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NEWS
Popular asthma medicine discontinued // 7

LUNG CANCER
Inhaler and urine test used to detect disease? // 8

LONG COVID
Condition may mimic brain injury // 9

VOL. 19 • NO. 3 • MARCH 2024

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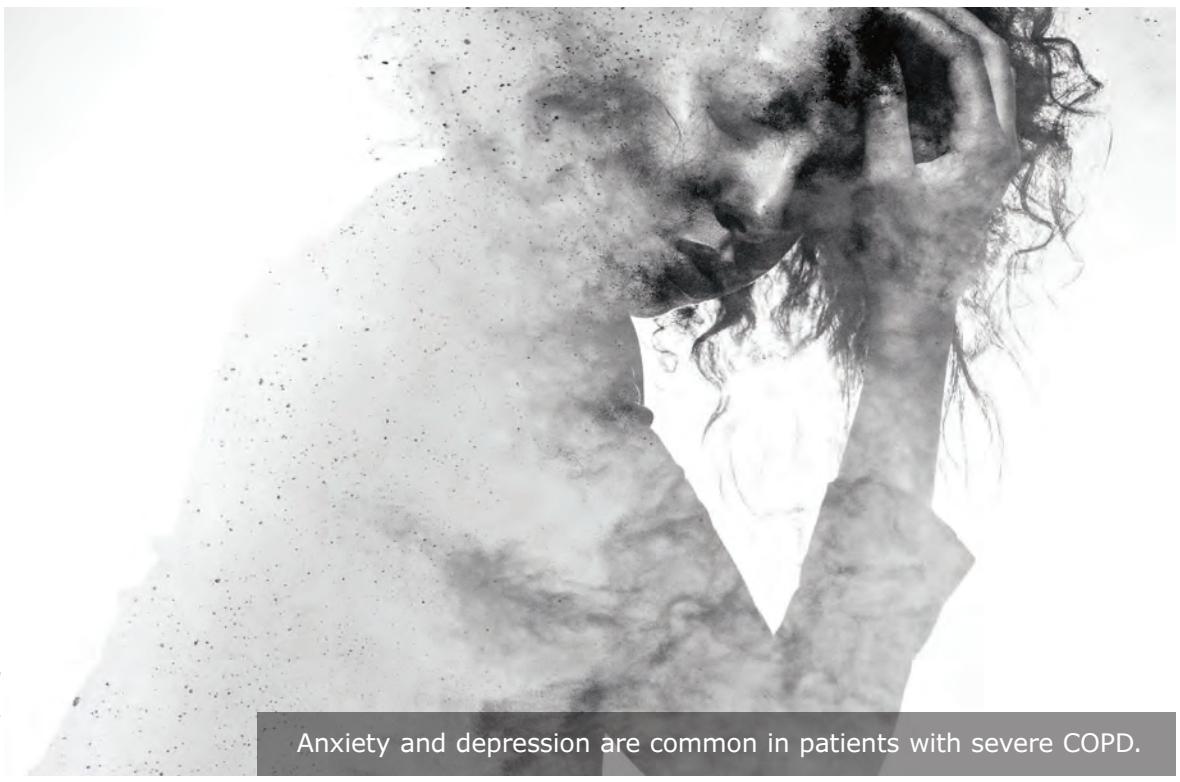

E+/Getty Images

Anxiety and depression are common in patients with severe COPD.

Patients haunted by fears of living with and dying from severe lung disease

BY NEIL OSTERWEIL

Many patients with chronic progressive pulmonary disease (COPD) feel anxious and depressed as their conditions advance, as breathing becomes increasingly labored and difficult, and as performing even small daily tasks leaves them exhausted.

Persons with severe COPD frequently report fears of suffocation and death, as well as anxieties about abandoning family and friends, and these negative, intrusive thoughts can have an adverse effect on COPD outcomes.

Disease-related mental distress can lead to increased disability, more frequent use of costly healthcare resources, higher morbidity, and elevated risk of death, investigators say. "Individuals with severe COPD are twice as likely to develop depression than patients with mild COPD. Prevalence rates for clinical anxiety in COPD range from 13% to 46% in outpatients and 10% to 55% among inpatients," wrote Abebaw Mengitsu Yohannes, PhD, then from Azusa Pacific University in Azusa, California, and colleagues in an article published jointly by *The Journal of Family Practice* and *The Cleveland Clinic Journal of Medicine.*

FEARS // *continued on page 6*

The emerging physician-scientist crisis in America

BY AADEL CHAUDHURI, MD, PHD

Recent reporting has shown the number of physician-scientists — doctors who both practice medicine and perform scientific research — in the United States is dropping rapidly. That's a problem, because physician-scientists are uniquely equipped to make scientific discoveries in the laboratory and translate them to the clinic. Indeed, many of the discoveries that have transformed medicine for the better were made by physician-scientists. For example, Jonas Salk developed the polio vaccine, Timothy Ley sequenced the first cancer genome, and Anthony Fauci coordinated public health responses to both the HIV/AIDS and COVID-19 pandemics. Indicative of their sheer impact, at least a third and as many as half of all Nobel Prizes and Lasker Awards in physiology/medicine have gone to physician-scientists.

So why is the supply of physician-scientists shrinking so precipitously at a time when medical discoveries are being made at a record-high rate? Immunotherapy and proton therapy are transforming cancer care; RNA technology led

SCIENTIST // *continued on page 5*

INSIDE HIGHLIGHT

NEWS FROM CHEST

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Page 18

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CHEST PHYSICIAN (ISSN 1558-6200) is published marchly for the American College of Chest Physicians by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102.

Subscription price is $251.00 per year. Phone 973-206-3434, fax 973-206-9378.

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SCIENTIST

// *continued from page 1*

to COVID vaccines; and CRISPR is facilitating gene editing and treatment of diseases like sickle cell anemia. Yet, as exciting as medical science has become, only 1.5% of American doctors work as physician-scientists, more than a threefold drop compared with 30 years ago when the figure was a more robust 4.7%. What's going on?

Residency training programs at prestigious academic medical centers have standard infolded research years; for example, neurosurgery residents at academic medical centers will often get 2 years of protected research time. And the National Institutes of Health has training grants dedicated to physician-scientists, such as the K08 award program. Several foundations are also dedicated to supporting early-career physician-scientists. Yet, the number of physicians deciding to become physician-scientists remains low, and the attrition rate of those who do decide to go this route is high.

The underlying issue is multifold. Funding rates from the federal government for grants have become competitive to the point of being unrealistic. For example, the current funding rate for the flagship R01 program from the National Cancer Institute is only 12%. Promotions are typically tied to these grant awards, which means physician-scientists who are unable to acquire substantial grant funding are unable to pay for their research or win promotion — and often exit the physician-scientist track altogether.

Compounding this issue is a lack of mentorship for early-career physician-scientists. With the rise of "careerism" in medicine, senior-level physician-scientists may have less incentive to mentor those who are earlier in their careers. Rather, there seems to be greater reward to "managing up" — spending time to please hospital administrators and departmental leadership. Being involved in countless committees appears to carry more value in advancing an established investigator's career than does mentorship.

Finally, physician-scientists typically earn less than their clinician colleagues, despite juggling both scientific and clinical responsibilities. While many are comfortable with this arrangement when embarking on this track, the disparity may become untenable, especially as departmental leadership will often turn to physician-scientists to fill clinical coverage gaps when faculty leave the department, or as the medical center expands to satellite centers outside the primary hospital. Indeed, physician-scientists get pulled in several directions, which can lead to burnout and attrition, with many who are highly equipped for this track ultimately seeking more clinical or private industry-oriented opportunities.

Every academic medical center operates differently. Some clearly have done a better job than others promoting and fostering physician-scientists. What we find in the centers that manage to retain physician-scientists is leadership plays a major role: If a medical center values the importance of physician-scientists, they will do things to foster the success of those people, such as assembling mentorship committees, establishing clear criteria for promotion and career advancement, protecting research time while maintaining some level of pay equity, advocating for team science approaches, and supporting investigators in cases of gaps in federal funding. Different countries also have different models for physician-scientist training, with Germany, for example, allowing medical residents to have 3 years of protected time to engage in research after their second year of residency.

Image generated by Adobe Firefly

The stakes here are high. If we can't address the physician-scientist recruitment/retention crisis in America now, we risk falling behind other countries in our ability to innovate and deliver world-class care.

Dr. Chaudhuri is a tenure-track physician-scientist at Washington University in St. Louis, Missouri, a Paul and Daisy Soros Fellow, and a Public Voices Fellow of The OpEd Project. He has disclosed no relevant financial relationships. ■

Cough syrup recalled because of fungus concerns

BY LISA O'MARY

Some Robitussin cough syrup products are being recalled nationwide because of potentially deadly microbial contamination. The company that makes Robitussin syrups did not specify which microorganisms may be in the products. The recall announcement from the global consumer health products company Haleon stated the contamination could lead to fungal infections or the presence of fungi or yeasts in a person's blood. So far, the company has not received any reports of people being sickened by the recalled products.

The recall applies to bottles of Robitussin Honey CF Max Day and Robitussin Honey CF Max Nighttime. Both varieties are for adults. Affected products were sold nationwide and have specific lot numbers printed at the bottom of the back of the bottles. Consumers can view the lot numbers on the FDA's recall webpage.

People with weakened immune systems have a higher risk of life-threatening health problems due to the cough syrup, the company warned.

"In non-immunocompromised consumers, the population most likely to use the product, life-threatening infections are not likely to occur," the recall notice from Haleon stated. "However, the occurrence of an infection that may necessitate medical intervention cannot be completely ruled out."

People who have affected products should stop using them immediately. The company asked that anyone with the products email Haleon at mystory.us@haleon.com, or call the company at 800-245-1040 Monday through Friday from 8 a.m. to 6 p.m. Eastern time. ■

FEARS // *continued from page 1*

Patients with COPD may experience major depressive disorders, chronic mild depression (dysthymias) and minor depression, generalized anxiety disorder, phobias, and panic disorders, the investigators say. "Growing evidence suggests the relationship between mood disorders, particularly depression, and COPD is bidirectional, meaning that mood disorders adversely impact prognosis in COPD, whereas COPD increases the risk of developing depression," Yohannes et al. wrote.

Dr. Yohannes

Jamie Garfield, MD, professor of thoracic medicine and surgery at Temple University's Lewis Katz School of Medicine in Philadelphia, Pennsylvania, told *CHEST Physician* the association between severe chronic diseases and mood disorders is well known. "I don't think that it's specific to chronic lung diseases; in people with chronic heart disease or malignancies we see that co-existence of depression and anxiety will worsen the course of disease," she said.

Dr. Yohannes, who is currently a professor of physical therapy at the University of Alabama School of Health Professionals in Birmingham, said depression and anxiety are often underdiagnosed and undertreated in patients with obstructive pulmonary diseases because the conditions can share symptoms such as dyspnea (for example, in anxiety) or fatigue (in depression). "Therefore, unless one begins to explore further, it's hard for physicians to be able to identify these conditions," he said in an interview with *CHEST Physician*.

Fears of dying (and living)

The causes of depression and anxiety among patients with obstructive pulmonary disorders are multi-factorial, and may require a variety of treatment and coping strategies, according to Susann Strang, PhD, RN, and colleagues from the University of Gothenburg, Sweden.

They conducted qualitative in-depth interviews with 31 men and women with stage III or IV COPD, and found the majority of patients had anxiety associated with their disease. "Analyses revealed three major themes: death anxiety, life anxiety, and counterweights to anxiety," the investigators wrote in a study published in the journal *Palliative and Supportive Care* in 2014.

Factors contributing to anxiety surrounding death included fear of suffocation, awareness of impending death, fear of the process of death, and anxiety about being separated from loved ones. In contrast, some patients expressed dread of living with the limitations and loneliness imposed on them by their disease, so called "life anxiety." Patients also reported "counterweights" to anxiety as a way of coping. For some, this involved trust in their health care professionals and adherence to medication, inhalers, and supplemental oxygen.

"The patients also placed hope in new treatments, better medication, surgery, stem cell treatment, or lung transplants," Dr. Strang and colleagues reported. Others reported avoiding talking about death, sleeping more, or using humor to "laugh off this difficult subject."

Screening and diagnosis

Primary care practitioners are often the first health professionals patients with COPD see, but these clinicians often don't have the time to add screening to their already crammed schedules. In addition, "the lack of a standardized approach in diagnosis, and inadequate knowledge or confidence in assessing psychological status (particularly given the number of strategies available for screening patients for mood disorders)," can make it difficult for PCPs to detect and manage anxiety and depression in their patients with significant healthcare burdens from COPD and other obstructive lung diseases, Dr. Yohannes and colleagues noted.

In addition to commonly used screening tools for anxiety and depression such as the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (PHQ-9), there are at least two designed to evaluate patients with lung disease: the Anxiety Inventory for Respiratory (AIR) Disease scale, developed by Dr. Yohannes and colleagues, and the COPD Anxiety Questionnaire.

The COPD Assessment Test and Clinical COPD Questionnaire, while not specifically designed to screen for mental disorders, include questions that can point to symptoms of distress, Dr. Yohannes said.

"In truth I think there are few providers who will routinely do this on all their patients in terms of quantifying the severity or the presence or absence of depression, but in my own practice, I very much ask questions that align with the questions in these tools to determine whether my patient appears to have high levels of anxiety and depression," Dr. Garfield said.

Listen to patients and families

Among the most powerful tools clinicians have at their disposal for treating anxiety and depression in patients with chronic lung disease are their ears and their minds, said Anthony Saleh, MD, a pulmonologist at NewYork-Presbyterian Brooklyn Methodist Hospital in Brooklyn, New York. "I think just listening to the patient, that's a little bit forgotten yet so important," he said.

"When I have someone with advanced lung disease, like idiopathic pulmonary fibrosis, like advanced emphysema, one of the most important things, I think, is to listen to the patient, and not just to listen to the answers of your perfunctory 'how's your breathing? Any chest pain?' and those sort of rote medical questions, but listen to their thoughts, and it will given them a safe space to say 'Hey, I'm nervous, hey I'm worried about my family, hey I'm worried if I die what's going to happen to my wife and kids,' and that's something I think is invaluable." It's also vital to listen to the concerns of the patients family members, who may be the primary caregivers and may share the patient's stresses and anxieties, he said.

Pulmonary rehabilitation

All of the experts interviewed for this article agreed a combination of medical, social, and mental health support services is important for treatment for patients with chronic obstructive lung diseases. One of the most effective means of helping patients with both acute breathing problems and disease-related anxiety and depression is pulmonary rehabilitation. Depending on disease severity, this multidisciplinary approach may involve exercise, patient education, psychological and nutrition counseling, and training patients how to conserve energy and adopt breathing strategies to help them better manage their symptoms.

"Pulmonary rehabilitation is one of the first interventions we should be recommending for our patients," Dr. Garfield said. "It's physical therapy for patients with chronic lung diseases, backed by respiratory therapists, and it offers not only physical rehabilitation — improving strength and coordination, but also it helps our patients get as much as possible out of what they've got."

FEARS *continued on following page*

Flovent brand discontinuation likely smooth for many, difficult for some

BY WALTER ALEXANDER

A recent alert posted on the Asthma and Allergy Foundation of America (AAFA) website blog announced, "Flovent HFA and Flovent Diskus Asthma Medicine Being Discontinued." A further heading stated: "Generic versions of the same medicines and devices are available but you need to check your insurance." While it is generally thought few will have trouble finding suitable alternatives, the warning captured the reality for some asthma sufferers whose insurance coverage may be lacking.

The AAFA blog included a GSK (GlaxoSmithKline) November 2023 statement to AAFA regarding the brand, Flovent, discontinuation. It noted the launch of an authorized Flovent HFA (fluticasone propionate inhalation aerosol) generic in May 2022 and a planned (October 2023) launch of an authorized generic for Flovent Diskus (fluticasone propionate inhalation powder) as "part of our commitment to be ambitious for patients." The GSK statement continues: "These GSK manufactured authorized generics will provide patients in the U.S. with potentially lower cost alternatives. We recognize patients have a number of options in the therapeutic area and remain committed to ensuring the affordability of our medicines." GSK will manufacture the authorized generics, but they will be distributed by Prasco LLC.

Medicaid rebate cap removed

As a Forbes January article ("New Medicaid Rebate Rule Causes Problems For Asthma Patients On Flovent") points out, the Flovent January 1, 2024, discontinuation coincided with the removal of the Medicaid rebate cap (American Rescue Plan Medicaid Drug Rebate Program) targeting manufacturers who had previously raised medication prices at rates higher than the inflation rate. The Forbes story notes GoodRx data showing a 47% increase in Flovent price since 2014. The implication is drug manufacturers could be forced to sell a drug to Medicaid at a loss because of the rebate cap removal. An authorized generic introduced at a lower price under a private label with no price history, however, would not be subject to the higher Medicaid rebates.

Motivation considerations aside, the fallout for patients may or may not include a lower cost alternative. The authorized generic versions of Flovent HFA and Flovent Diskus are identical to the branded products with respect to the drugs and the devices. The GSK statement expressed hope most insurance plans will replace the brand name with the authorized generic. The possibility persists, however, that there may be some that do not — resulting in a need to find the right substitute and/or higher out-of-pocket costs.

"Even though some patients may experience disruption initially in their prescriptions, fortunately, there are quite a few alternatives, and we don't anticipate significant problems," said Diego J. Maselli, MD, FCCP, professor and chief, division of pulmonary diseases and critical care, UT Health at San Antonio, Texas, and a member of the *CHEST Physician* Editorial Board. "It will be a wrinkle for some of the patients with regard to coverage, but there are definitely many alternatives that can provide good enough treatment for them."

Similar alternative inhalers?

The alternatives have specific properties and qualities, but the vast majority of experts, Dr. Maselli said, consider them to be very similar.

For CAREMARK CVS, a major pharmaceutical benefits manager, the preferred Flovent substitute is Pulmicort Flexhaler, a dry-powder inhaler that contains budesonide rather than fluticasone. While Flovent HF is a metered-dose inhaler with a propellant, the Pulmicort device contains budesonide as a dry powder and requires activation through inhalation, which can be problematic for young children, AAFA CEO Kenneth Mendez said. To address that issue, he said, CVS Caremark is covering the authorized fluticasone metered-dose inhaler generic for children under 6 years old. "Those individuals 6 years and older with severe asthma who can't breathe deeply enough to get the medicine into their lungs will have to work with their doctors to apply for a formulary exception. And that's a complicated process," Mr. Mendez observed. "And it can take some time," he added.

Another key issue, he emphasized, is "how complicated this system is." The US drug pricing ecosystem involves multiple manufacturers, pharmacy benefit managers, insurance companies and their various plans, and federal policies potentially creating situations that may reduce access to critical medicines for patients, Mr. Mendez said. "Some people will be scurrying and scrambling to try to get coverage. The scope of the impact is actually unknown, but we're going to find out now. As a nonprofit, we monitor social media and we're listening closely."

AAFA's further concern is the rising costs of asthma medications. "It's the number one thing we hear about as a patient organization," Mr. Mendez said. In January, AAFA praised recent news from the US Senate Committee on Health, Education, Labor & Pensions ("Chairman Sanders, Baldwin, Luján, Markey Launch HELP Committee Investigation Into Efforts by Pharmaceutical Companies to Manipulate the Price of Asthma Inhalers). In it, Senator Bernie Sanders pointed to the 12-fold higher cost in the US versus the United Kingdom for GSK's fluticasone and a beta2-agonist inhaler. The Senate HELP Committee has sent letters to the CEOs of major inhaler manufacturers (AstraZeneca, Boehringer Ingelheim, GSK, and Teva), stating: "These prices force patients, especially the uninsured and underinsured, to ration doses or abandon their prescriptions altogether. The results are predictable and devastating." AAFA research confirms when asthma medicine costs become a barrier, people ration or discontinue medication. An AAFA press release also includes Mr. Mendez's plea for a national conversation. "We are hopeful the HELP Committee investigation will lead to a national conversation about asthma drug costs and produce action that breaks down barriers to affordable treatment. The bottom line is cost drives access." AAFA's blog advises when an insurance plan does not cover the generic or offer a formulary exception, options include ArmonAir Digihaler and Arnuity Ellipta. ■

FEARS *continued from previous page*

For example, patients can be taught how to decrease their respiratory rate when they're feeling a sense of urgency or panic. Patients can also learn how to change body positions to help them breathe more effectively when they feel their breath is restricted, she said.

"Once you're into medical interventions, pulmonary rehab is phenomenal," Dr. Saleh said. Pulmonary rehabilitation helps patients to feel better about themselves and about their abilities, but "unfortunately it's not as available as we like," he said.

Many patients don't live near a pulmonary rehabilitation center, and the typical two to three weekly sessions for 4-12 weeks or longer can be a significant burden for patients and caregivers, he acknowledged. "You have to sit [with the patient] and be honest and tell them it's a lot of diligence involved and you have to be really motivated," he said.

Other treatment options include pharmacological therapy with antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and anxiolytic agents. "SSRIs are the current first-line drug treatment for depression, and have been shown to significantly improve depression and anxiety in patients with COPD in some, but not all, trials published to date. However, it is important to note a diagnosis of bipolar disorder must be ruled out before initiating standard antidepressant therapy," Dr. Johannes and colleagues wrote.

Defiant joy

Importantly, even with the burden of life with COPD, many patients found ways to experience what Strang et al. called "a defiant joy."

"It was remarkable that when the patients were asked about what gave their lives meaning today, many talked about what had given their life meaning in the past, prior to becoming ill. In light of the things they had lost because of the disease, many felt their previous sources of joy no longer existed. Despite this, many still hoped to be able to get out into the fresh air, to be able to do errands or that tomorrow might be better," the investigators wrote.

Dr. Yohannes, Dr. Garfield, and Dr. Saleh all reported having no relevant conflicts of interest. ■

OSA

Coping strategies while driving may indicate higher risk for accidents in patients with OSA

BY EVE BENDER

According to study results, participants with OSA were more likely to feel sleepy while driving than controls (P = .0002). Participants with OSA were significantly more likely than were controls to use at least one coping strategy "frequently" vs control participants (43.7% vs 10.5%; $P \leq .0001$).

Strategies included rolling down the window, drinking tea or coffee, or listening to music at a high volume.

Participants with OSA were significantly more likely to have either reported an accident or have been involved in an accident irrespective of any insurance claims in the last year than controls (16.8% vs 2.85%; $P \leq .0013$). "Our research suggests that untreated OSA patients often use coping strategies that could be surrogate markers of sleepiness," lead author Akshay Dwarakanath, MD, said in a press release.

"Asking about these strategies in the clinic may help doctors identifying patients who are at risk of driving incidents and to advise appropriately."

Potential for recall bias

Study limitations included that investigators evaluated only patients with OSA with symptoms severe enough to warrant a CPAP trial and who needed to be assessed to determine if they should be allowed to continue to drive. Participant reporting and recall bias was another potential limitation.

The study was led by Dr. Dwarakanath of St. James University Hospital in Leeds, England, and was published online on January 17, 2024, in *ERJ Open Research* (doi: 10.1183/23120541.00638-2023).

No information was provided about study funding, and study authors had no disclosures. ■

Sai Venkateshiah, MD, FCCP, comments: OSA is associated with an increased risk of motor vehicle accidents. The mean crash-rate ratio associated with OSA is likely to fall within the range of 1.21-4.89 in commercial motor vehicle (CMV) drivers (Tregear S et al. J Clin Sleep Med. 2009). A Swedish traffic accident registry data study showed that patients with sleep apnea were nearly 2.5 times more likely to be the driver in a motor vehicle accident, compared with a control group of other drivers in the general population (Karimi M et al. Sleep 2015).

Identifying OSA patients who are at increased risk of an accident in clinical practice is often very challenging. There are no set criteria or a definitive objective test which will inform clinicians about the risk of motor vehicle accidents in patients with OSA. Patients may not necessarily be forthcoming regarding the history of sleepiness while driving because they might be afraid of losing their driving privileges. This is particularly relevant to commercial drivers who may be afraid of losing their driving licenses and livelihood. Asking patients about the countermeasures used to combat fatigue/sleepiness while driving may be a less intimidating way to elicit the history of sleepiness while driving and thereby identify individuals at higher risk of motor vehicle accidents. In this study, OSA patients (diagnosed based on an apnea-hypopnea index or oxygen desaturation index on portable sleep study) who had an Epworth sleepiness score of greater than 10 and being considered for CPAP trial either due to excessive symptoms and/or severity of OSA were included and compared with a control population of subjects with an Epworth score of less than 10.

The subjects completed questions about driving, including a modified questionnaire like Epworth Sleepiness Scale (ESS) termed as the driving sleepiness scale (DSS) and also answered 10 questions about various countermeasures (stopping for a nap, stopping for a walk/exercise, opening the window, turning up the radio, etc.) that they adopt in order to stay awake while driving. Results were reported as not frequently (never or occasionally) and frequently occurring. OSA patients were more likely to use at least one coping strategy "frequently" when compared with controls (43.7% vs 10.5%, P value, < .0001, odds ratio [OR], 6.6, 95% CI; 3.2-13.6). Interestingly, 29.4% of OSA patients used more than three different coping strategies "frequently" when compared with the controls. OSA subjects who used more than three such strategies had worse ESS, were more likely to feel sleepy while driving, and had more reported accidents (22.85% vs 2.38%), all of which were statistically significant when compared with patients with OSA who used fewer than three strategies.

I believe this study is a reminder to the clinicians to ask patients with OSA (both treated and untreated) about countermeasures taken to combat fatigue during driving to obtain additional information apart from the usual questionnaires such as ESS to identify individuals at higher risk for motor vehicle accidents to counsel them appropriately.

Dr. Venkateshiah is a member of the CHEST Physician *Editorial Board.*

LUNG CANCER

How a urine test could reveal early-stage lung cancer

BY CHRISTINA SZALINSKI

Lung cancer is the deadliest cancer in the world, and many patients are diagnosed with advanced disease. Screening for patients at risk could help, yet screening rates remain critically low. In the United States, only about 6% of eligible people get screened, according to the American Lung Association. Contrast that with screening rates for breast, cervical, and colorectal cancer, which all top 70%.

But what if lung cancer detection was as simple as using an inhaler and following up with a urine test? Researchers at the Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, have developed nanosensors that target lung cancer proteins and can be delivered via inhaler or nebulizer, according to research published in *Science Advances*. If the sensors spot these proteins, they produce a signal in the urine that can be detected with a paper test strip. "It's a more complex version of a pregnancy test, but it's very simple to use," said Qian Zhong, PhD, an MIT researcher and co-lead author of the study.

Currently, the only recommended screening test for lung cancer is low-dose CT. But not everyone has access to screening facilities, said the other co-lead author Edward Tan, PhD, a former MIT postdoc and currently a scientist at the biotech company Prime Medicine, also in Cambridge. "Our focus is to provide an alternative for early detection of lung cancer that does not rely on resource-intensive infrastructure," Dr. Tan said. "Most developing countries don't have such resources" — and residents in some parts of the US don't have easy access, either, he said. The sensors are polymer nanoparticles coated in DNA barcodes, short DNA sequences that are unique and easy to identify. The researchers engineered the particles to be targeted by protease enzymes linked to stage I lung adenocarcinoma. Upon contact, the proteases cleave off the barcodes, which make their way into the bloodstream and

TEST *continued on following page*

LONG COVID

New evidence suggests disorder could be a brain injury

BY SARA NOVAK

Brain fog is one of the most common, persistent complaints in patients with long COVID. It affects as many as 46% of patients who also experience memory loss and difficulty concentrating. Now, researchers believe they know why. A new study has found these symptoms may be the result of a viral-borne brain injury that may cause persistent cognitive and mental health issues. Researchers found 351 patients hospitalized with severe COVID-19 had evidence of a long-term brain injury a year after contracting the SARS-CoV-2 virus. The findings were based on a series of cognitive tests, self-reported symptoms, brain scans, and biomarkers.

As part of the study, participants took a cognition test with their scores age-matched to those who had contracted severe COVID-19. Then a blood sample was taken to look for specific biomarkers, showing elevated levels of certain biomarkers were consistent with a brain injury. Using brain scans, researchers also found certain regions of the brain associated with attention has reduced volume. Patients who participated in the study were "less accurate and slower" in their cognition, and suffered from at least one mental health condition, such as depression, anxiety, or posttraumatic stress disorder, according to researchers.

The brain deficits found in COVID-19 patients were equivalent to 20 years of brain aging and provided proof of what doctors have feared: This virus can damage the brain and result in ongoing mental health issues. "We found global deficits across cognition," said lead study author Benedict Michael, PhD, director of the Infection Neuroscience Lab at the University of Liverpool, Liverpool, England. "The cognitive and memory problems that patients complained of were associated with neuroanatomical changes to the brain."

Cognitive deficits were common among all patients, but the researchers said they don't yet know whether the brain damage causes permanent cognitive decline. The research does provide patients who have been overlooked by some clinicians with proof their conditions aren't imagined, said Karla L. Thompson, PhD, lead neuropsychologist at the University of North Carolina School of Medicine's COVID Recovery Clinic in Chapel Hill. "Even though we're several years into this pandemic, there are still providers who don't believe their patients are experiencing these residual symptoms," Dr. Thompson said. "That's why the use of biomarkers is important, because it provides an objective indication the brain has been compromised in some way."

COVID-related brain injuries

Researchers are unsure what's causing these brain injuries, though they have identified some clues. Previous research has suggested such injuries might be the result of a lack of oxygen to the brain, especially in patients who were hospitalized, like those in this study, and were put on ventilators. Brain scans have previously shown atrophy to the brain's gray matter in COVID-19 patients, likely caused by inflammation from a heightened immune response rather than the virus itself. This inflammatory response seems to affect the central nervous system. As part of the new study, researchers found some neuroprotective effects of using steroids to reduce inflammation.

The results suggest clinicians should consider the possibility their patients have suffered a brain injury and should be treated appropriately, said James C. Jackson, PsyD, a neuropsychiatrist at Vanderbilt University School of Medicine, Nashville, Tennessee. He contends treatments used for patients who have brain injuries have also been shown to be effective in treating long COVID–related brain fog symptoms. These may include speech, cognitive, and occupational therapy, and neuropsychiatrist therapy.

A new path forward

Treating long-COVID brain fog like a brain injury can help patients get back to some semblance of normalcy, researchers said. "What we're seeing in terms of brain injury biomarkers and differences in brain scans correlates to real-life problems these patients are dealing with on a daily basis," Dr. Jackson said. These include problems at work and in life with multitasking, remembering details, meeting deadlines, synthesizing large amounts of information, and maintaining focus on the task at hand, he said.

There's also a fear that even with treatment, the aging of the brain caused by the virus might have long-term repercussions and this enduring injury may cause the early onset of dementia and Alzheimer's disease in those who were already vulnerable to it. One study, from the National Institute of Neurological Disorders and Stroke (NINDS), found in those infected with COVID-19 who already had dementia, the virus "rapidly accelerated structural and functional brain deterioration."

"We already know the role neuroinflammation plays in the brains of patients with Alzheimer's disease," Dr. Thompson said. "If long COVID is involved in prolonged inflammation of the brain, it goes a long way in explaining the mechanism underlying [the study's reported] brain aging."

Still more to learn

Researchers don't know about the impact on those who had less serious cases of the virus. For Ziyad Al-Aly, MD, chief of research and development at the Veterans Affairs St. Louis Health Care System in Missouri the concern is that some long-COVID patients may be suffering from cognitive deficits that are more subtle but still impacting their daily lives, and that they're not getting the help they need.

What's more, Dr. Al-Aly said, it's unclear whether

BRAIN *continued on following page*

TEST *continued from previous page*

are excreted in urine. A test strip can detect them, revealing results in about 20 minutes.

Researchers tested this system in mice genetically engineered to develop human-like lung tumors. Using aerosol nebulizers, they delivered 20 sensors to mice with the equivalent of stage I or II cancer. Using a machine learning algorithm, they identified the four most accurate sensors. With 100% specificity, those four sensors exhibited sensitivity of 84.6%. "One advantage of using inhalation is it's noninvasive, and another advantage is it distributes across the lung quite homogeneously," Dr. Tan said. The time from inhalation to detection is also fast — in mice; the whole process took about 2 hours, and Dr. Zhong speculated it would not be much longer in humans.

An injectable version of this technology, also developed at MIT, has been tested in a phase 1 clinical trial for diagnosing liver cancer and nonalcoholic steatohepatitis. The injection works in tandem with a urine test, the researchers showed in 2021. According to Tan, his research group (led by Sangeeta Bhatia, MD, PhD) was the first to describe this type of technology to screen for diseases.

The lab is also working toward using inhalable sensors to distinguish between viral, bacterial, and fungal pneumonia. And the technology could also be used to diagnose other lung conditions like asthma and chronic obstructive pulmonary disease, Dr. Tan said.

The tech is certainly "innovative," remarked Gaetano Rocco, MD, a thoracic surgeon and lung cancer researcher at Memorial Sloan Kettering Cancer Center, Basking Ridge, New Jersey, who was not involved in the study.

Still, challenges may arise when applying it to people. Many factors are involved in regulating fluid volume, potentially interfering with the ability to detect the compounds in the urine, Dr. Rocco said. Diet, hydration, drug interference, renal function, and some chronic diseases could all limit effectiveness. Another challenge: Human cancer can be more heterogeneous, so four sensors may not be enough, Dr. Zhong said. He and colleagues are beginning to analyze human biopsy samples to see whether the same sensors that worked in mice would also work in humans. If all goes well, they hope to do studies on humans or nonhuman primates. ■

Saadia A. Faiz, MD, FCCP, comments: This article explores an innovative nonradiographic technology for early detection of lung cancer in animal models. The inhalable sensor later detected through urine sample specifically targets protease enzymes linked to early-stage adenocarcinoma of the lung. Clearly, further study will be needed; however, this modality may also have applications in other pulmonary disease, including infection.

Dr. Faiz is a member of the CHEST Physician *Editorial Board*.

LONG COVID

Why are women more likely to get long COVID?

BY TINKER READY

Annette Gillaspie, a nurse in a small Oregon hospital, hoped she would be back working with patients by now. She contracted COVID-19 on the job early in the pandemic and ended up with long COVID. After she recovered a bit, her fatigue and dizziness returned, and she is still working a desk job. She has also experienced more severe menstrual periods than before she had COVID.

"Being a female with long COVID definitely does add to the roller-coaster effect of symptoms," Ms. Gillaspie said. Long COVID affects nearly twice as many women as men, with 6.6% of women reporting long COVID compared with 4% of men, according to a recent Census Bureau survey reported by the Centers for Disease Control and Prevention (CDC). Researchers are trying to determine why, what causes the gender disparity, and how best to treat it. Scientists are also starting to look at the impact of long COVID on female reproductive health, including menstruation, pregnancy, and menopause.

Sex differences are common in infection-associated illnesses, said Beth Pollack, MS, a research scientist specializing in long COVID in the Massachusetts Institute of Technology's (MIT) Department of Biological Engineering, Cambridge, Massachusetts. "It informs research priorities and the lens with which we understand long COVID."

For example, reproductive health issues for women, such as puberty, pregnancy, and menopause, can alter the course of illness in a subset of women in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS), a condition that can cause dizziness and worse. "This suggests that sex hormones may play key roles in immune responses to infections," Ms. Pollack said.

ME/CFS and long COVID in women

Some of the research into long COVID is being led by teams studying infection-associated chronic illnesses like ME/CFS. The problem: Advocates say ME/CFS has been underresearched. Poorly understood for years, the condition is one of a handful of chronic illnesses linked to infections, including Lyme disease and now long COVID. Perhaps not coincidently, they are more likely to affect women.

Many of the research findings about long COVID mirror data that emerged in past ME/CFS research, said Jaime Seltzer, the scientific director at #MEAction, Santa Monica, California, an advocacy group. One point in particular: ME/CFS strikes women about twice as much as men, according to the CDC.

Ms. Seltzer said the response to long COVID could be much further ahead if the research community acknowledged the work done over the years on ME/CFS. Many of the potential biomarkers and risk factors emerging for long COVID were also suspected in ME/CFS, but not thoroughly studied, she said. She also said not enough work has been done to unravel the links between gender and these chronic conditions.

"We're stuck in this Groundhog Day situation," she said. "There isn't any research, so we can't say anything definitively."

Some new research, some new clues

Scientists like Ms. Pollack are slowly making inroads. She was lead author on a 2023 review investigating the impact of long COVID on female reproductive health. The paper highlights long COVID links to ME/CFS, POTS, and Ehlers-Danlos syndrome (EDS), and female reproductive health issues. The hope is physicians will examine how the

WOMEN *continued on following page*

BRAIN *continued from previous page*

the impacts of the brain damage are permanent or how to stop them from worsening. Researchers and clinicians need a better understanding of the mechanism that allows this virus to enter the brain and do structural damage. If it's inflammation, will anti-inflammatory or antiviral medications work at preventing it? Will steroids help to offset the damage? "It's critical we find some answers," he said.

"SARS-CoV-2 isn't going anywhere," Dr. Al-Aly said. "It will continue to infect the population, so if this is indeed a virus that damages the brain in the long term or permanently, we need to figure out what can be done to stop it." ■

LONG COVID

Five predictions for progress in 2024

BY SARA NOVAK

With a number of large-scale clinical trials underway and researchers on the hunt for new therapies, long COVID scientists are hopeful this is the year patients — and doctors who care for them — will finally see improvements in treating their symptoms. Here are five predictions — all based on encouraging research — that could happen in 2024. At the very least, they are promising signs of progress against a debilitating and frustrating disease.

1) We'll gain a better understanding of each long COVID phenotype

This past year, a wide breadth of research began showing that long COVID can be defined by a number of different disease phenotypes that present a range of symptoms. Researchers identified four clinical phenotypes: chronic fatigue-like syndrome, headache, and memory loss; respiratory syndrome, which includes cough and difficulty breathing; chronic pain; and neurosensorial syndrome, which causes an altered sense of taste and smell.

Identifying specific diagnostic criteria for each phenotype would lead to better health outcomes for patients instead of treating them as if it were a "one-size-fits-all disease," said Nisha Viswanathan, MD, director of the long COVID program at UCLA Health, Los Angeles, California.

2) Monoclonal antibodies may change the game

We're starting to have a better understanding that what's been called "viral persistence" as a main cause of long COVID may potentially be treated with monoclonal antibodies. These are antibodies produced by cloning unique white blood cells to target the circulating spike proteins in the blood that cause the immune system to react as if it's still fighting acute COVID-19.

Smaller-scale studies have shown promising results. A January 2024 study published in *The American Journal of Emergency Medicine* followed three patients who completely recovered from long COVID after taking monoclonal antibodies. Larger clinical trials are underway at the University of California, San Francisco (UCSF), to test targeted monoclonal antibodies. If the results show that monoclonal antibodies are beneficial, then it could be a game changer for a large swath of patients around the world, said David F. Putrino, PhD, who runs the long COVID clinic at Mount Sinai Health System in New York City. "The idea is the downstream damage caused by viral persistence will resolve itself once you wipe out the virus," Dr. Putrino said.

3) Paxlovid could prove effective for long COVID

The US Food and Drug Administration granted approval for Paxlovid last May for the treatment of mild to moderate COVID-19 in adults at a high risk for severe disease. The medication is made up of two drugs packaged together. The first, nirmatrelvir, works by blocking a key enzyme required for virus replication. The second, ritonavir, is an antiviral that's been used in patients with HIV and helps boost levels of antivirals in the body.

In a large-scale trial headed up by Dr. Putrino and his team, the oral antiviral is being studied for use in the post-viral stage in patients who test negative for acute COVID-19 but have persisting symptoms of long COVID. Similar to monoclonal antibodies, the idea is to quell viral persistence. The treatment has been controversial because it's life-changing for some patients and ineffective for others. In addition, it can cause a range of side effects such as diarrhea, nausea, vomiting, and an impaired sense of taste.

4) Anti-inflammatories like metformin could prove useful

Many of the inflammatory markers persistent in patients with long COVID were present in patients with autoimmune diseases like rheumatoid arthritis (RA), according to a study published in *JAMA*. The hope is anti-inflammatory medications may be used to reduce inflammation causing long COVID symptoms. But drugs used to treat RA like abatacept and infliximabcan have serious side effects, including increased risk for infection, flu-like symptoms, and burning of the skin. "Powerful anti-inflammatories can change a number of pathways in the immune system," said Grace McComsey, MD, who leads the long COVID RECOVER study at University Hospitals Health System in Cleveland, Ohio. However, a study published in *The Lancet Infectious Diseases* found the diabetes drug metformin reduced a patient's risk for long COVID up to 40% when the drug was taken during the acute stage. Metformin is an inexpensive and widely available drug with relatively few side effects compared with other medications.

5) Serotonin levels — and selective serotonin reuptake inhibitors (SSRIs) — may be keys to unlocking long COVID

A study published in the journal *Cell* found lower circulating serotonin levels in patents with long COVID than in those who did not have the condition. The study also found the SSRI fluoxetine improved cognitive function in rat models infected with the virus.

Researchers found the reduction in serotonin levels was partially caused by the body's inability to absorb tryptophan, an amino acid that's a precursor to serotonin. Overactivated blood platelets may also have played a role.

Michael Peluso, MD, an assistant research professor of infectious medicine at the UCSF School of Medicine, hopes to take the finding a step further, investigating whether increased serotonin levels in patients with long COVID will lead to improvements in symptoms. If patients show an improvement in symptoms, the next step is looking into whether SSRIs boost serotonin levels in patients and reduce their symptoms. ■

WOMEN *continued from previous page*

menstrual cycle, pregnancy, and menopause affect symptoms and illness progression of long COVID.

The Tal Research group at MIT (where Ms. Pollack works) has also added long COVID to the list of infection-associated illnesses it studies. The lab is conducting a large study looking into both Lyme disease and long COVID. The goals are to identify biomarkers that can predict who will not recover and to advance available treatments.

Barriers to progress remain

Alba Azola, MD, an assistant professor of physical medicine at Johns Hopkins Medicine, Baltimore, Maryland, has worked with long COVID patients and is now seeing people with ME/CFS, said the symptoms of infection-associated chronic illness can mimic menopause, and many of her patients received that misdiagnosis. She recommends doctors rule out long COVID for women with multiple symptoms before attributing symptoms to menopause.

Seeing that some long COVID patients were developing ME/CFS, staff at the Bateman Horne Center in Salt Lake City, Utah, set up a program for the condition in 2021. They were already treating patients with ME/CFS and what they call "multi-symptom chronic complex diseases."

Jennifer Bell, a certified nurse practitioner at the center, said she has not seen any patients with ovarian failure but plenty with reproductive health issues. "There definitely is a hormonal connection, but I don't think there's a good understanding about what is happening," she said. Most of her patients are female, and the more serious patients tend to go through a worsening of their symptoms in the week prior to getting a period, she said.

One thing Ms. Bell said she's noticed in the past year is an increase in patients with EDS, which is also more common in women. Like long COVID, many of the conditions traditionally treated at the center have no cure. But Ms. Bell said the center has developed expertise in treating postexertional malaise, a common symptom of long COVID, and keeps up with the literature for treatments to try, like the combination of guanfacine and the antioxidant N-acetyl cysteine to treat brain fog, an approach developed at Yale.

With long COVID, researchers have warned that symptoms vary so much that treatment will need to be targeted. Ms. Pollack agrees and sees a role for personalized medicine. We need to "identify phenotypes within and across these overlapping and co-occurring illnesses so we can identify the right therapeutics for each person," she said.

As for Ms. Gillaspie, she still hopes her long COVID will subside so she can return to her normal nursing duties. "I just got to a point where I realized I'm likely never going to be able to do my job," she said. "It was incredibly heartbreaking, but it's the reality of long COVID, and I know I'm not the only one to have to step away from a job I loved." ■

NETWORKS

Biologics in COPD, managing respiratory infections, improving inpatient sleep, and more

AIRWAYS DISORDERS NETWORK
Asthma and COPD Section

Emerging role of biologics in COPD: A new direction

Remodeling of airways and destruction of parenchyma by immune and inflammatory mechanisms are the leading cause of lung function decline in patients with COPD. Type 2 inflammation has been recognized as an important phenotypic pathway in asthma. However, its role in COPD has been much less clear, which had been largely associated with innate immune response.


Dr. Alismail

Activation of Interleukin (IL)-25, IL-33, thymic stromal lymphopoietin (TSLP) produces type 2 cytokines IL-4, IL-5, and IL-13, either by binding to ILC2 or by direct Th2 cells resulting in elevated eosinophils in sputum, lungs, and blood, as well as fractional exhaled nitric oxide. The combined inflammation from this pathway underpins the pathological changes seen in airway mucosa, causing mucous hypersecretion and hyperresponsiveness.

Prior trials delineating the role of biologics, such as mepolizumab and benralizumab, showed variable results with possible benefit of add-on biologics on the annual COPD exacerbations among patients with eosinophilic phenotype of COPD.

More recently, the BOREAS trial evaluated the role of dupilumab as an add-on therapy for patients with type 2 inflammation-driven COPD established using blood eosinophil count of at least 300/mL at initial screening. Dupilumab is a human monoclonal antibody that blocks combined IL-4 and IL-13 pathways with a broader effect on the type 2 inflammation. It included patients with moderate to severe exacerbations despite maximal triple inhaler therapy with blood eosinophilia. Patients with asthma were excluded. This 52-week trial showed reduction in annual moderate to severe COPD exacerbations, sustained lung function improvement as measured by prebronchodilator FEV_1, and improvement in patient-reported respiratory symptoms. Evaluation of sustainability of these results with therapy step-down approaches should be explored.

–Maria Azhar, MD, Section Fellow-in-Training
–Abdullah Alismail, PhD, RRT, FCCP, Section Member
–Raghav Gupta, MD, FCCP, Section Member

CHEST INFECTIONS AND DISASTER RESPONSE NETWORK
Disaster Response and Global Health Section

Management of severe respiratory viruses in 2024

Viral infections frequently cause acute respiratory failure requiring ICU admission. In the United States, influenza causes over 50,000 deaths annually and SARS-CoV2 resulted in 170,000 hospitalizations in December 2023 alone. RSV lacks precise incidence data due to inconsistent testing but is increasingly implicated in respiratory failure.

Patients with underlying pulmonary comorbidities are at increased risk of severe infection. RSV induces bronchospasm and increases the risk for severe infection in patients with obstructive lung disease. Additionally, COPD patients with viral respiratory infections have higher rates of ICU admission, mechanical ventilation, and death compared with similar patients admitted for other etiologies.


Dr. Kattih

Diagnosis typically is achieved with nasopharyngeal PCR swabs. Positive viral swabs correlate with higher ICU admission and ventilation rates in patients with COPD. Coinfection with multiple respiratory viruses leads to higher mortality rates and bacterial and fungal coinfection further increases morbidity and mortality.

Treatment includes respiratory support with noninvasive ventilation and high-flow nasal cannula, reducing the need for mechanical ventilation. Inhaled bronchodilators are particularly beneficial in patients with RSV infection. Oseltamivir reduces mortality in severe influenza cases, while remdesivir shows efficacy in SARS-CoV2 infection not requiring invasive ventilation. Severe SARS-CoV2 infection can be treated with immunomodulators. However, their availability is limited. Corticosteroids reduce mortality and mechanical ventilation in patients with SARS-CoV2; however, their use is associated with worse outcomes in influenza and RSV.

Vaccination remains crucial for prevention of severe disease. RSV vaccination, in addition to influenza and SARS-CoV2 immunization, presents an opportunity to reduce morbidity and mortality.

–Zein Kattih, MD, Section Fellow-in-Training
–Kathryn Hughes, MD
–Brian Tran, MD

CRITICAL CARE NETWORK
Palliative and End-of-Life Care Section

Compassionate extubation and beyond: Is there a need for more guidance in managing end-of-life in the intensive care unit?


Dr. Birdwell

For providers caring for critically ill patients, navigating death and dying in the intensive care unit (ICU) with proficiency and empathy is essential. Approximately 20% of deaths in the United States occur during or shortly after a stay in the ICU and approximately 40% of ICU deaths involve withdrawal of artificial life support (WOALS) or compassionate extubation.

This is a complex process that may involve advanced communication with family, expertise in mechanical ventilation, vasopressors, dialysis, and complex symptom management. Importantly, surrogate medical decision-making for a critically ill patient can be a challenging experience associated with anxiety and depression. How the team approaches WOALS can make a difference to both patients and decision-makers. Unfortunately, there is striking variation in practice and lack of guidance in navigating issues that arise at end-of-life in the ICU. One study of 2,814 hospitals in the US with ICU beds found that 52% had intensivists while 48% did not. This highlights the importance of developing resources focusing on end-of-life care in the ICU setting regardless of the providers' educational training.

Important elements could include the role for protocol-based WOALS, use of oxygen, selection and dosing strategy of comfort-focused medications, establishing expectations, and addressing uncertainties. This would be meaningful in providing effective, ethical end-of-life care based on evidence-based strategies. While death may be unavoidable, a thoughtful approach can allow providers to bring dignity to the dying process and lessen the burden of an already difficult experience for patients and families alike.

–Angela L. Birdwell, DO, MA, Section Chair
–Nehan Sher, MD, Section Member

SLEEP MEDICINE NETWORK
Nonrespiratory Sleep Section

The not-so-silent night: Challenges in improving sleep in inpatients with Dr. Vineet Arora

Q: Are there interventions that can be readily implemented to improve sleep quality for hospitalized patients?


Dr. Arora

Dr. Arora: A patient's first night in the hospital is probably not the night to liberalize sleep; you're still figuring out whether they're stable. But by the second or third day, you should be questioning—do you need vitals at night? Do you need a 4 AM blood draw?

We did an intervention called SIESTA that included both staff education about batching care and system-wide, electronic health record-based interventions to remind clinicians that as patients get better, you can deintensify their care. And we're currently doing a randomized controlled trial of educating and empowering patients to ask their teams to help them get better sleep.

Q: Does hospital sleep deprivation affect patients after discharge?

Dr. Arora: Absolutely. "Posthospital syndrome" is the idea that 30 days after discharge, you're vulnerable to getting readmitted – not because of the disease you came in with, but something else. And people who report sleep complaints in the

hospital are more likely to be readmitted.

When people are acutely sleep deprived, their blood pressure is higher. Their blood sugar is higher. Their cytokine response and immune function are blunted. And our work shows that sleep deficits from the hospital continue even when you go home. Fatigue becomes a very real issue. And when you're super fatigued, are you going to want to do your physical therapy? Will you be able to take care of yourself? Will you be able to learn and understand your discharge instructions?

We have such a huge gap to improve sleep. It's of interest to people, but they are struggling with how to do it. And that's where I think empowering frontline clinicians to take the lead is a great project for people to take on.

Vineet Arora, MD, MAPP, is the Dean for Medical Education at the University of Chicago and an academic hospitalist who specializes in the quality, safety, and experience of care delivered to hospitalized adults.

–Alison Szabo, MD
–Lisa Wolfe, MD, Section Member

THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK

Lung Cancer Section

Nurturing health equity in smoking cessation care

Lung cancer stands as the leading cause of cancer-related deaths globally, with its prevalence casting a long and challenging shadow. The most important risk factor for lung cancer is tobacco use, a relationship strongly substantiated by data. The impact of smoking cessation to reduce lung cancer incidence is underscored by the US Preventive Services Task Force, which mandates that smoking cessation services be an integral component of lung cancer screening programs.


Dr. Ogake

However, beneath the surface of this overarching concern lies a web of factors contributing to racial and ethnic disparities in smoking cessation. Cultural intricacies play a pivotal role in shaping these disparities. Despite higher instances of light or intermediate smoking, racially ethnic minority groups in the general population often face greater challenges in achieving smoking cessation, as highlighted by Bacio, et al. Adding another layer to this complex scenario is the profound impact of sustained smoking during cancer treatment. Research suggests that for individuals diagnosed with lung cancer, smoking cessation can markedly boost treatment efficacy, reduce the risk of secondary tumors, and even double the chances of survival.

A study by Harris, et al. delving into the preferences of current smokers within a lung cancer screening setting uncovered noteworthy insights. White participants exhibited a fourfold greater likelihood of favoring a digital format for receiving smoking cessation information, while their Black counterparts expressed a preference for face-to-face support, phone assistance, or printed materials.

Moreover, a meta-analysis conducted by Jabari, et al. sheds light on the efficacy of culturally targeted smoking interventions. This comprehensive review describes a dual-level approach to tailoring smoking cessation health interventions: surface and deep. Surface adaptations encompass elements like language and imagery, which aim to enhance the acceptability of interventions within specific communities. Simultaneously, deep-tailored elements identify culturally significant factors that can fundamentally influence the behavior of the target population. The findings of this meta-analysis reveal that the integration of culturally tailored components into standard interventions significantly enhances their efficacy in facilitating smoking cessation.

In conclusion, sustained smoking cessation is a crucial element in combating the global burden of lung cancer. Recognizing the importance of individualized approaches in health care, it is imperative to tailor smoking cessation communications and interventions to diverse cultural influences and socioeconomic factors. Culturally tailored smoking cessation programs that account for nuances specific to each community have the potential to significantly enhance their effectiveness. This necessitates a shift towards individualized smoking cessation care, with a targeted focus on increasing cessation rates among racial and ethnic minority groups. In doing so, we take a step closer to a more equitable landscape in the battle against lung cancer.

–Stella Ogake, MD, FCCP, Section Member

All references available online at chestphysician.org.

Leading with integrity

A values-driven year

BY JACK D. BUCKLEY, MD, MPH, FCCP

As the President of the American College of Chest Physicians (CHEST), I have the privilege of regularly addressing CHEST members through a quarterly column where I can share updates and expand on topics that we hold in high regard.

Dr. Buckley

As such, I'd like to focus on the CHEST commitment to social responsibility and the work we have done and will continue to do throughout this year and beyond.

In 2023, under the leadership of my predecessor, Doreen Addrizzo-Harris, MD, FCCP, CHEST made strong changes to our organizational focus, including cementing Social Responsibility as a formal pillar of CHEST. In addition to our other four pillars—Education, People, Products, and Growth—this new pillar is a sign of our stronger commitment to be more explicit in our aspirations, measure our success, and move the bar higher.

As part of the new social responsibility pillar, CHEST philanthropy evolved from what was known as the CHEST Foundation and defined a new giving strategy that reflects our organizational commitment to clinical research, community impact, support for the profession, and fostering education. Through growth in our research support and furthering community impact, 2024 will be a strong year of providing grant support aligned to this new giving strategy.

In addition, we formalized how CHEST will pursue our new social responsibility pillar. In 2023, we articulated our organizational values—Community, Inclusivity, Innovation, Advocacy, and Integrity—which will serve as a consistent reminder of who we are as an organization and guide us in decisions as we pursue our mission.

Led by these values, CHEST will use its voice and capabilities to promote change that equitably impacts our community. In 2024 specifically, the organization looks forward to engaging actively with social responsibility by expanding volunteer opportunities local to CHEST headquarters and in conjunction with the location of the annual meeting.

It is also my hope that 2024 will be known as a year of member input, starring feedback from none other than you, our members.

For those who recall my address from the Opening Session at CHEST 2023, I very much encourage you to reach out to share with me your thoughts, your CHEST experience, and more at president@chestnet.org. I look forward to having this regular touchpoint with all of you, and I welcome your input on topics you'd like to hear more on.

Until next time,
Jack D. Buckley, MD, MPH, FCCP

Find your community with CHEST Interest Groups

Learn about the LGBTQ+ at CHEST, Respiratory Care, and Women in Chest Medicine Interest Groups

The value of member community is highly prized at CHEST. In order to provide supportive and engaging spaces where members can convene, share resources, and learn from other members who share similar lived experiences and interests, we were proud to add Interest Groups to our member offerings in 2023.

Dr. Danckers

Dr. O'Neil

Dr. Pisani

The introduction of Interest Groups has proven to be an effective way to organically connect CHEST members with shared interests and passions. Membership in one of these groups allows for networking in a smaller setting, with the goals of supporting career development and enriching an individual's professional path.

To learn more about the three existing Interest Groups, we spoke with each group's chair: Margaret Pisani, MD, FCCP, Chair of the Women in Chest Medicine Interest Group; Kevin O'Neil, MD, FCCP, Chair of the Respiratory Care Interest Group; and Mauricio Danckers, MD, FCCP, Chair of the LGBTQ+ at CHEST Interest Group.

1) Tell us about the key issues that your Interest Group is trying to address and who should join this group.

Mauricio Danckers: Our LGBTQ+ community continues to be the target of unrelenting discrimination. Current disparities toward sexual and gender-diverse individuals persistently hinder their personal and professional growth. There are several key issues currently affecting the LGBTQ+ community; among those are ongoing health care disparities, lack of education of our providers on LGBTQ+ health issues, underrepresentation of scientific research in the LGBTQ+ community, and scarce opportunities for mentorship and networking among LGBTQ+ health professionals. Our Interest Group seeks to provide a space to work together to overcome these shortcomings. Through the exchange of ideas, the opportunity for interprofessional collaborations, resource development and dissemination, scholar productivity, organic mentoring, and patient and provider advocacy, we seek to create change and better serve the LGBTQ+ identity in our CHEST community.

Anyone who is ready to make a change for the LGBTQ+ community, their care, and their well-being is encouraged to join. Self-identification as a member of the LGBTQ+ community is not a prerequisite for joining our group. We welcome individuals committed to advancing gender-affirming health, wellness, and education approaches to reduce health disparities.

Kevin O'Neil: The Respiratory Care Interest Group is invested in a number of focus areas, including improving collaboration between pulmonary/critical care/sleep physicians and respiratory care providers with a goal of improved and more efficient patient care, addressing critical shortages in the respiratory therapist (RT) workforce in collaboration with respiratory care organizations by identifying and supporting strategies to grow the workforce, and promoting wellness in all members of the community by providing tools and resources to mitigate stress and reduce burnout.

This Interest Group is for any CHEST member with an interest in respiratory care education or care delivery.

Margaret Pisani: The Women in Chest Medicine Interest Group has two overarching goals. The first is focused on ensuring that content around sex as a biologic variable and the impact of gender—as they relate to lung disease and critical care—are addressed in the educational activities of CHEST. The second is to provide mentorship and aid with career advancement for women in pulmonary, critical care, and sleep medicine (PCCSM) who are members of CHEST.

Anyone who does research on the impact of sex and gender as biologic variables—and the importance of these variables in lung disease—is welcome in this Interest Group. Persons who would like to be involved in mentoring the next generation of women and junior members who would like to learn more about how to be active at CHEST are also encouraged to join.

2) What motivated you to lead an Interest Group?

Danckers: My path in medicine as an LGBTQ+ individual has been unique and personal. It has opened the opportunity to witness the urgency of the changes needed to serve our LGBTQ+

COMMUNITY *continued on following page*

SLEEP STRATEGIES

Daylight Saving Time

Saving light but endangering health

BY SUBODH K. ARORA, MD, AND JENNIFER L. CREAMER, MD

Dr. Arora (left) is a sleep medicine attending physician and pediatrician and the Associate Program Director of the Sleep Medicine Fellowship at Walter Reed National Military Medical Center. Dr. Creamer is the Chief of Sleep Medicine at Walter Reed National Military Medical Center as well as the Program Director of the Sleep Medicine Fellowship.

The American Academy of Sleep Medicine recently published its position statement reaffirming its support of utilizing permanent Standard Time (ST) as opposed to Daylight Saving Time (DST). DST usually occurs on the second Sunday in March when we "spring forward" by advancing the clock by 1 hour. The analogous "fall back" on the first Sunday in November refers to reversion back to the original ST, which is more synchronous with the sun's natural pattern of rise and fall.

The earliest argument for DST practice dates back to the 1700s when Benjamin Franklin wrote a satirical piece in the *Journal of Paris* suggesting that advancing the clock to rise earlier in the summer would lead to economization in candle usage and save significant resources for Parisians. The modern version of this assertion infers that increased daylight in the evening will lead to increased consumer activity and work productivity with consequent economic benefits. Interestingly, the adoption of DST has demonstrated the opposite—a reduction in work productivity and economic losses. Another often-cited claim is that increased daylight in the evening could lead to fewer motor vehicle accidents. However, the reality is that DST is associated with more frequent car accidents in the morning.

The greatest drawback of Daylight Saving Time is that, initially, it leads to sleep deprivation and chronically drives asynchronization between the circadian clock and the social clock.

The greatest drawback of DST is that, initially, it leads to sleep deprivation and chronically drives asynchronization between the circadian clock and the social clock. Humans synchronize their internal clock based on several factors, including light, temperature, feeding, and social habits. However, light is the strongest exogenous factor that regulates the internal clock. Light inhibits secretion of melatonin, an endogenous hormone that promotes sleep onset. While there is some individual variation in circadian patterns, exposure to bright light in the morning leads to increased physical, mental, and goal-directed activity.

Conversely, darkness or reduced light exposure in the evening hours promotes decreased activity and sleep onset via melatonin release. DST disrupts this natural process by promoting increased light exposure in the evening. This desynchronizes solar light from our internal clocks, causing a relative phase delay. Acutely, patients experience a form of imposed social jet lag. They lose an hour of sleep due to diminished sleep opportunity, as work and social obligations are typically not altered to allow for a later awakening. With recurrent delays, this lends to a pattern of chronic sleep deprivation which has significant health consequences.

Losing an hour of sleep opportunity as the clock advances in spring has dire consequences. The transition to DST is associated with increased cardiovascular events, including myocardial infarction, stroke, and admissions for acute atrial fibrillation. A large body of work has shown that acute reduction of sleep is associated with higher sympathetic tone, compromised immunity, and increased inflammation. Further, cognitive consequences can ensue in the form of altered situational awareness, increased risky behavior, and worse reaction time—which manifest as increased motor vehicle accidents, injuries, and fatalities. Emergency room visits and bounce-back admissions, medical errors and injuries, and missed appointments increase following the switch to DST. Psychiatric outcomes, including deaths due to suicide and overdose, are worse with the spring transition.

Is the problem with DST merely limited to springtime, when we lose an hour of sleep? Not quite. During the "fall back" period, despite theoretically gaining an hour of sleep opportunity, people exhibit evidence of sleep disruption, psychiatric issues, traffic accidents, and inflammatory bowel disease exacerbations. These consequences likely stem from a discordance between circadian and social time, which leads to an earlier awakening based on circadian physiology as opposed to the clock time.

The acute impact of changing our sleep patterns during transitions in clock time may be appreciated more readily, but the damage is much more insidious. Chronic exposure to light in the late evening creates a state of enhanced arousal when the body should be winding down. The chronic incongruency between clock and solar time leads to dyssynchrony in our usual

SLEEP *continued on following page*

COMMUNITY *continued from previous page*

community better. I wanted to lead this Interest Group to connect to other members interested in advancing health care equity for LGBTQ+ individuals, to inspire one another to achieve major changes in LGBTQ+ health education, and to ignite an educational and social initiative supported by CHEST to witness the LGBTQ+ medical community thriving while grounded on mentoring and advocacy.

O'Neil: I've been a CHEST member for more than 35 years and involved with respiratory care almost as long. The relationship between pulmonary/critical care physicians and RTs is unique, and RTs are critically important to my ability to care for my patients. I am committed to facilitating opportunities for collaboration between the two groups.

Pisani: I am motivated by my passion to ensure we are providing the best possible education to our members and patients and supporting the next generation of leaders in the PCCSM community.

3) What are the goals for your Interest Group in 2024?

Danckers: 2024 will be an exciting year, no doubt about it! Our goals for 2024 are: 1) to connect talented individuals with professional goals that align with the ones from the Interest Group and CHEST, 2) to increase the presence of the LGBTQ+ identity representation in our CHEST scientific meetings and educational offerings, 3) to build a resource platform for LGBTQ+ health education with the innovative approach CHEST is known to provide, and 4) to provide venues to inspire and support scholarly work within the LGBTQ+ community.

O'Neil: Growing the Interest Group membership and increasing opportunities for RTs to participate in CHEST activities by providing a landing space for new RT members are key initiatives for us. We are also hoping to increase the visibility of the Interest Group through events at the annual meeting, educational offerings, and other opportunities as they arise. We will also focus on improving communication between CHEST and other respiratory organizations.

Pisani: We are focused on ensuring that sex and gender topics are addressed during scientific presentations when relevant to research and patient care and developing resources on specific topics where there is data regarding the impact of sex and gender in lung disease. ■

To learn more about Interest Groups and how to join, go to chestnet.org/interest-groups.

CRITICAL CARE COMMENTARY

Implementing a critical care TEE program at your institution

Starting from the ground up!

BY KEVIN PROUD, MD, FCCP

Bedside-focused cardiac ultrasound assessment, or cardiac point-of-care ultrasound (POCUS), has become common in intensive care units throughout the US and the world. Many clinicians argue a POCUS cardiac assessment should be completed in most hypotensive patients and all cases of undifferentiated shock.

However, obtaining images adequate for decision making via standard transthoracic echo (TTE) is not possible in a significant number of patients; as high as 30% of critically ill patients, according to The American Society of Echocardiography (ASE) guidelines. Factors common to critically ill patients, such as invasive mechanical ventilation, external dressings, and limited mobility, contribute to poor image acquisition.

In almost all these cases, the factors limiting image acquisition can be eliminated by utilizing a transesophageal approach. In a recent study, researchers were able to demonstrate that adding transesophageal echocardiography (TEE) to TTE in critically ill patients yielded a new diagnosis or a change in management about 45% of the time.

Using transesophageal ultrasound for a focused cardiac assessment in hemodynamically unstable patients is not new — and is often referred to as rescue TEE or resuscitative TEE. A broader term, transesophageal ultrasound, has also been used to include sonographic evaluation of the lungs in patients with poor acoustic windows. At my institution, we use the term, critical care, to define TEE performed by a noncardiology-trained intensivist in an intubated critically ill patient.

Two barriers often work together to create a vicious cycle that stops the development of a TEE program at its start. These barriers include the lack of training and lack of equipment.

Regardless of the term, the use of transesophageal ultrasound by the noncardiologist in the ICU appears to be a developing trend. As with other uses of POCUS, ultrasound machines continue to be able to "do more" at a lower price point. In 2024, several cart-based ultrasound machines are compatible with transesophageal probes and contain software packages capable of common cardiac measurements.

Despite this growing interest, intensivists are likely to encounter barriers to implementing critical care TEE. Our division recently implemented adding TEE to our practice. Our practice involves two separate systems: a Veterans Administration hospital and a university-based county hospital. Our division has integrated the use of TEE in the medical ICU at both institutions. Having navigated the process at both institutions, I can offer some guidance in navigating barriers.

The development of a critical care TEE program must start with a strong base in transthoracic cardiac POCUS, at least for the foreseeable future. Having a strong background in TTE gives learners a solid foundation in cardiac anatomy, cardiac function, and ultrasound properties. Obtaining testamur status or board certification in critical care echocardiography is not an absolute must but is a definite benefit. Having significant experience in TTE image acquisition and interpretation will flatten the learning curve for TEE. Interestingly, image acquisition in TEE is often easier than in TTE, so the paradigm of learning TTE before TEE may reverse in the years to come.

Dr. Proud is Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Pulmonary and Critical Care Medicine Program Director, UT Health San Antonio.

Two barriers often work together to create a vicious cycle that stops the development of a TEE program at its start. These barriers include the lack of training and lack of equipment, specifically a TEE probe. Those who do not understand the value of TEE may ask, "Why purchase equipment for a procedure that you do not yet know how to do?" The opposite question can also be asked, "Why get trained to do something you don't have the equipment to perform?"

My best advice to break this cycle is to "dive in" to whichever barrier seems easier to overcome first. I started with obtaining knowledge and training. Obtaining training and education in a procedure that is historically not done in your specialty is challenging but is not impossible. It takes a combination of high levels of self-motivation and at least one colleague with the training to support you. I approached a cardiac anesthesiologist, whom I knew from the surgical ICU. Cardiologists can also be a resource, but working with cardiac anesthesiologists offers several advantages. TEEs done by cardiac anesthesiologists are similar to those done in ICU patients (ie, all patients are intubated and sedated). The procedures are also scheduled several days in advance, making it easier to integrate training into your daily work schedule. Lastly, the TEE probe remains in place for several hours, so repeating the probe manipulations again as a learner does not add additional risk to the patient. In my case, we somewhat arbitrarily agreed that I participate in 25 TEE exams. (CME courses, both online and in-person simulation, exist and greatly supplement self-study.)

Obtaining equipment is also a common barrier, though this has become less restrictive in the last several years. As previously mentioned, many cart-based ultrasound machines can accommodate a TEE probe. This changes the request from purchasing a new machine to "just a probe." Despite the higher cost than most other probes, those in charge

CRITICAL CARE *continued on following page*

SLEEP *continued from previous page*

functions, such as food intake, social and physical activity, and basal temperature. Consequently, there is an impetus to fall asleep later. This leads to an accumulation of sleep debt and its associated negative consequences in the general, already chronically sleep-deprived population. This is especially impactful to adolescents and young adults who tend to have a delay in their sleep and wake patterns and, yet, are socially bound to early morning awakenings for school or work.

The scientific evidence behind the health risk and benefit profile of DST and ST is incontrovertible and in favor of ST. The hallmark of appropriate sleep habits involves consistency and appropriate duration. Changing timing forward or backward increases the likelihood of an alteration of the baseline established sleep and circadian consistency.

Unfortunately, despite multiple polls demonstrating the populace's dislike of DST, repeat attempts to codify DST and negate ST persist. The latest initiative, the Sunshine Protection Act, which promised permanent DST, was passed by the US Senate but was thankfully foiled by Congress in 2022. The act of setting a time is not one that should be taken lightly or in isolation because there are significant, long-lasting health, safety, and socioeconomic consequences of this decision. Practically, this entails a concerted effort from all major economies since consistency is essential for trade and geopolitical relations. China, Japan, and India don't practice DST. The European Parliament voted successfully to abolish DST in the European Union in 2019 with a plan to implement ST in 2021. Implementation has yet to be successful due to interruptions from the COVID-19 pandemic as well as the current economic and political climate in Europe. Political or theoretical political victories should not supersede the health and safety of an elected official's constituents. As a medical community, we should continue to use our collective voice to encourage our representatives to vote in ways that positively affect our patients' health outcomes. ■

All references available online at chestphysician.org.

Philips to halt US sales of breathing devices

On January 25, Philips Respironics announced that the company would not return to the sale of hospital ventilation products, certain home ventilation products, portable and stationary oxygen concentrators, and sleep diagnostic products in the US. It will instead focus on the sale of consumables and accessories, including masks.

The company noted that these changes would not affect its commitment to the remediation of devices affected by the June 2021 recall of certain CPAP, BiPAP, and mechanical ventilator devices.

CHEST is working with its society partners to understand next steps for health care providers and will provide additional guidance as it is available, including in future issues of CHEST Physician.

For more information, visit the Philips website at https://www.usa.philips.com/healthcare/e/sleep-and-respiratory-care/src-portfolio-update. ■

CRITICAL CARE *continued from previous page*

of purchasing are often more open to purchasing "a probe" than to purchasing an ultrasound machine.

Additionally, the purchasing decision regarding probes may fall to a different person than it does for an ultrasound machine. If available, POCUS image archiving into the medical record can help offset the cost of equipment, both by increasing revenue via billing and by demonstrating that equipment is being used. If initially declined, continue to ask and work to integrate the purchase into the next year's budget. Inquire about the process of making a formal request and follow that process. This will often involve obtaining a quote or quotes from the ultrasound manufacturer(s).

Keep in mind that the probe will require a special storage cabinet specifically designed for TEE probes. It is prudent to include this in budget requests. If needed, the echocardiography lab can be a useful resource for additional information regarding the cabinet requirements. It is strongly recommended to discuss TEE probe models with sterile processing before any purchasing. If options are available, it is wise to choose a model the hospital already uses, as the cleaning protocol is well established. Our unit purchased a model that did not have an established protocol, which took nearly 6 months to develop. If probe options are limited, involving sterile processing early to start developing a protocol will help decrease delays.

Obtaining hospital privileges is also a common barrier, though this may not be as challenging as expected. Hospitals typically have well-outlined policies on obtaining privileges for established procedures. One of our hospital systems had four different options; the most straightforward required 20 hours of CME specific to TEE and 10 supervised cases by a proctor currently holding TEE privileges.

Discussions about obtaining privileges should involve your division chief, chair of medicine, and the cardiology division chief. Clearly outlining the plan to perform this procedure only in critically ill patients who are already intubated for other reasons made these conversations go much more smoothly. In the development of delineation of privileges, we used the term critical care TEE to clearly define this patient population. During these conversations, highlight the safety of the procedure; ASE guidelines estimate a severe complication rate of less than 1 in 10,000 cases and explain the anticipated benefits to critically ill patients.

In conclusion, at an institution that is already adept at the use of POCUS in the ICU, the additional of critical care TEE within 1 to 2 years is a very realistic achievement. It will undoubtedly require patience, persistence, and self-motivation, but the barriers are becoming smaller every day. Stay motivated! ■

All references available online at chestphysician.org.

In Memoriam

CHEST has been informed of the following deaths of CHEST members. We remember our colleagues and extend our sincere condolences.

William J. Ackerman, MD, FCCP
Joel L. Adams, MD
Eveline A. M. Faure, MD
Thomas A. Sullivan, MD

This month in the journal CHEST® *Editor's picks*

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

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Using Trajectories of Bedside Vital Signs to Identify COVID-19 Subphenotypes
By Sivasubramanium V. Bhavani, MD, et al.

Preserved Ratio Impaired Spirometry and COPD Accelerate Frailty Progression
By Di He, BS, et al.

Changes in Respiratory Mechanics With Trunk Inclination Differs Between Obese and Non-Obese ARDS Patients
By Shailesh Bihari, PhD, et al.

Prospective Evaluation of Venous Excess Ultrasound for Estimation of Venous Congestion
By August Longino, MD, MPH, et al.

Massive Hemoptysis Simulation Curriculum Improves Performance
By Melissa L. New, MD, et al.

Oxygen Therapy in Patients With Intermediate-Risk Acute Pulmonary Embolism
By Deisy Barrios, MD, PhD, et al.

How I Do It: Managing Pulmonary Arterial Hypertension With Cardiopulmonary Comorbidities
By Steeve Provencher, MD, et al.

What do you recommend for this patient with COPD?

BY JERRY A. KRISHNAN, MD, PHD, AND MUHAMMAD ADRISH, MD, FCCP

"Janice Turner" (name changed to protect confidentiality) is a 66-year-old woman with a 40-pack per year history of smoking. She quit smoking 1 year ago and presents to your office for a follow-up visit after discharge from the hospital 14 days ago. This was her second hospitalization for a COPD exacerbation in the past 12 months. She is very worried about having another COPD exacerbation and wants to know if there are additional medications she could try.

Over the past 2 weeks, her respiratory symptoms have improved and returned to her baseline. She has a daily cough with white phlegm on most days and dyspnea on exertion at one-half block on level ground. She reports using her medications as prescribed and is enrolled in a pulmonary rehabilitation program, which she attends twice per week. She uses 2 to 4 inhalations of albuterol each day.

She is on the following regimen for her COPD, which is unchanged compared with what she has been prescribed for the past 12 months: 1) combination inhaled fluticasone furoate, umeclidinium, and vilanterol via the Ellipta® device, one actuation once daily and 2) inhaled albuterol, two puffs as needed every 4 hours via metered dose inhaler. She demonstrates mastery of inhaler technique for both inhaled devices. Her vaccinations are current (pneumococcus, influenza, respiratory syncytial virus, and COVID-19).

On examination, she can complete sentences without respiratory difficulty, and her vital signs are normal. She has decreased breath sounds in all lung fields, with occasional rhonchi. Heart sounds

COPD *continued on following page*

COPD *continued from previous page*

distant, but regular, at 92 beats per minute, and she has no peripheral edema. Arterial blood gas at rest on room air indicates a pH of 7.38, PaO_2 of 63 mm Hg, and $PaCO_2$ of 42 mm Hg. An electrocardiogram shows sinus rhythm and a QTc interval of 420 milliseconds.

Three months ago, when she was clinically stable, you obtained spirometry, a complete blood count with differential, and a chest radiograph to exclude alternate diagnoses for her ongoing respiratory symptoms. She had severe airflow limitation (post-bronchodilator FEV_1 = 40% predicted, FVC = 61% predicted, FEV_1/FVC = 65%). At the time, she also had peripheral eosinophilia (eosinophil count of 350 cells/μL) and hyperinflation without parenchymal infiltrates.

In summary, Ms. Turner has severe smoking-associated COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3E and chronic bronchitis with two severe exacerbations in the past 12 months. She is currently prescribed triple inhaled maintenance therapy with corticosteroids, long-acting β_2-agonist, and long-acting muscarinic antagonist. She has a normal QTc interval.

Three months ago, when she was clinically stable, you obtained spirometry, a complete blood count with differential, and a chest radiograph to exclude alternate diagnoses for her ongoing respiratory symptoms.

So what would you recommend to reduce Ms. Turner's risk of future exacerbations?

In 2011, the US Food and Drug Administration (FDA) approved roflumilast 500 mcg by mouth per day, a selective phosphodiesterase 4 (PDE4) inhibitor, as maintenance therapy to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis. The FDA approval was based on a review of the efficacy and safety of roflumilast in eight randomized, double-blind, controlled clinical trials in 9,394 adults with COPD.

Two subsequently completed randomized clinical trials in 2015 (REACT, 1,945 adults) and 2016 (RE2SPOND, 2,354 adults) also found that maintenance oral treatment escalation with roflumilast significantly reduced the risk of COPD exacerbations compared with placebo. The most common adverse effects reported with long-term use of roflumilast are related to the gastrointestinal tract (diarrhea, nausea, decreased appetite), weight loss, and insomnia. Four weeks of roflumilast at 250 mcg per day prior to dose escalation to 500 mcg per day reduces the risk of treatment discontinuation and improves tolerability compared with initiating treatment with the maintenance dose.

In 2022, the FDA approved a generic version of roflumilast, providing an opportunity for patients to use roflumilast at a lower cost than was previously possible. Importantly, the FDA Prescribing Information includes a warning to avoid the use of roflumilast in patients being treated with strong cytochrome P450 enzyme inducers (eg, rifampin, phenytoin). The FDA Prescribing Information also recommends weighing the risks and benefits of roflumilast in patients with a history of depression or suicidal thoughts or behavior, or patients with unexplained or clinically significant weight loss.

In 2011 (the same year as the FDA approval of roflumilast), the National Institutes of Health/National Heart, Lung, and Blood Institute-funded COPD Clinical Research Network reported that maintenance treatment with azithromycin reduced the risk of COPD exacerbations compared with placebo in a randomized clinical trial of 1,142 adults with COPD (MACRO study). Subgroup analyses indicated that the reduction in the risk of COPD exacerbations with azithromycin was observed in participants with or without chronic bronchitis but not in participants who currently smoked.

Subsequently, two other smaller randomized clinical trials in 2014 (COLUMBUS, 92 participants) and in 2019 (BACE, 301 participants) also demonstrated a reduction in the risk of COPD exacerbations with maintenance azithromycin treatment compared with placebo. Azithromycin can prolong the QT interval and, in rare cases, cause cardiac arrythmias, especially when used with other medications that can prolong the QT interval. There are also concerns that maintenance azithromycin therapy could lead to decrements in hearing or promote the development of macrolide-resistant bacteria. Maintenance treatment with azithromycin to prevent COPD exacerbations is not an FDA-approved indication. The FDA approval for azithromycin is currently limited to treatment of patients with mild to moderate infections caused by susceptible bacteria, but it is often prescribed off-label as maintenance treatment for COPD.

Dr. Krishnan (left) is Professor of Medicine, Division of Pulmonary, Critical Care, Sleep & Allergy, and Professor of Public Health, Division of Epidemiology and Biostatistics, University of Illinois Chicago. Dr. Adrish is Associate Professor, Pulmonary, Critical Care and Sleep Medicine, Baylor College of Medicine, Houston.

On the basis of this body of evidence from clinical trials in COPD, the 2015 CHEST and Canadian Thoracic Society (CTS) guidelines, the 2017 European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, and the 2024 GOLD Strategy Report all include recommendations for treatment escalation with maintenance roflumilast or azithromycin to reduce the risk of COPD exacerbations. For example, the 2024 GOLD Strategy Report recommends roflumilast in patients with severe COPD and chronic bronchitis who continue to have exacerbations despite inhaled maintenance treatment with combination long-acting β_2-agonist and long-acting muscarinic antagonist or with triple therapy with inhaled corticosteroids, long-acting β_2-agonist, and long-acting muscarinic antagonist. An alternative, 2024 GOLD-recommended strategy in this population is maintenance therapy with azithromycin, "preferentially in former smokers." GOLD's preference for using azithromycin in patients with smoking history is based on post-hoc (ie, not part of the original study design) subgroup analyses "suggesting lesser benefit in active smokers" in the MACRO study. Results of such analyses have not been reported in other studies.

There are no results from clinical trials that have directly compared the harms and benefits of initiating maintenance therapy with roflumilast or azithromycin in patients with COPD.

There are no results from clinical trials that have directly compared the harms and benefits of initiating maintenance therapy with roflumilast or azithromycin in patients with COPD. The roflumilast or azithromycin to prevent COPD exacerbations (RELIANCE; NCT04069312) multicenter clinical trial is addressing this evidence gap. The RELIANCE study is funded by the Patient-Centered Outcomes Research Institute and co-led by the COPD Foundation, a not-for-profit organization founded by John W. Walsh, a patient advocate with α1-related COPD. Also, results of two recently completed phase 3 clinical trials with nebulized ensifentrine (ENHANCE-1 and ENHANCE-2), a novel inhibitor of PDE3 and PDE4, were recently published. ENHANCE-1 and ENHANCE-2 studies indicate that twice daily nebulized ensifentrine reduces the risk of COPD exacerbations in patients with moderate or severe COPD. Ensifentrine is under review by the FDA, and a decision about its use in the US is expected in the summer of 2024.

Until the results from the RELIANCE clinical trial and the decision by the FDA about ensifentrine are available, we recommended a discussion with Ms. Turner about whether to initiate treatment with maintenance roflumilast or azithromycin. Both can reduce the risk of exacerbations, and the relative benefits and risks of these two evidence-based options are not yet known. Unless Ms. Turner has specific preferences (eg, concerns about specific adverse effects or differences in out-of-pocket cost) in favor of one over the other, she could flip a coin to decide between initiating maintenance roflumilast or azithromycin. ■

All references are available online at chestwphysician.org.

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