions with a grandchild on his lap.

However, it meant a lack of opportunities to ask clarifying questions of the presenters, which is a common activity at the end of a session, and the opportunity to see and catch up with old friends and colleagues was missing. Simulations, of course, could not be hands-on, but virtual educational games matured significantly. The satisfaction scores from both attendees and faculty were good, if slightly below our usual scores for live meetings. They told us that we all prefer our in-person meetings, but that content is deliverable and receivable in an online format. Overall, we have to consider the CHEST 2020 online platform to be a successful endeavor.

Which brings me to our plans for future meetings. The Board of Regents discussed the alternatives for CHEST 2021. Should we hold a live meeting in Vancouver, as planned? Should we hold another online meeting like the one we just discussed? None of us has the crystal ball that tells us exactly how COVID-19 is going to develop. We don't know exactly how many people will be vaccinated either north or south of the US-Canada border.

While those of us who care for patients in the United States have had the opportunity to be vaccinated, we don't know if the professional staff from CHEST headquarters who travel to the annual meeting will be vaccinated, even though that prospect is currently looking very reasonable. We don't know if the Canadian government will be allowing US residents to visit Canada without quarantine. There are just quite a few things that we can't know. However, convention centers need to know if we will be there, and we needed to decide.

In the end, a couple of things swayed us—the unexpected availability of a US convention center and uncertainty about travel to Canada. We are planning to hold CHEST 2021 in Orlando, Florida, during our usual late October time frame. CHEST 2021 is slated to be the first in-person pulmonary, critical care, and sleep conference to be held in the United States in 2 years.

Dr. Simpson

The Executive Program Committee has met, and program selections have been made. Very soon, invitations will go to our prospective faculty, and we will be underway. We are planning CHEST 2021 as what we call a "hybrid" meeting, a meeting that will provide an excellent experience whether one attends in person at the Orlando Convention Center or partakes of the meeting from home. Some sessions will be broadcast live and others will be prerecorded. Needless to say, the experience will not be equal for in-person and at-home learners, but it will be equitable. Regardless of how you choose to partake, CHEST 2021 will have excellent content to suit your needs. This plan also allows us the ability to convert to a fully online meeting, should the COVID-19 circumstances dictate that we must. Having sat in on the program committee meetings, I am excited about what we have to offer. So, dig around and find your old mouse ears or your red forehead scar. CHEST 2021 will be a dynamite experience for us all to share.

Our board review sessions, which are also among the most highly valued of CHEST activities, will be different out of necessity. Again, decisions had to be made many months ahead of time, and we have chosen to hold our board reviews online again this year. COVID-19 uncertainties certainly play into our decision to not put attendees in a room together. However, the ability to play and replay, slow down and speed up video content, and ability to watch any session any time are all well suited to reviewing for an examination. We think this is the appropriate decision for 2021, but we may be back together again for future sessions. Frankly, we are listening to hear which format our attendees like more. And, we are plotting how to make the online platform review even better.

The Board of Regents has been hard at work on a lot of fronts, but I want to focus on one of them, for now. It is important to the Board of Regents and to me, personally, that CHEST be the single most inclusive and diverse professional medical society, bar none. It is of utmost importance that we remove any barriers that might have inadvertently been put into place that would hamper the success of any of our members or their patients. In other words, we hope to find any implicit biases in attitude and behavior and to illuminate and remedy them. We have begun the process by focusing on what CHEST is all about – making a difference with our patients and corporate self and being an inclusive and diverse professional organization.

We believe that we must look at ourselves in three separate, but related, ways. We must examine our patient-facing side and the ways in which we help our members to serve their patients. We must examine our headquarters and our hiring, working, and promoting practices to ensure an inclusive and welcoming environment for the staff who do our day to day business. Finally, we must examine ourselves and our member-based organization, to ensure that all can participate freely in CHEST opportunities and, for those who aspire to lead our organization, to ensure that there are no implicit biases that hold them back.

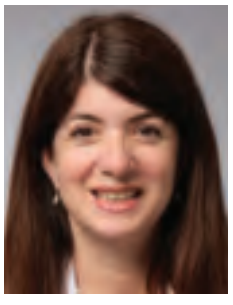
We began the process with a series of regional listening sessions across the United States, sponsored by the CHEST Foundation, in which we heard from both patients and community leaders of color. We learned of challenges that our patients face in accessing care, communicating with their doctors, and obtaining the medications they need for their illness. Our professional staff has organized an anti-racism task force and is working to ensure that we can be proud of a diverse and inclusive work environment. For our members, we have held two board development sessions, so that our Board of Regents can examine us and our attitudes toward race and toward inclusiveness in our organization. We will soon be holding a listening session with CHEST members of color with the express purpose of allowing those of us who are not persons of color to better understand the challenges faced by our members and to understand where organizational changes could be necessary to help make their professional lives better. As a long time CHEST member, I believe that CHEST is not purposefully exclusive of anyone. We are, nevertheless, a part of the larger fabric of society, and because of that, we are subject to having implicit biases and practices as an organization. Our best path to be aware of them and to deal with them is to hear from our members who experience them, and we shall.

I will end on a note that is somber but important. In the past year, we have all lost friends and colleagues with whom we worked side by side, to COVID-19. Many of them have been CHEST members. Because of the pandemic, we have often not been able to mourn those we have cared about in the same ways that we normally would, in the company of friends and family. Yet, it is important for us to remember our colleagues and to share our memories. So, we established CHEST Remembers, a memorial wall on the CHEST website where we can post the news of our friends' passing, along with our remembrances of them. If your friend or colleague has died of COVID-19, please feel free to share with the CHEST community. You can find the link to do that at www.chestnet.org.

Introducing President-Designate Doreen J. Addrizzo-Harris, MD, FCCP

Doreen J. Addrizzo-Harris, MD, FCCP, is a pulmonary/critical care physician with an extensive background in bronchiectasis and non-tuberculous mycobacterial infection and medical education.

Dr. Addrizzo-Harris is currently a Professor of Medicine at the NYU Grossman School of Medicine. She serves as the Associate Division Director for Clinical and Faculty Affairs, is the Director of the NYU Bronchiectasis and NTM Program, and is Co-Director of the NYU Pulmonary Faculty Practice. She is now serving in her 20th year as the Program Director of NYU's Pulmonary and Critical Care Medicine Fellowship.



Dr. Addrizzo-Harris

Dr. Addrizzo-Harris received her medical degree and completed her residency and fellowship training at New York University School of Medicine. Since completing her training, she was recruited to stay as a faculty member at NYU, where she has been a critical presence over the past 25 years. She has been instrumental in educating the next generation of pulmonary/critical care physicians and has won a number of awards for her teaching skills, most recently, the 2021 Outstanding Educator Award from the APCCMPD.

Dr. Addrizzo-Harris has served on the board of the Association of Pulmonary and Critical Care Medicine Program Directors (APCCMPD), including serving as President from 2006-2007. Academically, she authored 44 peer-reviewed publications and 57 scientific abstracts presented at international conferences. She has participated in numerous clinical trials, many as PI. Dr. Addrizzo-Harris has been recognized as a Distinguished CHEST Educator each year since its inception in 2017 and received the Distinguished Service Award in 2019.

During her leadership tenure with CHEST, Dr. Addrizzo-Harris has served on the Marketing Committee, the Health and Science Policy Committee (Chair from 2007-2009), Government Relations Committee, Scientific Program Committee, Education Committee, Governance Committee, Editorial Board for *CHEST Physician*, Professional Standards Committee (Chair 2016-2018), Board of Regents, and CHEST Foundation Board of Trustees. Most recently, Dr. Addrizzo-Harris served as the President of the CHEST Foundation from 2018-2019 and Co-Chair of the Foundation Awards Committee from 2015-2020. She will serve as the sixth woman to lead the American College of Chest Physicians.

CHEST 2021 moves to Orlando and online – your choice

CHEST is excited to announce that CHEST 2021 will be held in Orlando, Florida, from October 17-21 at the Orange County Convention Center. CHEST 2021 will be offered as both an in-person and online experience. Since travel restrictions remain unknown, CHEST is working to ensure that everyone has access to the same top-tier learning – wherever they are.

"Learning together as a community is an important aspect of the CHEST annual meeting. Whether we are face-to-face or online, the knowledge gained from expert presenters, simulations and games, and talking with one another can't be duplicated elsewhere. In whatever way you can attend, join us at CHEST 2021 to discuss the critically relevant topics affecting our patients and chest medicine," said CHEST President Steven Q. Simpson, MD, FCCP.

It is also essential that those who cannot travel can still avail themselves of the engaging and interactive learning offered at the CHEST conference. Everyone – whether online or in-person – will be able to experience the meeting in real-time, including expert faculty presentations, simulated learning experiences, gaming, and more.

What to expect

Through bite-sized, immersive learning, experts in the field will cover the latest updates in pulmonary, critical care, and sleep medicine. CHEST 2021 offers you the opportunity to learn from a diverse set of knowledgeable educators representing different viewpoints and experiences.

Team-based learning is an indispensable component of the annual meeting. The activities support collaborative discovery and help you build relationships with your peers. Known for its development of simulation courses, at CHEST 2021, you can take part in the latest in "hands-on" learning. In addition, gaming will allow for friendly competition among colleagues, whether playing from home or on-site.

Getting involved

Make your mark by submitting your original abstracts and case reports to be presented at CHEST 2021. Because of the past year's challenges, new discoveries were made in the treatment and approaches to managing chest medicine diseases. This work is important and will inform the way patients receive care in the future.

Showcase COVID-19 research, among other topics you are working on, for a chance to share your findings with colleagues, gain feedback from expert faculty, collaborate with other professionals in the field, and expand your professional portfolio. The deadline to submit is April 28. [https://bit.ly/3qXgytH]

Keeping safe

It's been a long time since in-person conferences were possible. CHEST is closely monitoring the status of the pandemic throughout the planning process. The Orange County Convention Center was selected because the venue is large enough to support social distancing. The CHEST team is establishing protocols that limit the number of individuals in a space, promote good traffic flow, require the wearing of masks, and other safety measures. All on-site participants and CHEST support staff will be required to attest to having received a COVID-19 vaccination to attend.

Continue to watch for more information. Registration for CHEST 2021 will open in May. We've missed you, and we look forward to seeing you in Orlando, Florida, October 17-20.

CHEST to offer research matching service

CHEST Analytics has announced its new resource for members interested in serving as investigators in industry-sponsored clinical trials.

The new program, CHEST Clinical Trials Solutions, will pair members who have indicated their interest in specific research topics with companies seeking investigators. According to CHEST President Steven Q. Simpson, MD, FCCP: "For members who would like to be involved in research and for companies that have defined distinct criteria for their studies, CHEST Analytics can pair qualifying parties to facilitate communication between researcher and sponsor. It's a great way for young investigators to get started or accomplished members to share their experience while helping industry expedite introducing new products that improve patient care." More information regarding enrollment will be available at info.chestnet.org/clinical-trials.

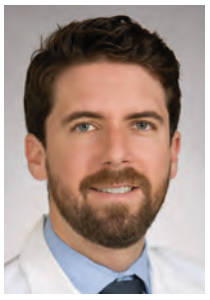
SLEEP STRATEGIES

Home noninvasive ventilation in hypercapnic COPD: Progress but important unanswered questions

BY JEREMY E. ORR, MD

Patients with COPD may develop sustained hypercapnia, often defined as an awake arterial P_{CO_2} of >45 mm Hg. Other synonymous terms include alveolar hypoventilation or chronic hypercapnic respiratory failure, noting that the specific terminology used may reflect local practice, an assessment of patient severity, or specific insurance requirements. Regardless, available data suggest that hypercapnic COPD patients are at high risk for adverse health outcomes (Yang H, et al. *BMJ Open.* 2015;5[12]:e008909). Moreover, there appears to have been a growing interest in this population driven by a focus on reducing COPD hospitalizations, increasing recognition of sleep-disordered breathing, and progress in potential therapeutic strategies.

There are a number of factors that might drive COPD patients to develop hypercapnia. Lower airway obstruction, expiratory flow limitation, and air trapping cause mechanical load on breathing, as well as a trade-off between time spent in inspiration vs prolonged expiration. The function of the diaphragm is impacted by hyperinflation leading to mal-positioning, as well as possibly by local and/or systemic myopathy. The net result is often decreased overall minute ventilation. In terms of gas exchange, increased dead space and ventilation-perfusion mismatching leads to reduced efficiency of ventilation toward CO_2 removal. Breathing changes during sleep play an important role, as evidenced by worsened hypercapnia during sleep that can drive chronic CO_2 retention (O'Donoghue FJ, et al. *Eur Respir J.* 2003;21[6]:977). The pathogenesis includes reduced central respiratory drive, increased upper airway resistance and/or obstructive hypopneas and apneas, and respiratory muscle atonia, particularly during REM sleep. The extent to which each of these factors contributes to hypercapnia varies across individual patients, in accordance with the known substantial heterogeneity of COPD.



Dr. Orr

Regardless of underlying traits, patients with COPD who develop hypercapnia have sufficiently severe perturbations to disrupt the normally tight control over CO_2 homeostasis.

Nocturnal home noninvasive ventilation (NIV) has been examined as a potential therapeutic strategy for patients with hypercapnic COPD. While older studies have not shown consistent benefits, more recent evidence suggests that NIV can reduce hospitalizations, improve quality of life, and potentially reduce mortality among those with hypercapnic COPD. Accordingly, the American Thoracic Society recently released a clinical practice guideline regarding the use of NIV in patients with chronic stable hypercapnic COPD (Macrea M, et al. *Am J Respir Crit Care Med*. 2020;202[4]:e74-e87). Recommendations from the guideline included:

1. The use of nocturnal NIV for patients with chronic stable hypercapnic COPD
2. Screening for OSA before initiation of long-term NIV
3. Not using in-hospital initiation of long-term NIV after an episode of acute or chronic hypercapnic respiratory failure, favoring instead reassessment for NIV at 2–4 weeks after resolution
4. Not using an in-laboratory overnight PSG to initially titrate NIV
5. Targeting normalization of P_{aCO_2}.

Although it now seems clear that efforts should be made to use NIV in COPD to decrease chronic hypercapnia, there are a number of important questions that remain, particularly surrounding the topic of concurrent OSA, titration, and devices:

- What is the appropriate approach toward patients with suspected concurrent OSA? Most studies of NIV have excluded patients with OSA, or otherwise at higher risk of OSA. Nonetheless, such patients may be common, both based on continued high prevalence of obesity, as well as the potential role that upper airway obstructive events may play toward elevations in CO_2 (Resta O, et al. *Sleep Breath*. 2002;6[1]:11-18). COPD epidemiologic studies indicate obesity as a risk factor for several poor outcomes, including severe COPD exacerbation (Lambert AA, et al. *Chest*. 2017;151[1]:68-77), while studies of COPD and OSA suggest that the presence of hypercapnia defines a high-risk group (Jaoude P., *Lung*. 2014;192:215). Recognizing the potential importance of OSA in this group, ATS guidelines recommend that a general questionnaire-based screening be performed. If screening is positive, the implication would be to perform diagnostic polysomnography to confirm the diagnosis of OSA. However, this may be a challenge for chronically ill patients, and likely would result in delays in NIV initiation. Of note, emerging evidence suggests that home sleep apnea testing (HSAT) might have reasonable accuracy in this group, which may facilitate formal diagnosis. Other concerns in this area include the lack of questionnaire validation in COPD patients.
- Should patients with OSA be managed differently than those without OSA? A diagnosis of OSA might impact several subsequent management decisions related to appropriate NIV therapy and titration. Patients with OSA have increased upper airway collapsibility, which might necessitate higher EPAP support than the minimal EPAP used in NIV trials with non-OSA patients (often fixed at 4 cm water). Potential strategies for optimizing EPAP include use of an NIV device with auto-titrating EPAP, titration in the sleep laboratory (discussed below), or outpatient titration based on clinical parameters and subsequent device download follow-up. On the other hand, one might consider all patients to be at risk for upper airway obstruction and need for additional EPAP titration, which would obviate the need for OSA diagnostic testing.
- What is the role of the sleep laboratory toward successful titration?

The inpatient hospital setting has been the traditional site to initiate home NIV in some institutions but is highly resource-intensive and increasingly impractical in many health systems. On the other hand, advances in home remote device monitoring now provide the clinician with the ability to examine daily usage, estimated leak, tidal volumes, respiratory rate, and other parameters – often reported as recently as the prior night. In addition, setting changes can be made via these remote monitoring tools (for nonventilator devices), allowing titration to be performed over time on outpatients. Several studies support the effectiveness of this approach over hospital titration in neuromuscular disease and now in COPD (Duiverman ML, et al. *Thorax*. 2020;75[3]:244-52). Similarly, data suggest that titration under polysomnographic guidance might not be necessary (Patout M, et al. Polysomnography versus limited respiratory monitoring and nurse-led titration to optimize non-invasive ventilation set-up: a pilot randomised clinical trial. *Thorax*. 2019;74:83-86).

- Limitations toward the sleep lab as the site of initial titration include waiting time, cost and insurance coverage, and the need to accommodate issues such as impaired mobility or reliance on a caretaker. In addition, titration goals must be clearly outlined in protocols and via staff training specific to NIV. The sleep laboratory may be most appropriately utilized in the minority of patients in whom outpatient titration is unsuccessful. Relatively common issues that might be best addressed in the lab setting include excessive mask leaks, residual apneas and hypopneas, failure to control CO_2, or other sleep complaints. In general, studies should probably be focused primarily on titrating EPAP to alleviate upper airway obstructive events. The goals in terms of IPAP titration (or ventilation titration, in the case of "VAPS" modes) are less clear, and overly aggressive increases may complicate the picture with excessive leaks or airway obstruction due to glottic closure. Attempting to accomplish "too much" often leads to a study with limited utility. In contrast, simply performing the study in the patient's home settings can provide useful diagnostic information regarding the problem one is trying to solve.
- When and where should one initiate NIV following a severe COPD exacerbation? In contrast to the ATS guidelines, the European Respiratory Society guidelines suggest that patients recovering from severe COPD exacerbations be initiated on NIV during that hospitalization, noting that this is a group at high risk for early rehospitalization and mortality (Ergan B, et al. *Eur Respir J.* 2019;54[3]:1901003). ATS guidelines had the concern of unnecessary start of NIV in those who might normalize their CO_2 after recovery, and the possibility of prolonging hospitalizations for titration. For the clinician, the decision will probably be individualized based on risk and available resources. For patients with frequent ICU admissions and/or difficulty with close outpatient follow-up, earlier NIV initiation is certainly a reasonable approach, but adherence and effectiveness remains a concern and, thus, more data are needed.
- Which patients should receive a bedside respiratory assist device (RAD, ie, BiPAP machine) vs. a noninvasive ventilator? Two classes of devices can be used for home NIV. While both can provide similar positive pressure ventilation, ventilators are designed as life support with alarms and batteries, and may have modes not otherwise available (auto-titrating EPAP). On the other hand, RAD devices are more convenient for patients and less expensive, but difficult qualification requirements (particularly for devices capable of bilevel ST or VAPS) have likely resulted in their underutilization. CHEST is spearheading an effort to reconsider Medicare coverage determinations (current rules are from 1998), which will hopefully better align device qualification requirements with emerging evidence regarding patient needs and preferences.

Home noninvasive ventilation can improve outcomes in these high-risk patients with hypercapnic COPD, and the new clinical practice guidelines are an important step in outlining appropriate management. Further progress is needed to delineate an individualized approach based on underlying patient pathophysiology, COPD manifestations/phenotypes, and systems-based practice considerations.

Dr. Orr is Assistant Professor, Division of Pulmonary, Critical Care, and Sleep Medicine, UC San Diego.

NETWORKS

Disaster response and global health. Interstitial and diffuse lung disease. Practice operations. Transplant.

Disaster response and global health

One step forward, two back…

No adult alive today will live to see global gender parity. The 2020 World Economic Forum Global Gender Gap Report, published December 2019, assessed four dimensions of gender inequality – health, economic opportunities, educational advancement, and political empowerment.

The report stated that despite some advances, overall global gender parity would not be reached for 99 years. The gender gap is not solely a developing nation's problem. The US standing as the 51st in gender parity fell to 53rd during the previous 2-year period. And these numbers were before COVID-19.

Disasters, including pandemics, negatively affect female subjects disproportionately. COVID-19 has unmasked and exacerbated both gender and minority disparity. Global health care workers (HCW) are overwhelmingly female, exposing them to a higher risk of contagion. This risk was exceptionally high among Black, Asian, and minority ethnic HCW (Nguyen et al. *Lancet Public Health*. 2020;5[9]:E475). The gender pay gap, where women are paid 80% of their male counterparts and women of color make 63%, has led to a greater financial burden among female HCW during Covid COVID-19. Women, including HCW, provide the majority of the unpaid work, ie, childcare, elder care, and home care. 2020 saw an unprecedented loss of women in the workplace, including health care. Both clinical practice and research have been affected. The long-term effect on women HCW careers is unknown at present. Global gross domestic product growth loss due to this decline in the female workforce is estimated at 1 trillion USD over the next decade.

Dr. Reed

Disaster and gender parity are entwined. COVID-19 has revealed the persistence of inequalities that needs to be considered in future disaster planning.

Mary Jane Reed, MD, FCCP
Steering Committee Ex-Officio

Interstitial and diffuse lung disease

Emergence and benefits of home monitoring and telemedicine for patients with ILD

Patients with interstitial lung disease (ILD) require regular monitoring with outpatient clinic visits and pulmonary function tests.

The emergence of COVID-19 forced an unprecedented transition to telemedicine and a new reliance on home monitoring. Home spirometry enables quick detection of rapidly progressive disease and is more sensitive than hospital-based spirometry in predicting prognosis (Russel, et al. *Am J Respir Crit Care Med*. 2016;194[8]:989). Patients with idiopathic pulmonary fibrosis randomized to a home monitoring program had improved psychological wellbeing and higher patient satisfaction with individually tailored treatment decisions (Moor, et al. *Am J Respir Crit Care Med*. 2020 ;202[3]:393). However, there are some inaccuracies in home monitoring. For instance, pulse oximetry is less reliable in African American patients receiving supplemental oxygen (Sjoding, et al. *N Engl J Med*. 2020;383:2477). It is critical to protect ILD patients from potential COVID-19 exposure given the high risk of serious complications. Telemedicine should be offered to all

Dr. Gersten

patients and may actually increase access to care in ILD patients, a population with disabling dyspnea and supplemental oxygen needs that require specialist care unavailable in many geographic regions. African American patients, those older than 65, and patients with lower socioeconomic status are less willing to engage in videoconferencing (Fischer, et al. *JAMA Netw Open*. 2020;3[10]:e2022302). It is essential that telephone visits be offered to minimize disparities in access to care. Many telemedicine platforms enable caregivers and family members to attend visits from separate locations and provide a unique opportunity to address advance care planning. In-person visits should be arranged for patients with no access to internet or telephone or those with poor medical literacy or insufficient social support to conduct a productive remote visit. Telemedicine and home monitoring have proved invaluable during the COVID-19 pandemic and have the potential to continually increase access to and quality of care.

Rebecca Anna Gersten, MD
Steering Committee Member

Practice operations

Use of media platforms to eliminate the COVID-19 infodemic

We were shocked when we read a tweet in December 2020 from a health care worker stating, "My biggest concern is the lack of data and the quick development time. Feels like we are a bunch of guinea pigs" in reference to the new COVID-19 vaccine.

We reflected back on the last pandemic in 2009, H1N1, and remembered when the new vaccine developed in 174 days was first released to pregnant women and children after phase 3 trials. How did we get here? What do we do to fix it?

This misinformation is labeled as the "COVID-19 infodemic." In the last year, we have seen the media, more specifically social platforms, quickly spread medical misinformation. In the book "Made to Stick: Why Some Ideas Survive and Some Die," the authors described core elements that make an idea "sticky." Use of those exact same sticky techniques can be used to circulate accurate information and to halt the spread of this infodemic. Although, numerous media companies, including Twitter, are making an effort to remove the false content from their platforms, their efforts require a lengthy process and are delayed. Therefore, it is crucial for the public health figures and community at large in partnership with various national organizations to establish a robust connection with the social platforms in a dynamic and timely fashion to help spread the verified information across social media, digital

Dr. Khan

Dr. Anjum

and traditional media outlets.

The UN has launched an initiate called "Verified." This is a worldwide effort to help individuals spread reliable information regarding COVID-19 to their friends and families via social platforms as various media platforms and businesses have partnered with Verified. Also, we encourage our members to access the CHEST COVID-19 resource center and benefit from the various clinical and practice management tools along with validated patient information materials.

Roozera Khan, DO, FCCP
Steering Committee Member
Humayun Anjum, MD, FCCP
Chair

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Transplant

COVID-19 + lung transplant

The COVID-19 pandemic has created a dilemma for lung transplantation, with a new group of patients with refractory respiratory failure secondary to the viral illness. As transplant centers worldwide receive referrals for COVID-19 related respiratory failure, information regarding evaluation, listing, and posttransplant care continues to be published, but further research will be needed to care for this complex population.

The first lung transplant for COVID-19 in the United States occurred at Northwestern Hospital on June 5th, 2020, and was publicized for its innovativeness. Information from their three lung transplants completed thus far includes information regarding pathologic findings of the explanted lung tissue; pulmonary fibrosis was the dominant feature, suggesting COVID-19-induced acute respiratory distress syndrome with prolonged time supported by mechanical support may only be survivable with the use of lung transplant (Bharat, et al. *Sci Transl Med*. 2020;12(574):eabe4282).

Lung transplant in the setting of COVID-19 fibrosis increases surgical complexity as well, with case reports of dense adhesions and distortion of regular surgical planes (Bharat, et al. *Sci. Transl. Med.* 2020; Lang, et al. *Lancet Respir Med.* 2020;8:1057). Recognizing the difficulty with deciding to use transplantation after an infectious disease,

Dr. Louis

Dr. Turner

The International Society for Heart and Lung Transplant (ISHLT) has created guidelines regarding indications for transplantation (ISHLT.org). Continued research will be necessary to identify those at the highest likelihood for success from transplantation, preparation for the increased complexity, and long-term outcomes. Further information is available in a CHEST webinar titled "Lung Transplantation in the Era of COVID-19" (http://www.chestnet.org/Guidelines-and-Resources/Online-Series/Webinar/Lung-Transplantation-in-the-Era-of-COVID-19).

Clauden Louis, MD
Grant Turner, MD
Fellows-in-Training NetWork Members

Women's lung health

Pregnancy in cystic fibrosis

The newest in the line of modulator therapy, Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor), is expected to improve life expectancy and quality of life for patients with cystic fibrosis (CF). This evolution in therapy will shape how providers care for their patients, particularly women of reproductive age. Conventionally, women with significantly impaired lung function due to CF have been advised to avoid pregnancy due to potential complications for mother and baby. It is likely that now, with improved lung function while receiving Trikafta, more women will feel better equipped to attempt pregnancy.

There are several considerations in this setting, including the need for careful drug safety and monitoring, creating a plan of action for possible decline in lung function while off certain CF-related medications, and counseling on drug interactions during lactation. In our experience with women becoming pregnant while receiving Trikafta or contemplating pregnancy, all have opted to discontinue modulator therapy with declines in lung function. Trikafta does not report teratogenicity based on animal studies of the individual components of the drug; however, ivacaftor is known to cause impairment in fertility and reproductive indices, including nonviable embryos and implantation failure in a rat model at five times the maximum recommended human dose, dosed prior to and during early embryogenesis. Small mammal models have decreased birth weight at high doses of elexacaftor, tezacaftor and ivacaftor administered individually. There is evidence of placental transfer of ivacaftor and breast milk concentrations of tezacaftor and ivacaftor are higher than plasma concentrations in rats. There are no human data in parturient or lactating women or infants. Three women became pregnant during the phase 3 clinical study of Trikafta, one with elective termination, one pregnancy was carried to full term with normal birth outcome, and one ended in a spontaneous abortion, which was deemed not to be related to the study drug. Translating this information into recommendations for patients has important implications.

Dr. Banerjee

Debasree Banerjee, MD, MS
Steering Committee Member

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Syndromic Testing: The Right Test, The First Time.

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2. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Filmarray® Pneumonia (PN) Panel.
3. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Blood Culture Identification 2 (BCID2) Panel.

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