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VOL. 15 · NO. 11 · NOVEMBER 2020

CHEST Physician®

Courtesy American College of Chest Physicians

Dr. Anthony S. Fauci said his optimism is based in part on animal studies and phase 1 data that demonstrate robust neutralizing antibody responses to a vaccine that are equivalent to, if not greater than, natural infection with the SARS-CoV-2 virus.

Fauci: Cautious optimism for COVID-19 vaccine by end of 2020

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2020 ▪ Anthony S. Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases, addressed the virtual American College of Chest Physicians annual meeting as keynote speaker, and delivered a cautiously optimistic message.

A COVID-19 vaccine could be proven effective within the last months of 2020, with distribution of first doses possible before the end of the year, he told meeting attendees.

"Given the rate of infection that's going on in this country, and the distribution of the clinical trial sites involving tens of thousands of volunteers, we project that we will have an answer as to whether or not we have a safe and effective vaccine by November or December," Dr. Fauci explained.

If that timing does come to pass, Dr. Fauci said, it is possible that distribution of doses could start at the end of the year, continuing throughout the beginning and middle of 2021.

Although there are no guarantees, Dr. Fauci is "cautiously optimistic" regarding the timeline. He said that his optimism is based in part on animal studies and phase 1 data that demonstrate robust neutralizing antibody responses to a vaccine that are equivalent to, if not greater than, natural infection with the SARS-CoV-19.

VACCINE // *continued on page 6*

Burnout and depression: Half of pulmonology trainees report symptoms

BY DOUG BRUNK
MDedge News

FROM CHEST® ▪ Half of fellows training in pulmonary and critical care medicine screened positive for either burnout or depressive symptoms, results from a national survey demonstrated.

"Given the high prevalence of burnout and depressive symptoms among fellows training in pulmonary and critical care medicine, it is crucial for fellowship training programs and academic hospitals to consider policies and programs that can improve this public health crisis," first author Michelle Sharp, MD, MHS, and colleagues wrote in a study published in the journal *CHEST*.

Dr. Sharp, of the division of pulmonary and critical care medicine at Johns Hopkins University, Baltimore, and colleagues developed a cross-sectional electronic survey to assess burnout and depression symptoms in fellows enrolled in pulmonary and critical care medicine training programs in the United States. Between January and February 2019, a total of 976 fellows received

BURNOUT // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Sleep Strategies

Sleep-disordered breathing in neuromuscular disease

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INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

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

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

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

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

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

Drug Interactions:

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

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

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

Genentech
A Member of the Roche Group

AN IPF TREATMENT BACKED BY EXPERIENCE

Used in more than 60 countries worldwide for the treatment of idiopathic pulmonary fibrosis (IPF)[1]*

MORE THAN

136,000

PATIENT-YEARS

were derived from the volume of global sales of Esbriet and the estimated total amount taken by patients with IPF worldwide, from February 2011 through February 2019[1]

>5 YEARS

IN CLINICAL TRIALS[2]

The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials

Demonstrated safety and efficacy

In ASCEND and CAPACITY 004, Esbriet delayed disease progression by slowing lung function decline vs placebo[2,3]

In CAPACITY 006, no statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed[2,4]

Serious AEs, including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and GI disorders, have been reported with Esbriet[1]

Learn more at **EsbrietHCP.com**

*Countries include Albania, Argentina, Australia, Austria, Belgium, Bulgaria, Brazil, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong (special administrative region), Hungary, Iceland, Ireland, Israel, Italy, Kosovo, Kuwait, Lithuania, Luxembourg, Macao (special administrative region), Malaysia, Malta, Montenegro, Myanmar, the Netherlands, New Zealand, Norway, Oman, Qatar, Paraguay, Poland, Portugal, Peru, Romania, Russia, Saudi Arabia, Serbia, Singapore, Spain, Slovakia, Slovenia, Sweden, Switzerland, Turkey, Ukraine, the United Arab Emirates, the United Kingdom, the United States, and Uruguay.[1]

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

Specific Populations:

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

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

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

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

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when on Esbriet.

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

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

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

References: 1. Data on file. Genentech, Inc. 2019. **2.** Esbriet Prescribing Information. Genentech, Inc. July 2019. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med*. 2014;371(12):1172]. *N Engl J Med*. 2014;370(22):2083–2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760–1769.

Esbriet® (pirfenidone) tablets 267 mg 801 mg

Doctors challenge FDA standards for COVID-19 vaccine

BY KERRY DOOLEY YOUNG

Researchers and several medical groups have pressed for changes to the Food and Drug Administration's current plans for deciding how to eventually clear vaccines for COVID-19, arguing tougher standards would help bolster confidence in these critical medicines.

The FDA's Vaccines and Related Biological Products Advisory Committee met for a wide-ranging discussion beginning around 10 am. The FDA did not ask the panel to weigh in on any particular vaccine. Instead, the FDA asked for the panel's feedback on a series of questions, including considerations for continuing phase 3 trials if a product were to get an interim clearance known as an emergency-use authorization (EUA).

Speakers at the hearing made a

variety of requests, including asking for data showing COVID-19 vaccines can prevent serious illness and urging transparency about the agency's deliberations for each product to be considered.

FDA staff are closely tracking the crop of experimental vaccines that have made it into advanced stages of testing, including products from Pfizer, AstraZeneca, Johnson & Johnson, and Moderna.

'Time for a reset'

Among the speakers at the public hearing was Peter Lurie, MD, who served as an FDA associate commissioner from 2014 to 2017. Now the president of the Center for Science in the Public Interest, Dr. Lurie was among the speakers who asked the agency to make its independence clear.

President Trump has been making predictions for months about COVID-19 vaccine approvals that have been overly optimistic. In one example, the president, who was seeking re-election, spoke in September about being able to begin distributing a vaccine in October.

"Until now the process of developing candidate vaccines has been inappropriately politicized with an eye on the election calendar, rather than the deliberate timeframe science requires," Dr. Lurie told the FDA advisory panel. "Now is the time for a reset. This committee has a unique opportunity to set a new tone for vaccine deliberations going forward."

Dr. Lurie asked the panel to press the FDA to commit to hold an advisory committee meeting on requests by drugmakers for EUAs. He also asked the panel to demand that informed consent forms and minutes from institutional review board (IRB) discussions of COVID-19 vaccines trials be made public.

Also among the speakers at the public hearing was Peter Doshi, PhD, an associate professor at the University of Maryland School of Pharmacy, who argued that the current trials won't answer the right questions about the COVID-19 vaccines.

"We could end up with approved vaccines that reduce the risk of mild infection, but do not decrease the risk of hospitalization, ICU use, or death – either at all or by a clinically relevant amount," Dr. Doshi told the panel.

Risks of a 'rushed vaccine'

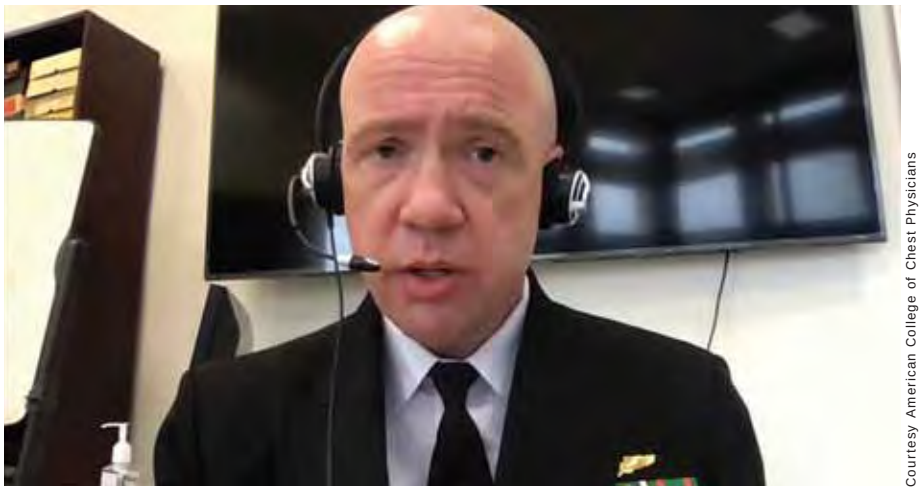
Other complaints about the FDA's approach included criticism of a 2-month follow-up time after vaccination, which was seen as too short. ECRI, a nonprofit organization that seeks to improve the safety, quality, and cost-effectiveness of medicines, has argued that approving a weak COVID-19 vaccine might worsen the pandemic.

In an Oct. 21 statement, ECRI noted the risk of a partially effective vaccine, which could be welcomed as a means of slowing transmission of the virus. But public response and attitudes over the past 9 months in the United States suggest that people would relax their precautions as soon as a vaccine is available.

"Resulting infections may offset the vaccine's impact and end up increasing the mortality and morbidity burden," ECRI said in the brief.

"The risks and consequences of a rushed vaccine could be very severe if the review is anything shy of thorough," ECRI Chief Executive Officer Marcus Schabacker, MD, PhD, said in a statement prepared for the hearing.

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



Courtesy American College of Chest Physicians

Dr. Ryan C. Maves: "We're lucky to have multiple phase 3 trials using multiple vaccine technologies in different platforms."

Vaccine distribution plans underway

// *continued from page 1*

Rapid development gives reason for hope

Ryan C. Maves, MD, FCCP, a critical care and infectious disease specialist at Naval Medical Center San Diego, said there is reason to be hopeful that a vaccine will be available by the end of the calendar year. He cautioned, however, that this timing is based on the assumption that one of the vaccines will be proven safe and effective very soon.

"We're lucky to have multiple phase 3 trials using multiple vaccine technologies in different platforms," Dr. Maves said in a panel discussion following Dr. Fauci's remarks. "I think the odds are very high that one of them will be effective."

Reaching communities of color will be an important consideration for prioritization given the disproportionate burden of disease on Black and Hispanic individuals, among other such populations.

"I'm hoping that multiple vaccines will be effective," Dr. Maves added. "Then we'll be in a good position of determining which is the best of several good options, as a society and as a world."

COVID-19 vaccine development over the past year has been remarkably fast, especially given the previous record set by the mumps vaccine, which took about 4 years to go from initial steps to rollout, Dr. Maves noted.

Dr. Fauci said the federal government has taken a "strategic approach" to the COVID-19 vaccine that includes direct involvement in the research and development of six different vaccine candidates, five of which are now in phase 3 trials.

As part of that strategic approach, the study protocols are harmonized to have a common data and safety monitoring board, common primary and secondary endpoints, and an independent statistical group to determine correlates of protection, Dr. Fauci said.

Prioritizing COVID-19 vaccine distribution

Who gets COVID-19 vaccine first will be a challenge for governmental organizations as well as bioethicists, who have proposed different strategies for fairly prioritizing different groups for access.

Reaching communities of color will be an important consideration for prioritization, according to Dr. Maves, given the disproportionate burden of disease on Black and Hispanic individuals, among other such populations.

COVID-19–related hospitalization rates have been substantially higher in communities of color, Dr. Fauci said in his keynote address. Age-adjusted hospitalization rates for Hispanic/Latinx and Black populations are 375 and 368 per 100,000, respectively, compared with just 82 per 100,000 for White non-Hispanics, according to data from the Centers for Disease Control and Prevention.

Outreach to those communities should include building trust in those populations that they will benefit from a safe and effective vaccine, and making sure that the vaccine is available to those communities as quickly as possible, Dr. Maves said.

Dr. Fauci and Dr. Maves provided no disclosures related to their presentations.

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Systemic solutions to burnout are needed at the programmatic level

// continued from page 1

the survey, which used the Maslach Burnout Index two-item measure to assess burnout and the two-item Primary Care Evaluation of Mental Disorders Procedure to screen for depressive symptoms. For both burnout and depression, the researchers constructed three multivariate logistic regression models to assess individual fellow characteristics, program structure, and institutional policies associated with the symptoms.

Of the 976 surveys sent, 502 completed both outcome measures, for a response rate of 51%. More than half (59%) were male, 57% described themselves as White/non-Hispanic, and 39% reported at least $200,000 in student loan debt. The researchers found that 50% of respondents screened positive for either burnout or depressive symptoms. Specifically, 41% met criteria for depressive symptoms, 32% were positive for burnout, and 23% were positive for both.

Factors significantly associated with a higher odds of burnout included working more than 70 hours in an average clinical week (adjusted odds ratio, 2.80) and reporting a somewhat negative or very negative impact of the EHR on joy in medicine (aOR, 1.91).

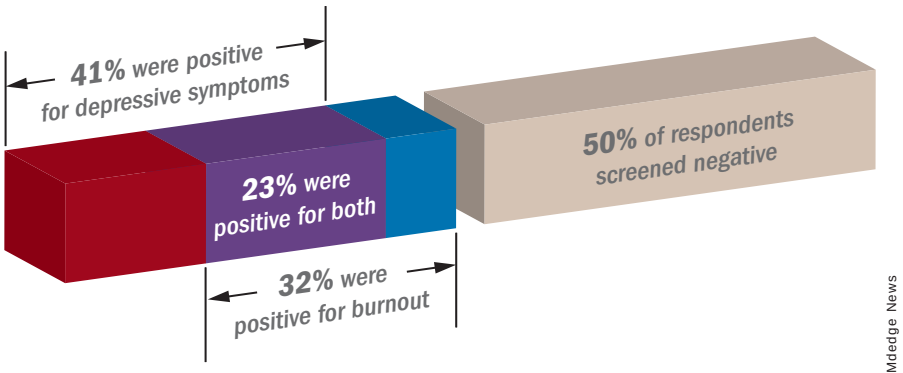
Factors significantly associated with a higher odds of depressive symptoms were financial concern (aOR, 1.13), being located in the Association of American Medical Colleges West region (aOR 3.96), working more than 70 hours in an average clinical week (aOR, 2.24), and spending a moderately high or excessive amount of time at home on the EHR (aOR, 1.71).

Of respondents who reported working in an institution with a coverage system for personal illness or emergency, 29% were uncomfortable accessing the system or felt comfortable only if unable to find their own coverage. In addition, among respondents who indicated that they had access to mental health resources through their place of employment, 15% said they were reluctant to access those resources if needed.

"Our results suggest that further study of systemic solutions at the programmatic and institutional levels rather than at the individual level are needed," Dr. Sharp and colleagues wrote. "Strategies such as providing an easily accessible coverage system, providing access to mental health resources, addressing work hour burden, reducing the EHR burden, and addressing financial concerns among trainees may help reduce burnout and/or depressive symptoms and should be further studied."

Depression and burnout in pulmonary/critical care fellows

Electronic survey used the Maslach Burnout Index two-item measure and the two-item Primary Care Evaluation of Mental Disorders Procedure.



Mdedge News

Note: The survey, conducted in January and February of 2019, received 502 responses.

Source: Dr. Sharp

In an interview, David A. Schulman, MD, FCCP, Editor in Chief of CHEST Physician, characterized the survey findings as "disheartening" but not surprising. "Burnout and depressive symptoms are a problem because almost everything we do to mitigate them works a little, but nothing works a lot," said Dr. Schulman, professor of medicine in the division of pulmonary, allergy, critical care, and sleep medicine at Emory University, Atlanta, who was not affiliated with the study. "The limited availability of resources to fight this is a challenge. The thing that seems to correlate best with mitigating burnout and depression rates is just giving people time. In my experience, most people just want the space and time they need to mitigate burnout in their own way by having schedule flexibility or arranging time to spend with family or involved in other wellness activities."

Dr. Sharp

"Strategies such as providing an easily accessible coverage system, providing access to mental health resources, addressing work hour burden, reducing the EHR burden, and addressing financial concerns among trainees may help reduce burnout and/or depressive symptoms and should be further studied."

Dr. Schulman, who served as training program director of pulmonary and critical care medicine fellows at Emory for 14 years until stepping down from that role in September 2020, said that nurturing a culture where trainees and seasoned colleagues are comfortable talking about burnout and depressive symptoms is one way to foster change. "It's weird to say that we should try to normalize burnout, but I don't think the health care system is changing anytime soon. The health care system can be harsh. It will continue to take and take from everyone involved in it until they have nothing left to give. It's unfortunate, because people are sick, and hospitals can be relatively understaffed, particularly in the context of a major public health emergency. What we really need to do is try to normalize this by saying to trainees: 'Hey. Everybody is under the gun. We're going to share in this workload together because we can't abandon our patients. We will do our best to make sure that the workload is shared amongst everybody.' "

"The health care system can be harsh. It will continue to take and take from everyone involved in it until they have nothing left to give. It's unfortunate, because people are sick, and hospitals can be relatively understaffed, particularly in the context of a major public health emergency."

Dr. Schulman

He emphasized that most trainees recognize the importance of the work they do, "and they don't shirk from it. But I think that drive sometimes gets in the way of self-care. I do think there needs to be a happy medium, where we definitely want you to work, because that's how you learn and the system needs you, but we also recognize that there's a need for you to take care of yourself."

Dr. Schulman recommended that such discussions take place not remotely on Zoom calls and the like but rather in person with small groups of trainees and seasoned clinicians, "where people are more comfortable candidly discussing how they're feeling. I don't think grand rounds on burnout or depression are particularly effective. It needs to be interactive, and we need to listen as much as we're talking."

Although the survey by Dr. Sharp and colleagues was completed prior to the COVID-19 pandemic, Dr. Schulman has a hunch that the current driver of burnout and depression has more to do with trainees feeling a sense of physical isolation than with being overwhelmed by their workload. "I don't think that's unique to medicine," he said. "When people get home from work, they can't go out with friends or out to dinner, or travel, whatever they do to decompress. I think that's a major driver for the current phenomenon, and I don't think that's unique to medicine. The psychological ramifications of isolation due to the coronavirus may eventually outpace the physical ramifications of all the illness that we have seen. Depression and burnout may not be as obviously damaging to people, but I think they're affecting many more people than the virus itself."

The survey was supported by the Association of Pulmonary and Critical Care Medicine Program Directors.

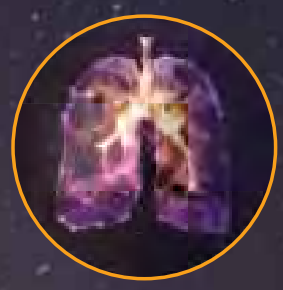
dbrunk@mdedge.com

SOURCE: Sharp M et al. CHEST 2020 Sept 18. doi:10.1016/j.chest.2020.08.2117

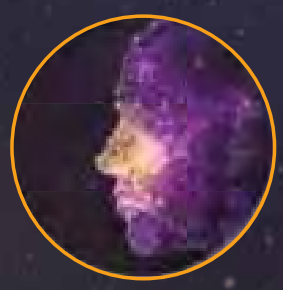
WHAT'S DRIVING INFLAMMATORY DISEASE IN YOUR PATIENTS?

IT COULD BE EOSINOPHILIC IMMUNE DYSFUNCTION

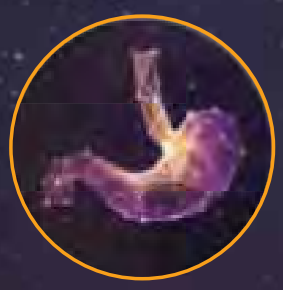
Eosinophils are key effector cells* in several debilitating inflammatory diseases[1-4]



Eosinophilic asthma (EA)

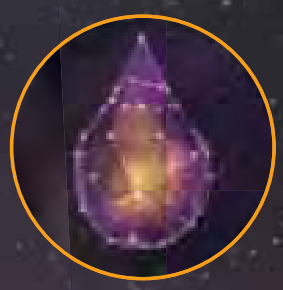


Chronic rhinosinusitis with nasal polyps (CRSwNP)



Eosinophilic esophagitis (EoE)

Eosinophilic granulomatosis polyangiitis (EGPA)



Hypereosinophilic syndrome (HES)

Millions of people are affected by these diseases[5-11]

Eosinophilic Immune Dysfunction (EID)

EID can be characterized as the dysregulation of biological processes involved with eosinophil recruitment and activation.[1]

Activated eosinophils can contribute to disease pathology through several mechanisms and play a key role in the self-perpetuating cycle of inflammatory damage in a range of diseases.[1-4]

*When activated, eosinophils modulate downstream immune and inflammatory signaling.[2]

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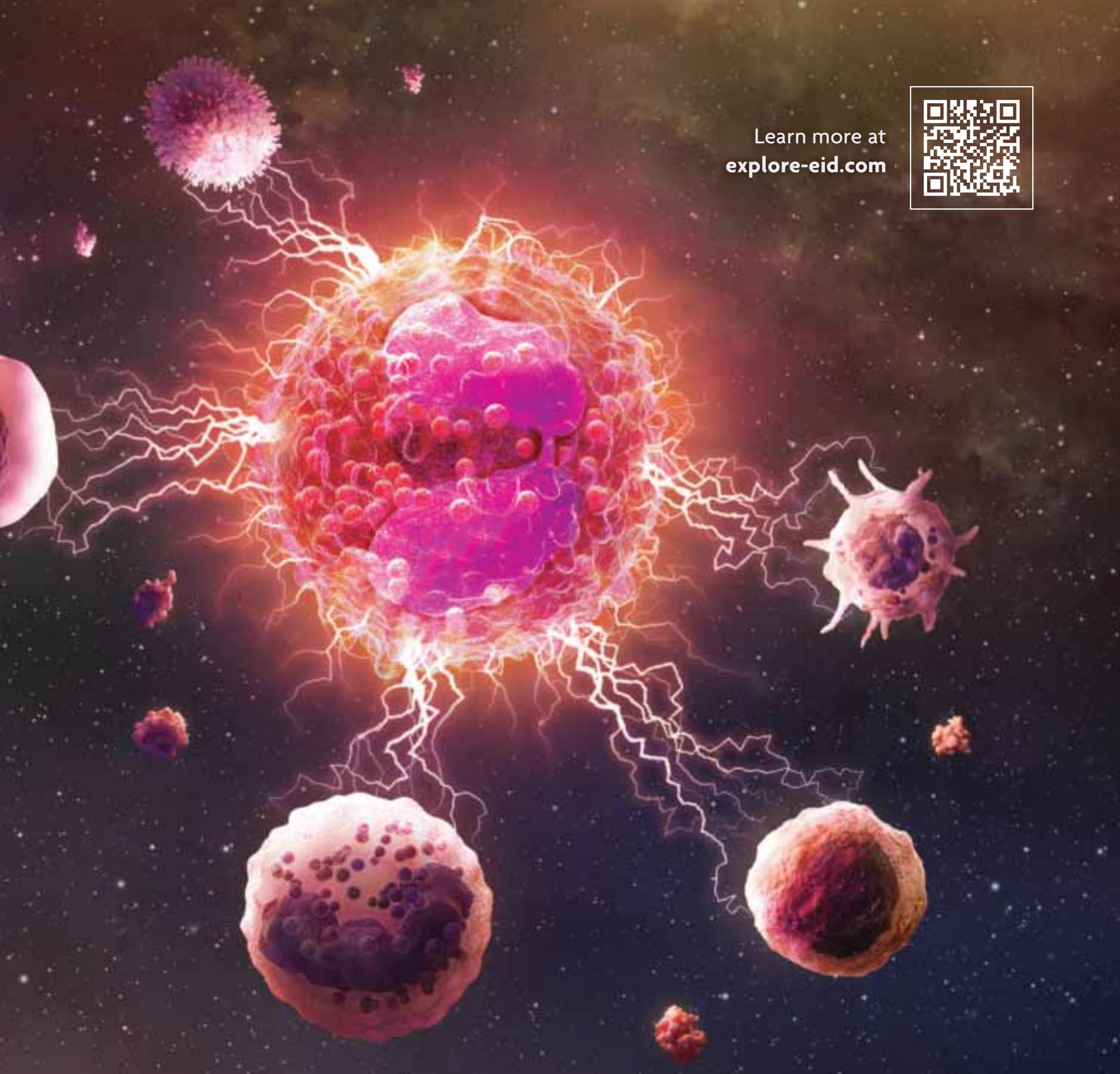

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AstraZeneca

COVID-19 hits medical education: No 'back to normal'

BY DOUG BRUNK
MDedge News

The COVID-19 pandemic has thrown a monkey wrench into the medical education landscape across the entire health care spectrum, disrupting the plans of medical students, residents, fellows, and program directors.

As cases of COVID-19 spread across the United States in early 2020, it became clear to training program directors that immediate action was required to meet the needs of medical learners. The challenges were unlike those surrounding the Ebola virus in 2014, "where we could more easily prevent students and trainees from exposure due to the fact that there were simply not significant numbers of cases in the United States," Tiffany Murano, MD, said at a Society for Critical Care virtual meeting: COVID-19: What's Next. Dr. Murano is professor of emergency medicine at Rutgers New Jersey Medical School, Newark, and president-elect of the Council of Residency Directors in Emergency Medicine. "COVID was a completely different scenario. We quickly realized that not only was personal protective equipment in short supply, but we also lacked the testing and tracking capabilities for potential exposures. Medical students and other supportive workers who were considered nonessential were removed from the clinical setting. This was after a trial of limiting who the students saw, essentially dampening the risk of exposure. But this proved to be flawed as COVID patients presented with symptoms that were unexpected."

To complicate matters, she continued, many medical clinics either shut down, had limited access, or converted to telemedicine. Elective surgeries were canceled. This led to an overall pause in clinical medical student rotations and no direct patient care activities. As social distancing mandates were instituted, licensing examination testing centers were closed, and exams and on-campus activities were postponed.

Limiting trainee exposure

On the graduate medical education front, some training programs attempted to limit exposure of their trainees to persons under investigation for COVID-19. "As the number of COVID cases grew and encompassed most of what we were seeing in the hospital, it was obvious that residents had to play a vital part in the care of these patients," said Dr. Murano, who is also a member of the American Council of Graduate Medical Education's emergency review and recognition committee. "However, there was a consensus among all of the specialties that the procedures that posed the highest risk of exposure would be limited to the most senior or experienced trainees or professionals, and closely supervised by the faculty."


Dr. Murano

ACGME activities such as accreditation site visits, clinical environment learning reviews, self-study, and resident and faculty surveys were suspended, postponed, or modified in some way, she said. The ACGME created stages of COVID status to guide sponsoring institutions to suspend learning curricula in order for patients to be cared for. Stage 1 was business as usual, "so there was no significant impact on patient care," Dr. Murano said. "Stage 2 was increased but manageable clinical demand, while stage 3 was pandemic emergency status, where there were extraordinary circumstances where the clinical demand was so high and strenuous that the routine patient care and education really needed to be reconfigured in order to care for the patients."

New requirements to manage training

The ACGME also implemented four requirements to manage training that were consistent among institutions, regardless of their COVID stage status. These included making sure that trainees continued to be held to work-hour limit requirements, ensuring adequate resources for training, ensuring that all residents had the appropriate level of supervision at all times, and allowing fellows to function in the core specialty in which they completed their residency training. "This was only possible if the fellows were ABMS [American Board of Medical Specialties] or AOA [American Osteopathic Association] board-eligible, or certified in their core specialty," Dr. Murano said. "The fellows had to be appointed to the medical staff at the sponsoring institution, and their time spent on the core specialty service would be limited to 20% of their annual education time in any academic year."

Mindful that there may have been trainees who required a 2-week quarantine period following exposure or potential exposure to COVID-19, some specialty boards showed leniency in residency time required to sit for the written exam. Subani Chandra, MD, FCCP, of the division of pulmonary, allergy, and critical care medicine at Columbia University, New York, is the internal medicine residency program director and the associate vice-chair of education for the department of medicine, and she recognized the problem created for medical trainees by the changes necessitated by the pandemic.


Dr. Chandra

"The variability in caseloads and clinical exposure has given thrust to the move toward competency-based assessments rather than number- or time-based criteria for determining proficiency and graduation," she wrote in an email interview. In addition, she noted the impact on medical meetings and the need to adapt. "Early on, before large regional and national conferences adapted to a virtual format, many were canceled altogether. Students, residents, and fellows expecting to have the opportunity to present their scholarly work were suddenly no longer able to do so. Understanding the importance of scholarly interaction, the virtual format of CHEST 2020 is designed with opportunities to present, interact with experts in the field, ask questions, network, and meet mentors."

No return to 'normal'

By April 2020, cases in the northeast continued to rise, particularly in the New York, New Jersey, and Connecticut region. "These states were essentially shut down in order to contain spread of the virus," she said. "This was a real turning point because we realized that things were not going to return to 'normal' in the foreseeable future." With the clinical experience essentially halted for medical students during this time, some medical schools allowed their senior students who met requirements to graduate early. "There were a lot of mixed feelings about this, recognizing that PPE [personal protective equipment] was still in short supply in many areas," Dr. Murano said. "So, institutions took on these early graduates into roles in which they were not learners in particular, but rather medical workers. They were helping with informatics and technology, telehealth, virtual or telephone call follow-ups, and other tasks like this. There was a movement to virtual learning for the preclinical undergraduate learners, so classes were now online, recorded, or livestreamed."

Early graduation, the Match, and residencies

On April 3, the ACGME released a statement regarding graduating students early and appointing them early to the clinical learning environment. "They pointed out that institutions that were in emergency pandemic status lacked the ability to offer the comprehensive orientation and training in PPE and direct supervision required for new residents at the start of their residency," Dr. Murano said. "Their opinion maintained that graduating medical students matriculate in their previously matched program, the National Resident Match Program start date, or other date that would be nationally determined to be the beginning of the 2020-2021 academic year."

As May 2020 rolled around, the overriding feeling was uncertainty regarding when, if, and how medical schools were going to open in the early summer and fall. "There was also uncertainty about how graduating medical students were going to function in their new role as residents," she said. "Same for the graduating residents. There were some who had signed contracts for jobs months before, and had them rescinded, and physicians were being furloughed due to financial hardships that institutions faced. There was also postponement of board certification exams, so people were uncertain about when they would become board certified."

July 2020 ushered in what Dr. Murano characterized as "a whole new level of stress." For medical students in particular, "we were entering the application season for residency positions," she said. "Due to travel restrictions placed by various states and institutions, away rotations were limited or nonexistent. Application release dates through the Electronic Residency Application Service

Continued on page 14

When your adult patients with obstructive sleep apnea (OSA) are struggling with excessive daytime sleepiness (EDS),

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is the first and only WPA proven to improve wakefulness through **9 HOURS**[1,2]*

*As seen at week 12.
WPA=wake-promoting agent.

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INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA).

Limitations of Use:

SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

Please see Brief Summary of full Prescribing Information on next page.

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2019.

Jazz Pharmaceuticals

SUNOSI® (solriamfetol) tablets, for oral use, CIV
BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information for complete product information.
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use

SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities.

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

Prior to initiating treatment with SUNOSI, ensure blood pressure is adequately controlled.

General Administration Instructions

Administer SUNOSI orally upon awakening with or without food. Avoid taking SUNOSI within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.

SUNOSI 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

SUNOSI has not been evaluated in patients with psychosis or bipolar disorders. Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Patients treated with SUNOSI should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI.

ADVERSE REACTIONS

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

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

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

The safety of SUNOSI has been evaluated in 930 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 37.5 mg (OSA only), 75 mg, and 150 mg once daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of SUNOSI than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia.

Table 1 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the narcolepsy population.

Table 1: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy (75 mg and 150 mg)

	Narcolepsy	
System Organ Class	**Placebo** N = 108 (%)	**SUNOSI** N = 161 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	9
Psychiatric Disorders		
Insomnia*	4	5
Anxiety*	1	6
Nervous System Disorders		
Headache*	7	16
Cardiac Disorders		
Palpitations	1	2
Gastrointestinal Disorders		
Nausea*	4	7
Dry mouth	2	4
Constipation	1	3

*"Insomnia" includes insomnia, initial insomnia, middle insomnia, and terminal insomnia. "Anxiety" includes anxiety, nervousness, and panic attack. "Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Table 2 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the OSA population.

Table 2: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in OSA (37.5 mg, 75 mg, and 150 mg)

	OSA	
System Organ Class	**Placebo** N = 118 (%)	**SUNOSI** N = 235 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	6
Psychiatric Disorders		
Anxiety*	1	4
Irritability	0	3
Nervous System Disorders		
Dizziness	1	2
Cardiac Disorders		
Palpitations	0	3
Gastrointestinal Disorders		
Nausea*	6	8
Diarrhea	1	4
Abdominal pain*	2	3
Dry mouth	2	3
General Disorders and Administration Site Conditions		
Feeling jittery	0	3
Chest discomfort	0	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0	2

*"Anxiety" includes anxiety, nervousness, and panic attack. "Nausea" includes nausea and vomiting. "Abdominal pain" includes abdominal pain, abdominal pain upper, and abdominal discomfort.

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

Other adverse reactions of < 2% incidence but greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have clinically significant implications.

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: feeling jittery, thirst, chest discomfort, chest pain

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of SUNOSI to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth (Table 3).

Table 3: Dose-Dependent Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy and OSA

	Placebo N = 226 (%)	**SUNOSI 37.5 mg** N = 58* (%)	**SUNOSI 75 mg** N = 120 (%)	**SUNOSI 150 mg** N = 218 (%)
Headache**	8	7	9	13
Nausea**	5	7	5	9
Decreased appetite	1	2	7	8
Anxiety	1	2	3	7
Dry mouth	2	2	3	4
Diarrhea	2	2	4	5

*In OSA only.

**"Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Adverse Reactions Resulting in Discontinuation of Treatment

In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of the 226 patients (< 1%) who received placebo. The adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).

Increases in Blood Pressure and Heart Rate

SUNOSI's effects on blood pressure and heart rate are summarized below. Table 4 shows maximum mean changes in blood pressure and heart rate recorded at sessions where the Maintenance of Wakefulness Test (MWT) was administered. Table 5 summarizes 24-hour ambulatory blood pressure monitoring (ABPM) and ambulatory heart rate monitoring performed in the outpatient setting.

Table 4: Maximal Mean Changes in Blood Pressure and Heart Rate Assessed at MWT Sessions from Baseline through Week 12: Mean (95% CI)*

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n	52		51	49	53
	SBP	3.5 (0.7, 6.4)	-	3.1 (0.1, 6.0)	4.9 (1.7, 8.2)	6.8 (3.2, 10.3)
	n	23		47	49	53
	DBP	1.8 (-1.8, 5.5)	-	2.2 (0.2, 4.1)	4.2 (2.0, 6.5)	4.2 (1.5, 6.9)
	n	48		26	49	53
	HR	2.3 (-0.1, 4.7)	-	3.7 (0.4, 6.9)	4.9 (2.3, 7.6)	6.5 (3.9, 9.0)
OSA *STUDY 2*	n	35	17	54	103	35
	SBP	1.7 (-1.4, 4.9)	4.6 (-1.1, 10.2)	3.8 (1.2, 6.4)	2.4 (0.4, 4.4)	4.5 (1.1, 7.9)
	n	99	17	17	107	91
	DBP	1.4 (-0.1, 2.9)	1.9 (-2.3, 6.0)	3.2 (-0.9, 7.3)	1.8 (0.4, 3.2)	3.3 (1.8, 4.8)
	n	106	17	51	102	91
	HR	1.7 (0.1, 3.3)	1.9 (-1.9, 5.7)	3.3 (0.6, 6.0)	2.9 (1.4, 4.4)	4.5 (3.0, 6.0)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*For study weeks 1, 4, and 12, SBP, DBP, and HR were assessed pre-dose and every 1-2 hours for 10 hours after test drug administration. For all time points at all visits, the mean change from baseline was calculated, by indication and dose, for all patients with a valid assessment. The table shows, by indication and dose, the mean changes from baseline for the week and time point with the maximal change in SBP, DBP, and HR.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 5: Blood Pressure and Heart Rate by 24-hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 8

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n*	46		44	44	40
	SBP	-0.4 (-3.1, 2.4)	-	1.6 (-0.4, 3.5)	-0.5 (-2.1, 1.1)	2.4 (0.5, 4.3)
	DBP	-0.2 (-1.9, 1.6)	-	1.0 (-0.4, 2.5)	0.8 (-0.4, 2.0)	3.0 (1.4, 4.5)
	HR	0.0 (-1.9, 2.0)	-	0.2 (-2.1, 2.4)	1.0 (-1.2, 3.2)	4.8 (2.3, 7.2)
OSA *STUDY 2*	n*	92	43	49	96	84
	SBP	-0.2 (-1.8, 1.4)	1.8 (-1.1, 4.6)	2.6 (0.02, 5.3)	-0.2 (-2.0, 1.6)	2.8 (-0.1, 5.8)
	DBP	0.2 (-0.9, 1.3)	1.4 (-0.4, 3.2)	1.5 (-0.04, 3.1)	-0.1 (-1.1, 1.0)	2.4 (0.5, 4.4)
	HR	-0.4 (-1.7, 0.9)	0.4 (-1.4, 2.2)	1.0 (-0.9, 2.81)	1.7 (0.5, 2.9)	1.6 (0.3, 2.9)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*Number of patients who had at least 50% valid ABPM readings.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Drugs that Increase Blood Pressure and/or Heart Rate

Concomitant use of SUNOSI with other drugs that increase blood pressure and/or heart rate has not been evaluated, and such combinations should be used with caution.

Dopaminergic Drugs

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUNOSI during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.

Risk Summary

Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 4 and 5 times and was teratogenic at doses 19 and ≥ 5 times, respectively, the maximum recommended human dose (MRHD) of 150 mg based on mg/m^2 body surface area. Oral administration of solriamfetol to pregnant rats during pregnancy and lactation at doses ≥ 7 times the MRHD based on mg/m^2 body surface area resulted in maternal toxicity and adverse effects on fertility, growth, and development in offspring *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately 1, 4, and 19 times the MRHD based on mg/m^2 body surface area. Solriamfetol at ≥ 4 times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight.

Solriamfetol was teratogenic at 19 times the MRHD; it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 4 times and for maternal and embryofetal toxicity is approximately 1 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately 2, 5, and 10 times the MRHD based on mg/m^2 body surface area. Solriamfetol at 10 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 2 times and for maternal toxicity is approximately 5 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately 2, 7, and 22 times the MRHD based on mg/m^2 body surface area. At ≥ 7 times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, decreased food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring after lactation day 20 included decreased body weight, decreased weight gain, and delayed sexual maturation. Mating and fertility of offspring were decreased at maternal doses 22 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 2 times the MRHD based on mg/m^2 body surface area.

LACTATION

Risk Summary

There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of SUNOSI in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (123/930) were 65 years of age or over.

No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients.

Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

Renal Impairment

Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2). Dosage adjustment is recommended for patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m^2). SUNOSI is not recommended for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

SUNOSI has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of SUNOSI 300 mg, 600 mg, and 1200 mg (two, four, and eight times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals experienced with the recreational use of stimulants. Results from this clinical study demonstrated that SUNOSI produced Drug Liking scores similar to or lower than phentermine. In this crossover study, elevated mood was reported by 2.4% of placebo-treated subjects, 8 to 24% of SUNOSI-treated subjects, and 10 to 18% of phentermine-treated subjects. A 'feeling of relaxation' was reported in 5% of placebo-treated subjects, 5 to 19% of SUNOSI-treated subjects and 15 to 20% of phentermine-treated subjects.

Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (e.g., methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., incrementation of doses, drug-seeking behavior).

Dependence

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of SUNOSI were also evaluated during the two-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

OVERDOSAGE

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

Consult with a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Potential for Abuse and Dependence

Advise patients that SUNOSI is a federally controlled substance because it has the potential to be abused. Advise patients to keep their medication in a secure place and to dispose of unused SUNOSI as recommended in the Medication Guide.

Primary OSA Therapy Use

Inform patients that SUNOSI is not indicated to treat the airway obstruction in OSA and they should use a primary OSA therapy, such as CPAP, as prescribed to treat the underlying obstruction. SUNOSI is not a substitute for primary OSA therapy.

Blood Pressure and Heart Rate Increases

Instruct patients that SUNOSI can cause elevations of their blood pressure and pulse rate and that they should be monitored for such effects.

Psychiatric Symptoms

Instruct patients to contact their healthcare provider if they experience, anxiety, insomnia, irritability, agitation, or signs of psychosis or bipolar disorders.

Lactation

Monitor breastfed infants for adverse reactions such as agitation, insomnia, anorexia, and reduced weight gain.

For more information, visit www.SUNOSI.com

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Protected by U.S. patent numbers: 8440715, 8877806, and 9604917
Revised: 06/2019

Continued from page 10

were moved to later in the year. The United States Medical Licensing Examination clinical skills exam was suspended, and there were modifications made for Education Commission for Foreign Medical Graduates requirements. Letters of recommendation were also going to be limited, so there had to be some degree of leniency within specialties to take a more holistic approach to review of applications for residencies."

On the graduate medical education front, the ACGME sunsetted the initial stages and created two categories: nonemergency, which was formerly stages 1 and 2, and emergency, which was formerly stage 3. "All emergency stages are applied for and granted at 1-month intervals," Dr. Murano said. Board certification exams were modified to accommodate either later exams or online formats, and specialties with oral examinations faced the task of potentially creating virtual oral exams. Despite the challenges, Dr. Chandra has seen medical training programs respond with new ideas. "The flexibility and agile adaptability of the entire educational enterprise has been remarkable. The inherent uncertainty in a very dynamic and changing learning environment can be challenging. Recognizing this, many programs are creating additional ways to support the mental, emotional, physical, and financial health of students, residents, and fellows and all health care workers. The importance of this innovative response cannot be overstated."

New learning formats

The pandemic forced Dr. Murano and other medical educators to consider unorthodox learning formats, and virtual learning took center stage. "Residency programs had shared national livestream conferences and grand rounds, and there were virtual curricula made for medical students as well as virtual simulation," she said. "Telemedicine and telehealth really became important parts of education as well, as this may have been the only face-to-face contact that students and residents had with patients who had non–COVID-related complaints."

To level the playing field for medical residents during this unprecedented time, a work group of the Coalition for Physician Accountability developed a set of recommendations that include limiting the number of letters of recommendation accepted, limiting the number of away rotations, and allowing alternative or less conventional letters of recommendation. "Keeping an open mind and taking a more holistic approach to applicants has really been needed during this time," Dr. Murano said. "Virtual interview days have been agreed upon for all specialties." Dr. Chandra agreed that virtual interviews are necessary but have inherent limitations. However, "we will all learn a lot, and very likely the future process will blend the benefits of both virtual and in-person interviews."

'We need to keep moving forward'

Dr. Murano concluded her presentation by noting that the COVID-19 pandemic has created opportunities for growth and innovation in medical education, "so we need to keep moving forward. I've heard many say that they can't wait for things to go back to normal. But I think it's important to go ahead to new and better ways of learning. "

Dr. Murano and Dr. Chandra reported having no financial disclosures.

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Avoid these malpractice risks during video visits

BY ALICIA GALLEGOS

During a telemedicine visit with his physician, a 62-year-old obese patient with an ankle injury reported new swelling of his leg. Three weeks had passed since the man visited an emergency department, where he underwent surgery and had a cast applied to the wound. The physician, during the telemedicine visit, advised the patient to elevate his leg and see an orthopedist within 24 hours. A Doppler ultrasound was ordered for 12:30 p.m. that same day.

The patient never made it to the appointment. He became unresponsive and went into full arrest hours later. His death fueled a lawsuit by his family that claimed failure to diagnose and treat deep venous thrombosis. The family contended the providers involved should have referred the patient to care immediately during the video visit.

The case, which comes from the claims database of national medical liability insurer The Doctors Company, illustrates the legal risks that can stem from video visits with patients, says Richard Cahill, JD, vice president and associate general counsel for The Doctors Company.

"By evaluating the patient remotely, the physician failed to appreciate the often subtle nuances of the clinical presentation, which undoubtedly could have been more accurately assessed in the office setting, and would probably have led to more urgent evaluation and intervention, thereby likely preventing the unfortunate and otherwise avoidable result," said Mr. Cahill.

According to a Harris poll, 42% of Americans reported using video visits during the pandemic, a trend that is likely to continue as practices reopen and virtual care becomes the norm. But as physicians conduct more video visits, so grows their risk for lawsuits associated with the technology.

Three problems with not being able to touch the patient

1. The primary challenge with video visits "is the inability to directly observe and lay hands on the patient," says Jonathan Einbinder, MD, assistant vice president of analytics for CRICO, a medical liability insurer based in Boston.

"While you can see them via video, it can be hard to get a full sense of how sick the patient is and whether other things might be going on than what they are reporting," said Dr. Einbinder, a practicing internist.

Such incomplete pictures can lead to diagnostic errors and the potential for lawsuits, as demonstrated by a recent CRICO analysis. Of 106 telemedicine-related claims from 2014 to 2018, 66% were diagnosis related, according to the analysis of claims from CRICO's national database. Twelve percent of the telemedicine-related claims were associated with surgical treatment, 11% were related to medical treatment, and 5% were associated with medication issues. "Because a 'typical' exam can't be done, there is the potential to miss things," said David L. Feldman, MD, chief medical officer for The Doctors Company Group. "A subtlety, perhaps a lump that can't be seen but only felt, and only by an experienced examiner, for example, may be missed."

2. Documentation dangers also loom, said William Sullivan, DO, JD, an emergency physician and an attorney who specializes in health care. The legal risk lies in documenting a video visit in the same way the doctor would document an in-person visit, he explained.

"Investigation into a potential lawsuit begins when there is some type of bad outcome related to medical care," Dr. Sullivan explained. "To determine whether the lawsuit has merit, patients/attorneys review the medical records to retrospectively determine the potential cause of the bad outcome. If the documentation reflects an examination that could not have been performed, a lawyer might be more likely to pursue a case, and it would be more difficult to defend the care provided."

3. Poorly executed informed consent can also give rise to a lawsuit. This includes informed consent regarding the use of telehealth as the accepted modality for the visit rather than traditional on-site evaluations, as well as preprocedure informed consent."Inadequate and/or poorly documented informed consent can result in a claim for medical battery," Mr. Cahill said.

Waivers may be weak protection

Since the pandemic started, a number of states have enacted emergency malpractice protections to shield health professionals from lawsuits. Some protections, such as those in Massachusetts, offer immunity to health professionals who provide general care to patients during the COVID-19 emergency, in addition to treatment of COVID-19 patients. Other protections, like those in Connecticut, apply specifically to care provided in support of the state's pandemic response.

Whether that immunity applies both to in-person visits and video visits during the pandemic is not certain, said J. Richard Moore, JD, a medical liability defense attorney based in Indianapolis. Indiana's immunity statute for example, does not make a specific provision for telehealth, he said.

"My best prediction is that, if considered by the courts, the immunity would be applied to telehealth services, so long as they are being provided 'in response to the emergency,' which is the scope of the immunity," he said. "I would not consider telehealth physicians to be either more or less protected than in-person providers."

Regulatory scrutiny for telehealth providers has also been relaxed in response to COVID-19, but experts warn not to rely on the temporary shields for ultimate protection.

In March, the U.S. Department of Health & Human Service's Office of Civil Rights (OCR) eased enforcement actions for noncompliance with Health Insurance Portability and Accountability Act requirements in connection with the good faith provision of telehealth during the COVID-19 health crisis. Under the notice, health providers can use popular applications such as Apple FaceTime, Facebook Messenger, Zoom, or Google Hangouts, to offer telehealth care without risk that OCR will impose fines or penalties for HIPAA violations.

But once the current health care emergency is mitigated, the waivers will likely be withdrawn, and enforcement actions will probably resume, Mr. Cahill said.

"It is recommended that, to avoid potential problems going forward, practitioners use due diligence and undertake best efforts to obey existing privacy and security requirements, including the use of technology that satisfies compliance regulations, despite the waiver by OCR," he said.

In addition, a majority of states have relaxed state-specific rules for practicing telehealth and loosened licensure requirements during the pandemic. At least 47 states have issued waivers to alter in-state licensure requirements for telemedicine in response to COVID-19, according to the Federation of State Medical Boards. Most of the waivers allow physicians licensed in other states to provide care in states where they do not hold licenses, and some enable doctors to treat patients without first having had an in-person evaluation.

But at least for now, these are temporary changes, reminds Amy Lerman, JD, a health care attorney based in Washington, who specializes in telehealth and corporate compliance. Given the current pandemic environment, a significant concern is that physicians new to the telemedicine space are reacting only to the most recent rules established in the context of the pandemic, Ms. Lerman said.

"As previously noted, the recent developments are temporary in nature – states and various federal agencies have been pretty clear in setting this temporal boundary," she said. "It is not advisable for providers to build telepractice models around temporary sets of rules. "Furthermore, the recent developments are not necessarily comprehensive relative to all of the state-specific and other requirements that telemedicine providers are otherwise expected to follow, so relying only on the most recent guidance may cause providers to create telepractice models that have key gaps with respect to regulatory compliance."

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

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: This is extremely important information to understand, especially since telehealth visits have increased exponentially during the public health emergency (PHE). However, when the PHE is no longer in force, many of the protections will lapse as well. In addition, a knowledge of the type of visits (video/audio, e-visit, audio only, etc.) that are reimbursed during and after the PHE will be important as well. Finally, this article provides useful suggestions about how to avoid litigation related to telehealth visits.

Pulmonary arterial hypertension (PAH, WHO Group I) is a silently progressive disease[1]

The ONLY Oral Prostacyclin Pathway Therapy Proven to Reduce the Risk of Disease Progression and PAH-related Hospitalization[2]

INDICATION

UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (eg, gemfibrozil) with UPTRAVI is contraindicated.

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

ADVERSE REACTIONS

Adverse reactions more frequent compared to placebo (≥3%) are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

DRUG INTERACTIONS

CYP2C8 Inhibitors

Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant use of UPTRAVI with strong inhibitors of CYP2C8 is contraindicated.

Concomitant administration of UPTRAVI with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7-fold. Reduce the dosing of UPTRAVI to once daily in patients on a moderate CYP2C8 inhibitor.

Please see additional Important Safety Information on the adjacent page.

BEFORE PROGRESSION TAKES MORE AWAY

Add UPTRAVI Earlier
in FC II and FC III

Add UPTRAVI as part of early comprehensive treatment to help delay disease progression

Visit UptraviHCP.com to learn more.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

CYP2C8 Inducers

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

Patients With Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Co-administration With Moderate CYP2C8 Inhibitors

When co-administered with moderate CYP2C8 inhibitors (eg, clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped.

Dosage Strengths

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

Please see Brief Summary of Prescribing Information on the adjacent page.

#1 MOST-PRESCRIBED ORAL PROSTACYCLIN PATHWAY THERAPY[2]*

*Based on Pharmacy Benefit Manager claims data from Express Scripts and Prime Therapeutics as of June 30, 2019.

FC=functional class; WHO=World Health Organization.

References: 1. Lau EM, Humbert M, Celermajer DS. Early detection of pulmonary arterial hypertension. *Nat Rev Cardiol.* 2015;12(3):143-155.
2. Data on file, Actelion Pharmaceuticals.

Uptravi® selexipag tablets | 200-1600 mcg

ACTELION | A JANSSEN PHARMACEUTICAL COMPANY OF Johnson & Johnson

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
Please see full Prescribing Information.

INDICATIONS AND USAGE
Pulmonary Arterial Hypertension UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

CONTRAINDICATIONS
Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) *[see Drug Interactions (CYP2C8 Inhibitors) and Clinical Pharmacology (Pharmacokinetics)]*.

WARNINGS AND PRECAUTIONS
Pulmonary Veno-Occlusive Disease (PVOD) Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

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

The safety of UPTRAVI has been evaluated in a long-term, placebo-controlled study enrolling 1156 patients with symptomatic PAH (GRIPHON study). The exposure to UPTRAVI in this trial was up to 4.2 years with median duration of exposure of 1.4 years.

The following list presents adverse reactions more frequent on UPTRAVI (N=575) than on placebo (N=577) by ≥3%: headache 65% vs 32%, diarrhea 42% vs 18%, jaw pain 26% vs 6%, nausea 33% vs 18%, myalgia 16% vs 6%, vomiting 18% vs 9%, pain in extremity 17% vs 8%, flushing 12% vs 5%, arthralgia 11% vs 8%, anemia 8% vs 5%, decreased appetite 6% vs 3%, and rash 11% vs 8%.

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

Laboratory Test Abnormalities
Hemoglobin In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from −0.34 to −0.02 g/dL in the selexipag group compared to −0.05 to 0.25 g/dL in the placebo group. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

Postmarketing Experience The following adverse reactions have been identified during postapproval use of Uptravi. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Symptomatic hypotension

DRUG INTERACTIONS
CYP2C8 Inhibitors Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated *[see Contraindications and Clinical Pharmacology (Pharmacokinetics)]*.

Concomitant administration of UPTRAVI with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7-fold. When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped *[see Clinical Pharmacology (Pharmacokinetics)]*.

CYP2C8 Inducers Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase dose up to twice of UPTRAVI when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped *[see Clinical Pharmacology (Pharmacokinetics)]*.

USE IN SPECIFIC POPULATIONS
Pregnancy *Risk Summary* There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures up to 50 times the human exposure at the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. *Data Animal Data* Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

Lactation It is not known if UPTRAVI is present in human milk. Selexipag or its metabolites were present in the milk of rats. Because many drugs are present in the human milk and because of the potential for serious adverse reactions in nursing infants, discontinue nursing or discontinue UPTRAVI.

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

Geriatric Use Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older, while 19 were 75 and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity cannot be ruled out.

Patients with Hepatic Impairment No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

UPTRAVI® (selexipag) Rx Only

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C). Avoid use of UPTRAVI in patients with severe hepatic impairment *[see Clinical Pharmacology (Pharmacokinetics)]*.

Patients with Renal Impairment No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate >15 mL/min/1.73 m^2.

There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates <15 mL/min/1.73 m^2 *[see Clinical Pharmacology (Pharmacokinetics)]*.

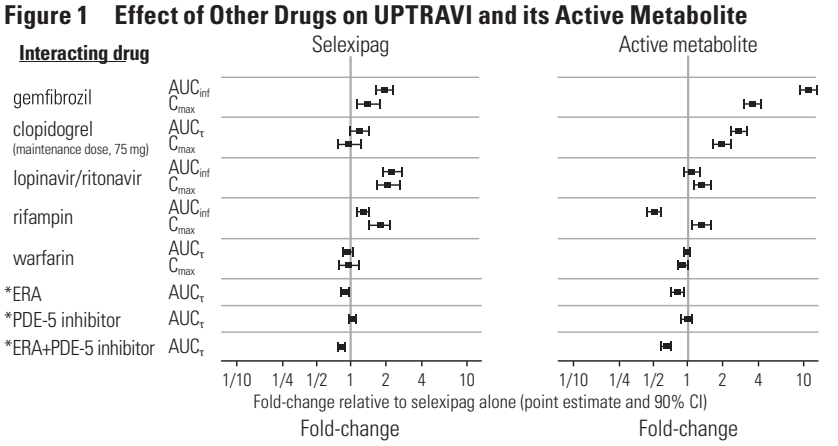
OVERDOSAGE
Isolated cases of overdose up to 3200 mcg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

CLINICAL PHARMACOLOGY
Pharmacokinetics Specific Populations: *Hepatic Impairment:* In subjects with mild *(Child-Pugh class A)* or moderate *(Child-Pugh class B)* hepatic impairment, exposure to selexipag was 2- and 4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. *[see Use in Specific Populations]*.

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, the exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in these patients during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice-daily regimen. *Renal Impairment:* A 40-70% increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate ≥ 15 mL/min/1.73 m^2 and < 30 mL/min/1.73 m^2) *[see Use in Specific Populations]*. Drug Interaction Studies: *In vitro studies* Selexipag is hydrolyzed to its active metabolite by carboxylesterases. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP). Selexipag and its active metabolite do not inhibit or induce cytochrome P450 enzymes and transport proteins at clinically relevant concentrations.

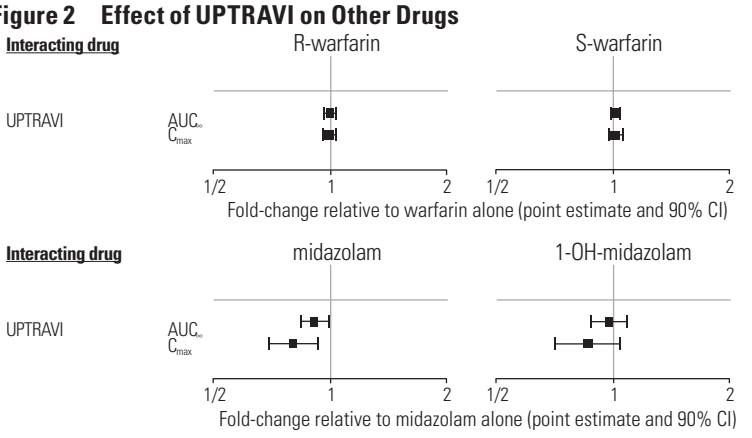
The results on in vivo drug interaction studies are presented in Figure 1 and 2.

Figure 1 Effect of Other Drugs on UPTRAVI and its Active Metabolite



*ERA and PDE-5 inhibitor data from GRIPHON.

Figure 2 Effect of UPTRAVI on Other Drugs



Manufactured for: Actelion Pharmaceuticals US, Inc. 5000 Shoreline Court, Ste. 200, South San Francisco, CA 94080, USA ACT20190806

Reference: UPTRAVI full Prescribing Information. Actelion Pharmaceuticals US, Inc.

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Optimal sedation strategies for patients with COVID-19 treated in ICU: A work in progress

BY DOUG BRUNK
MDedge News

According to the best available evidence, analagosedation remains the focus for managing COVID-19 ICU patients, according to Steven B. Greenberg, MD, FCCP. "The choice of sedation and analgesia is important," Dr. Greenberg, vice chair of education in the department of anesthesiology at Evanston Hospital, part of NorthShore University Health System, Chicago, said at a Society for Critical Care virtual meeting, COVID-19: What's Next.

Analgesia first

Prior to the current pandemic, the approach to sedation of patients in the ICU was based on the PADIS Guidelines of 2018, which call for an assessment-driven, protocol-based stepwise approach to pain and sedation management in critically ill adults (Crit Care Med. 2018;46:e825-73). "[A strategy for COVID-19 in the ICU] should focus on analagosedation defined as analgesia-first sedation rather than jumping to sedation first," Dr. Greenberg said. "We know that pain management should be a priority of sedation, because pain may increase the risk of delirium, anxiety, and endocrine suppression, and may increase the risk of release of endogenous catecholamines, ischemia, and hypermetabolic states."

Fentanyl appears to be the most common opioid analgesic used for patients in the ICU, "but fentanyl is a very lipophilic drug and has a long context-sensitive half-life," he said. "There are components to fentanyl that allow it to become a very long-acting drug upon days and days of infusion. Another opioid used is remifentanil, which is typically short-acting because it is broken down in the blood by esterases, but may cause rigidity at higher doses. Dilaudid seems to be the least affected by organ dysfunction. In our very critically ill, prolonged mechanically ventilated COVID-19 patients, we've been using methadone for its NMDA [N-methyl-D-aspartate] antagonistic effect and its opioid-sparing effects."

As for nonopioid analgesics, Dr. Greenberg said that clinicians have shied away from using NSAIDs because of their side effects. "Tramadol indirectly inhibits reuptake of norepinephrine and serotonin, and ketamine is being used a lot more because of its NMDA antagonist effect," he said. "Lidocaine and gabapentin have also been used."

ICU delirium: Risk factors, prevention

Delirium in COVID-19 patients treated in the ICU is of particular concern. According to a systematic review of 33 studies, 11 risk factors for delirium in the ICU were age, dementia, hypertension, emergency surgery, trauma, APACHE score of II, need for mechanical ventilation, metabolic acidosis, delirium on prior day, coma, and dexmedetomidine use (Crit Care Med. 2015;43:40-7). Risk factors for ICU delirium among COVID-19 patients, however, "are far different," Dr. Greenberg said. "Why? First and foremost, we are restricting visitation of family," he said. "That family connection largely can be lost. Second, there are limitations of nonpharmacologic interventions. There is less mobility and physical therapy employed because of the risk of health care workers' exposure to the virus. There's also uncertainty about the global pandemic. Anxiety and depression come with that, as well as disruptions to spiritual and religious services."


Dr. Greenberg

No ideal sedative agent

The 2018 PADIS Guidelines on the use of ICU sedation suggested strong evidence for modifiable risk factors producing delirium in the context of benzodiazepines and blood transfusion. They recommend a light level of sedation and the use of propofol or dexmedetomidine over benzodiazepines. They also recommend routine delirium testing such as using the CAM-ICU or Intensive Care Delirium Screening Checklist (ICDSC) and nonpharmacologic therapies such as reorientation, cognitive stimulation, sleep improvement, and mobilization.

Several sedation-related factors may be related to an increased risk of delirium. "The type, dose, duration, and mode of delivery are very important," Dr. Greenberg said. "The ideal sedative agent has a rapid, predictable onset; is short-acting; has anxiolytic, amnestic, and analgesic properties; is soluble; has a high therapeutic index; and no toxicity. The ideal sedative is also easy to administrate, contains no active metabolites, has minimal actions with other drugs, is reversible, and is cost effective. The problem is, there really is no ideal sedative agent. There is inadequate knowledge about the drugs [used to treat COVID-19 in the ICU] available to us, the dosage, and importantly, the pharmacokinetics and dynamics of these medications."

Choosing the right drug

The keys to success for sedation of ICU patients are choosing the right drug at the right dose for the right duration and the right mode of delivery, and applying them to the right population. However, as noted in a recent study, the pandemic poses unique challenges to clinicians in how they care for critically ill COVID-19 patients who require sedation (Anesth Analg. 2020 Apr 22. doi: 10.1213/ANE.0000000000004887). Dr. Greenberg said, "We've used alternate providers who are not necessarily familiar with the sedation and analgesic protocols and how to use these specific medications. Drug shortages have been on the rise, so there's a need to understand alternative agents that can be used."

COVID-19 patients face the potential risk for an increase in drug-drug interactions and side effects due to the polypharmacy that is often required to provide adequate sedation during mechanical ventilation. He noted that these patients may have "unusually high" analgesia and sedation requirements, particularly when they're mechanically ventilated. "A potential strategy for COVID-19 ICU patient sedation should be analgesia first, as indicated in the 2018 PADIS Guidelines," Dr. Greenberg advised. "We should also apply nonpharmacologic measures to reduce delirium. In nonintubated patients, we should use light to moderate sedation, targeting a RASS of –2 to +1, using hydromorphone or fentanyl boluses for analgesia and midazolam boluses or dexmedetomidine for sedation,."

For intubated patients, he continued, target a RASS of –3 to –4, or –4 to –5 in those who require neuromuscular blockade. "Use propofol first then intermittent boluses of benzodiazepines," said Dr. Greenberg, editor-in-chief of the Anesthesia Patient Safety Foundation newsletter. "For heavy sedation, use midazolam and supplement with ketamine and other analgesics and sedatives such as barbiturates, methadone, and even inhalation anesthetics in some cases."

Dr. Greenberg concluded his presentation by stating that more studies are required "to delineate the best analgesia/sedation strategies and monitoring modalities for COVID-19 ICU patients."

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VIEW ON THE NEWS

Mangala Narasimhan, DO, FCCP, comments: The recommendations regarding sedation highlight a struggle that ICU providers have been dealing with during the COVID-19 epidemic. There have been unique challenges with COVID-19 and intubated patients. We have seen severe ventilator dyssynchrony and prolonged duration of mechanical ventilation. I think we can all agree that these patients have extremely high metabolic rates, have required high levels of sedation, have an increased need for neuromuscular blockade, and have high levels of delirium for extended periods of time. The recommendations provided here are reasonable. Strategies to prevent delirium should be employed, pain management should be prioritized, and analgesics can help reduce the need for opioids. Alternatives to sedation are useful in this patient population and are well tolerated. Drug shortages have provided additional challenges to these strategies and have required us to think about the use of alternative agents. The recommendations echo the experience we have had with large numbers of intubated COVID-19 patients.

Bronchoscopy in COVID-19 patients: Worth the risk?

BY DOUG BRUNK
MDedge News

FROM CHEST® ▪ Bronchoscopy with intermittent apnea can be conducted safely for both patients with severe COVID-19 and health care workers, a recent study has found. In addition, the high rate of superinfection in these patients indicates that bronchoalveolar lavage (BAL) should be sent to the lab if there is any suspicion for secondary pneumonia.

Those are two key findings from a single-center retrospective study led by Stephanie H. Chang, MD, that was published in the journal *CHEST*.

"While there is a risk of aerosolization and transmission of COVID-19 with bronchoscopy, this can be mitigated with bronchoscopy under intermittent apnea and appropriate PPE [personal protective equipment] in a negative-pressure room, with no significant adverse patient outcomes and a 0% rate of transmission to health care workers," Dr. Chang, a thoracic surgeon in the department of cardiothoracic surgery at New York University Langone Health, said in an interview. "In appropriate clinical scenarios that will significantly impact patient care, bronchoscopy can be and should be safely performed in patients with COVID-19."

Although a recent statement from the American Association for Bronchoscopy & Interventional Pulmonology indicates that bronchoscopy is relatively contraindicated in patients with suspected and confirmed COVID-19 infections, it does support use of the procedure in a subset of such patients (J Bronchology Interv Pulmonol. 2020 Oct;27(4):e52-4). It reads: "The only role for bronchoscopy would be when less invasive testing to confirm COVID-19 are inconclusive, suspicion for an alternative diagnosis that would impact clinical management is suspected, or an urgent lifesaving intervention."

For the current study, Dr. Chang and colleagues retrospectively studied the records of 412 patients with confirmed COVID-19 who were admitted to NYU Langone Health's Manhattan campus between March 13 and April 24, 2020. Of these, 321 required intubation and 107 (33%) underwent bronchoscopy, with a total of 241 bronchoscopies being performed.

Primary outcomes of interest were patient and health care provider safety, defined as freedom from periprocedural complications and COVID-19 transmission, respectively. Secondary outcomes included secondary infection with bacterial or fungal pneumonia.

The bronchoscopy team included six cardiothoracic surgeons and four cardiothoracic surgery residents. Each procedure was performed by a sole bronchoscopist in a negative-pressure room, with a bedside nurse immediately available outside of the room. The bronchoscopist wore full PPE, which consisted of hair cover, a fitted N95 mask, a face shield, gown, and gloves. Each patient was preoxygenated for 2 minutes with a fraction of inspired oxygen at 1.0 in order to maximize apneic time. For patients who were not on sedation and/or neuromuscular blockade, periprocedural anesthesia with propofol and rocuronium was employed to decrease the risk of spontaneous breathing leading to aerosolization.


Dr. Chang

The bronchoscope used was the disposable Ambu aScope and a corresponding monitor. The device was used to clear all secretions, clot, or mucus plugs, and to collect BAL samples. If oxygen saturation decreased below 90%, the bronchoscopist interrupted the procedure and reconnected the patient to the ventilator. After an additional period of preoxygenation, bronchoscopy was then completed.

The mean age of the 107 patients was 62 years, and 81% were male. Dr. Chang and colleagues reported that, of the 241 bronchoscopies performed, no periprocedural complication of severe hypoxia requiring bag-valve ventilation, pneumothorax, or intraprocedural arrhythmias occurred, and that three patients required endotracheal tube advancement or replacement for dislodgment during the procedure.

About half of patients (51%) received a BAL, and 35 (65%) had a positive culture. Among 23 patients who had a negative tracheal culture, 8 patients had a positive BAL, which indicated a 35% diagnostic yield for patients with negative tracheal aspirates. In addition, three patients had differing cultures between the BAL and tracheal aspirate. One was growing *Pseudomonas* and *Klebsiella* in the tracheal aspirate with *Enterococcus* in the BAL, while the other two patients were growing an extra pathogen (*Escherichia coli* or *Serratia*) in the BAL.

"The most surprising data was the 65% rate of secondary infection with BAL, which is significantly higher than the rate in standard patients with acute respiratory distress syndrome," Dr. Chang said. "Additionally, the high rate of bronchoscopy (33% in intubated patients) is also significantly higher than that of standard viral ARDS patients. This increased rate of superimposed infection and need for bronchoscopy may be due to the abnormally thick secretions seen in patients with COVID-19."

> *"The most surprising data was the 65% rate of secondary infection with BAL, which is significantly higher than the rate in standard patients with acute respiratory distress syndrome."*

Of the 10 cardiothoracic surgery team members, 1 resident was COVID-19 positive by reverse transcriptase polymerase chain reaction (rtPCR) prior to performing any bronchoscopies. The remaining nine team members tested negative for COVID-19 via nasal pharyngeal swab for rtPCR assay, with at least one negative test performed 2 weeks after the last bronchoscopy performed during the study period.

"The use of apnea was well tolerated by the patients and likely contributed to the lack of transmission of COVID-19 to the health care providers," Dr. Chang said. "Additionally, this work demonstrates a higher rate of superinfection with bacterial or fungal pneumonia, compared to other reports. It is also the only one that describes the false negative rate for negative tracheal aspirates, which is the current recommended diagnostic test for secondary pneumonia in patients with COVID-19." She acknowledged certain limitation of the study, including its retrospective design. "Thus, the clinical impact of bronchoscopy on patient outcomes cannot be accurately assessed."

The authors reported having no financial disclosures.

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SOURCE: Chang SH et al. CHEST. 2020 Oct 8. doi: 10.1016/j.chest.2020.09.263.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Safety and efficacy must always be considered when evaluating critically ill patients for interventions. The research letter by Dr. Chang and co-workers presents retrospective, uncontrolled data concerning the performance of bronchoscopy in critically ill COVID-19 patients. They report that bronchoscopy was performed by their team in a cohort of patients without infection of team members and with potentially useful results. While interesting, this report raises more questions than it answers. Importantly, specimens obtained by bronchoscopy that indicate the presence of bacterial or fungal organisms should not always be considered to be synonymous with infection or pneumonia. We do not know if the results obtained by bronchoscopy led to changes in management, nor do we know if such management changes led to changes in important outcomes. The concept of using bronchoscopy for secretion control is controversial and has not been convincingly shown to improve patient outcomes. The ventilator strategies adopted by the Chang team during bronchoscopy could be postulated to pose risk for patients; larger studies with appropriate control subjects would be needed to confirm safety. Recent CHEST guidelines suggest a much more limited role for bronchoscopy in seriously ill COVID-19 patients, and this may be the most prudent recommendation for the present. As I often tell my residents during rounds regarding interventions, safety, and efficacy: "Just because you can do something doesn't mean that you should do it." Bronchoscopy in critically ill COVID-19 patients should be performed very selectively.

Link between vitamin D and ICU outcomes unclear

BY INGRID HEIN

FROM CHEST 2020 ▪ We can "stop putting money on vitamin D" to help patients who require critical care, said Todd Rice, MD, FCCP.

"Results from vitamin D trials have not been uniformly one way, but they have been pretty uniformly disappointing," Dr. Rice, from Vanderbilt University Medical Center, Nashville, Tenn., reported at the American College of Chest Physicians virtual annual meeting.

Dr. Rice

Low levels of vitamin D in critically ill COVID-19 patients have been reported in numerous recent studies, and researchers are looking for ways to boost those levels and improve outcomes.

We are seeing "the exact same story" in the critically ill COVID-19 population as we see in the general ICU population, said Dr. Rice. "The whole scenario is repeating itself. I'm pessimistic."

Still, vitamin D levels can be elevated, so in theory, "the concept makes sense," he said. There is evidence that, "when given enterally, the levels rise nicely" and vitamin D is absorbed reasonably well." But is that enough?

When patients are admitted to the ICU, some biomarkers in the body are too high and others are too low. Vitamin D is often too low. So far, though, "supplementing vitamin D in the ICU has not significantly improved outcomes," said Dr. Rice.

In the Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial, Dr. Rice and colleagues found no statistical benefit when a 540,000-IU boost of vitamin D was administered to 2,624 critically ill patients, as reported by this news organization.

"Early administration of high-dose enteral vitamin D_3 did not provide an advantage over placebo with respect to 90-day mortality or other nonfatal outcomes among critically ill, vitamin D–deficient patients," the researchers write in their recent report.

In fact, VIOLET ended before enrollment had reached the planned 3,000-patient cohort because the statistical analysis clearly did not show benefit. Those enrolled were in the ICU because of, among other things, pneumonia, sepsis, the need for mechanical ventilation or vasopressors, and risk for acute respiratory distress syndrome.

When patients are admitted to the ICU, some biomarkers in the body are too high and others are too low. Vitamin D is often too low. So far, though, "supplementing vitamin D in the ICU has not significantly improved outcomes," said Dr. Rice.

"It doesn't look like vitamin D is going to be the answer to our critical care problems," Dr. Rice said in an interview.

Maintenance dose needed?

One theory suggests that VIOLET might have failed because a maintenance dose is needed after the initial boost of vitamin D.

In the ongoing VITDALIZE trial, critically ill patients with severe vitamin D deficiency (12 ng/mL or less at admission) receive an initial 540,000-IU dose followed by 4,000 IU per day.

The highly anticipated VITDALIZE results are expected in the middle of next year, Dr. Rice reported, so "let's wait to see."

"Vitamin D may not have an acute effect," he theorized. "We can raise your levels, but that doesn't give you all the benefits of having a sufficient level for a long period of time."

Another theory suggests that a low level of vitamin D is simply a signal of the severity of disease, not a direct influence on disease pathology.

Some observational data have shown an association between low levels of vitamin D and outcomes in COVID-19 patients (Nutrients. 2020 May 9;12[5]:1359; medRxiv. 2020 Apr 24. doi: 10.1101/2020.04.24.20075838; JAMA Netw Open. 2020;3[9]:e2019722; FEBS J. 2020 Jul 23;10.1111/febs.15495; Clin Endocrinol [Oxf]. 2020 Jul 3;10.1111/cen.14276), but some have shown no association (medRxiv. 2020 Jun 26. doi: 10.1101/2020.06.26.20140921; J Public Health [Oxf]. 2020 Aug 18;42[3]:451-60).

Dr. Rice conducted a search of Clinicaltrials.gov immediately before his presentation, and he found 41 ongoing interventional studies – "not observational studies" – looking at COVID-19 and vitamin D.

"They're recruiting, they're enrolling; hopefully we'll have data soon," he said.

Researchers have checked a lot of boxes with a resounding yes on the vitamin D question, so there's reason to think an association does exist for ICU patients, whether or not they have COVID-19.

"Is there a theoretical benefit of vitamin D in the ICU?" Dr. Rice asked. "Yes. Is vitamin D deficient in patients in the ICU? Yes. Is that deficiency associated with poor outcomes? Yes. Can it be replaced safely? Yes."

However, "we're not really sure that it improves outcomes," he said.

A chronic issue?

"Do you think it's really an issue of the patients being critically ill with vitamin D," or is it "a chronic issue of having low vitamin D?" asked session moderator Antine Stenbit, MD, PhD, from the University of California, San Diego.

"We don't know for sure," Dr. Rice said. Vitamin D might not have a lot of acute effects; it might have effects that are chronic, that work with levels over a period of time, he explained.

"It's not clear we can correct that with a single dose or with a few days of giving a level that is adequate," he acknowledged.

Dr. Rice is an investigator in the PETAL network. Dr. Stenbit disclosed no relevant financial relationships.

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

Nerve damage linked to prone positioning in COVID-19

BY BATYA SWIFT YASGUR, MA, LSW

Among COVID-19 patients who undergo mechanical ventilation, lying in the prone position has been associated with lasting nerve damage. A new case series describes peripheral nerve injuries associated with this type of positioning and suggests ways to minimize the potential damage.

"Physicians should remain aware of increased susceptibility to peripheral nerve damage in patients with severe COVID-19 after prone positioning, since it is surprisingly common among these patients, and should refine standard protocols accordingly to reduce that risk," said senior author Colin Franz, MD, PhD, director of the Electrodiagnostic Laboratory, Shirley Ryan AbilityLab, Chicago.

The article was published online Sept. 4 in the British Journal of Anaesthesiology (2020 Sep 4. doi: 10.1016/j.bja.2020.08.045).

Unique type of nerve injury

Many patients who are admitted to the intensive care unit with COVID-19 undergo invasive mechanical ventilation because of acute respiratory distress syndrome (ARDS). Clinical guidelines recommend that such patients lie in the prone position 12-16 hours per day.

"Prone positioning for up to 16 hours is a therapy we use for patients with more severe forms of ARDS, and high-level evidence points to mortality benefit in patients with moderate to severe ARDS if [mechanical] ventilation occurs," said study coauthor James McCauley Walter, MD, of the pulmonary division at Northwestern University, Chicago.

With a "significant number of COVID-19 patients flooding the ICU, we quickly started to prone a lot of them, but if you are in a specific position for multiple hours a day, coupled with the neurotoxic effects of the SARS-CoV-2 virus itself, you may be exposed to a unique type of nerve injury," he said.

Dr. Walter said that the "incidence of asymmetric neuropathies seems out of proportion to what has been reported in non–COVID-19 settings, which is what caught our attention."

Many of these patients are discharged to rehabilitation hospitals, and "what we noticed, which was

Continued on page 25

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.
FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

WHEN EOSINOPHILIC ASTHMA IS UNCONTROLLED

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THE **POWER** PATIENTS DESIRE

FASENRA significantly reduced patients' exacerbations and improved lung function*[1-3]

THE **PROTECTION** PATIENTS DEMAND

FASENRA significantly reduced patients' need for OCS use†[1,4]

THE **CONVENIENCE** PATIENTS DESERVE

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*In SIROCCO (48 weeks), a 51% reduction was observed in annual rate of asthma exacerbations in patients treated with FASENRA + SOC (n=267) vs placebo + SOC (n=267) (0.74 vs 1.52, $P<0.0001$).[1,2] In CALIMA (56 weeks), a 28% reduction was observed in annual rate of asthma exacerbations in patients treated with FASENRA + SOC (n=239) vs placebo + SOC (n=248) (0.73 vs 1.01, $P<0.019$).[1,3] In SIROCCO, a significant improvement in FEV_1 was observed in patients treated with FASENRA + SOC (n=264) vs placebo + SOC (n=261) (398 mL vs 239 mL, $P=0.0006$).[1,2] In CALIMA, a significant improvement in FEV_1 was observed in patients treated with FASENRA + SOC (n=238) vs placebo + SOC (n=244) (330 mL vs 215 mL, $P<0.010$).[1,3]

†In ZONDA (28 weeks), a 75% reduction in median final OCS dose was observed in patients treated with FASENRA + SOC (n=73) vs 25% with placebo + SOC (n=75) ($P<0.001$).[1,4]

‡Every 8 weeks following the first 3 doses Q4W.[1] **Dosing comparisons do not imply comparable efficacy, safety, or FDA-approved indications.**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Please see additional Important Safety Information on next page and Brief Summary of Prescribing Information on following pages.

Q 8 W

MAINTENANCE DOSING*[1]

*Every 8 weeks following the first 3 doses Q4W[1]

AT-HOME
ADMINISTRATION

IN-OFFICE
ADMINISTRATION

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/fasenra.

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

PLEASE SEE BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION ON ADJACENT PAGE.

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

STUDY DESIGNS

SIROCCO AND CALIMA (Trials 1 and 2)

SIROCCO (48-week) and CALIMA (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (SIROCCO) and 1306 (CALIMA) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (SIROCCO) and medium- to high-dose ICS (CALIMA) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/µL and <300 cells/µL). The primary endpoint was annual exacerbation rate ratio vs placebo in patients with blood eosinophil counts of ≥300 cells/µL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (SIROCCO) and Week 56 (CALIMA) in the same population.[2,3]

ZONDA (Trial 3)

A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of **FASENRA** (30 mg SC) Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC) Q4W, and placebo (SC) Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and daily OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/µL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.[4]

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1. FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141. **4.** Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.

AstraZeneca

Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

General Administration Instructions

FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter.

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

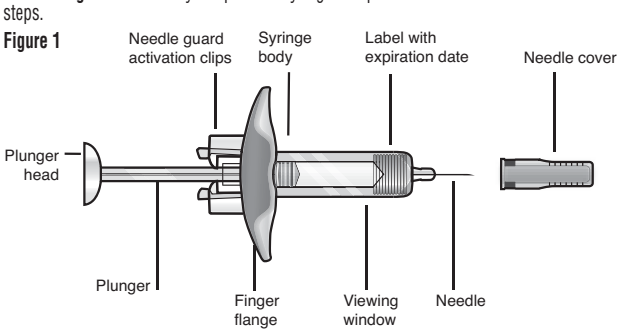
Autoinjector (FASENRA PEN™)

FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

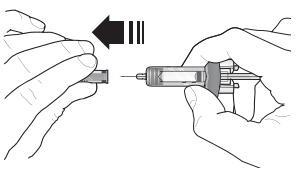
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

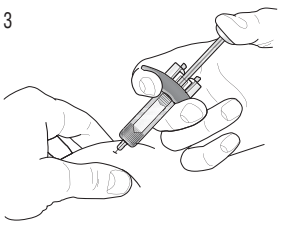
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



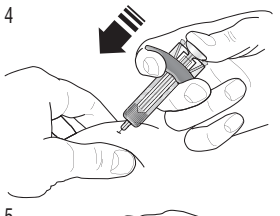
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



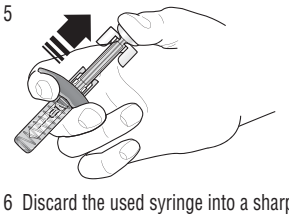
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

Refer to the FASENRA PEN 'Instructions for Use' for more detailed instructions on the preparation and administration of FASENRA PEN *[See Instructions for Use in the full Prescribing Information]*. A patient may self-inject or the patient caregiver may administer FASENRA PEN subcutaneously after the healthcare provider determines it is appropriate.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4) in the full Prescribing Information]*.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

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

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two Phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n=841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n=822), and placebo (n=847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N=822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions†	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

† Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n=73) or placebo (n=75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of FASENRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to FASENRA or a combination of these factors.

Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting mothertobaby.org/Fasenra.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see *Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n=320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use for FASENRA PEN) before the patient starts using FASENRA and each time the prescription is renewed as there may be new information they need to know.

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique using the FASENRA PEN, including aseptic technique, and the preparation and administration of FASENRA PEN prior to use. Advise patients to follow sharps disposal recommendations [*see Instructions for Use in the full Prescribing Information*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Manufactured by
AstraZeneca AB
Södertälje, Sweden SE-15185
US License No. 2059

Distributed by
AstraZeneca Pharmaceuticals LP,
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Rev. 10/19 US-30661 10/19

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unique about COVID-19 patients coming to our rehab hospital, was that, compared with other patients who had been critically ill with a long hospital stay, there was a significantly higher percentage of COVID-19 patients who had peripheral nerve damage," Dr. Franz said.

The authors described 12 of these patients who were admitted between April 24 and June 30, 2020 (mean age, 60.3 years; range, 23-80 years). The sample included White, Black, and Hispanic individuals. Eleven of the 12 post–COVID-19 patients with peripheral nerve damage had experienced prone positioning during acute management.

The average number of days patients received mechanical ventilation was 33.6 (range, 12-62 days). The average number of proning sessions was 4.5 (range, 1-16) with an average of 81.2 hours (range, 16-252 hours) spent prone.

A major contributor

Dr. Franz suggested that prone positioning is likely not the only cause of peripheral nerve damage but "may play a big role in these patients who are vulnerable because of viral infection and the critical illness that causes damage and nerve injuries.

"The first component of lifesaving care for the critically ill in the ICU is intravenous fluids, mechanical ventilation, steroids, and antibiotics for infection," said Dr. Walter. "We are trying to come up with ways to place patients in prone position in safer ways, to pay attention to pressure points and areas of injury that we have seen and try to offload them, to see if we can decrease the rate of these injuries," he added.

The researchers' article includes a heat map diagram as a "template for where to focus the most efforts, in terms of decreasing pressure," Dr. Walter said. "The nerves are accepting too much force for gravely ill COVID-19 patients to handle, so we suggest using the template to determine where extra padding might be needed, or a protocol that might include changes in positioning".

Dr. Franz described the interventions used for COVID-19 patients with prone positioning–related peripheral nerve damage. "The first step is trying to address the problems one by one, either trying to solve them through exercise or teaching new skills, new ways to compensate, beginning with basic activities, such as getting out of bed and self-care," he said.

Long-term recovery of nerve injuries depends on how severe the injuries are. Some nerves can slowly regenerate – possibly at the rate of 1 inch per month – which can be a long process, taking between a year and 18 months.

Dr. Franz said that therapies for this condition are "extrapolated from clinical trial work" on promoting nerve regeneration after surgery using electrical stimulation to enable nerves to regrow at a faster rate.

"Regeneration is not only slow, but it may not happen completely, leaving the patient with permanent nerve damage – in fact, based on our experience and what has been reported, the percentage of patients with full recovery is only 10%," he said.

The study received no funding. Dr. Franz, Dr. Walter, study coauthors, and Dr. Chung report no relevant financial relationships.

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

Vaping cessation: COVID-19 crisis may reverse progress

BY NEIL OSTERWEIL
MDedge News

It's an electronic cigarette maker's dream, but a public health nightmare: The confluence of social isolation and anxiety resulting from the COVID-19 pandemic has the potential to make recent progress against e-cigarette use among teens go up in smoke.

"Stress and worsening mental health issues are well-known predisposing factors for smoking, both in quantity and frequency and in relapse," said Mary Cataletto, MD, FCCP, clinical professor of pediatrics at New York University Winthrop Hospital, Mineola, during a webinar on e-cigarettes and vaping with asthma in the time of COVID-19, hosted by the Allergy & Asthma Network.

Prior to the pandemic, public health experts appeared to be making inroads into curbing e-cigarette use, according to results of the 2020 National Youth Tobacco Survey, a cross-sectional school-based survey of students from grades 6 to 12.

"In 2020, approximately 1 in 5 high school students and 1 in 20 middle school students currently used e-cigarettes. By comparison, in 2019, 27.5% of high school students (4.11 million) and 10.5% of middle school students (1.24 million) reported current e-cigarette use," wrote Brian A. King, PhD, MPH, and colleagues, in an article reporting those results (MMWR Morb Mortal Wkly Rep 2020;69:1310-12.).


Dr. Cataletto

"We definitely believe that there was a real decline that occurred up until March. Those data from the National Youth Tobacco Survey were collected prior to youth leaving school settings and prior to the implementation of social distancing and other measures," said Dr. King, deputy director for research translation in the Office on Smoking and Health within the National Center for Chronic Disease Prevention and Health Promotion at the Centers for Disease Control and Prevention.

"That said, the jury's still out on what's going to happen with youth use during the coming year, particularly during the COVID-19 pandemic" he said in an interview.

Flavor of the moment

Even though the data through March 2020 showed a distinct decline in e-cigarette use, Dr. King and colleagues found that 3.6 million U.S. adolescents still currently used e-cigarettes in 2020; among current users, more than 80% reported using flavored e-cigarettes.

On Jan. 2, 2020, the FDA reported a finalized enforcement policy directed against "unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint."

That enforcement policy applies only to prefilled cartridge e-cigarette products, such as those made by JUUL, and that, while sales of mint- or fruit-flavored products of this type declined from September 2014 to May 2020, there was an increase in the sale of disposable e-cigarettes with flavors other than menthol or tobacco.

Dr. Cataletto pointed out that this vaping trend has coincided with the COVID-19 pandemic, noting that, on March 13, 2020, just 2 days after the World Health Organization declared that spread of COVID-19 was officially a pandemic, 16 states closed schools, leaving millions of middle school– and high school–age children at loose ends. She said: "This raised a number of concerns. Would students who used e-cigarettes be at increased risk of COVID-19? Would e-cigarette use increase again due to the social isolation and anxiety as predicted for tobacco smokers?"

"It's possible that use may go down, because youth may have less access to their typical social sources or other manners in which they obtain the product." Dr. King said. "Alternatively, youth may have more disposable time on their hands and may be open to other sources of access to these products, and so use could increase."

There is evidence to suggest that the latter scenario may be true, according to investigators who surveyed more than 1,000 Canadian adolescents about alcohol use, binge drinking, cannabis use, and vaping in the 3 weeks directly before and after social distancing measures took effect.

Continued on following page

MIS-C cardiac evaluation requires more than EF

BY RICHARD MARK KIRKNER
MDedge News

Patients with multisystem inflammatory syndrome caused by COVID-19 typically seem to avoid coronary artery dilation early on, but they may be prone to cardiac injury and dysfunction longer term that requires a more discerning diagnostic approach to sort out.

The findings were revealed in a study of 28 children with COVID-19–related multisystem inflammatory syndrome (MIS-C) at Children's Hospital of Philadelphia. The study reported that cardiac injury and dysfunction are common in these patients – even those who have preserved ejection fraction – and that diastolic dysfunction is persistent. For comparison, the study also included 20 healthy controls and 20 patients with classic Kawasaki disease (KD).


Dr. Matsubara


Dr. Friedman

The study analyzed echocardiography findings in the patients, reporting left ventricular (LV) systolic and diastolic function were worse than in classic KD, which MIS-C mimics. Lead author Daisuke Matsubara, MD, PhD, and colleagues reported that four markers – LV global longitudinal strain, LV circumferential strain rate, right ventricular strain, and left atrial strain – were the strongest predictors of myocardial injury in these patients. After the acute phase, systolic function tended to recover, but diastolic dysfunction persisted.

'Strain' measurement boosts accuracy

While echocardiography has been reported to be valuable in evaluating coronary artery function in MIS-C patients, Dr. Matsubara of the division of cardiology at CHOP, said in an interview that study is the first to use the newer echocardiography indexes, known as "strain," to assess heart function.

"Strain is a more sensitive tool than more conventional indexes and can detect subtle decrease in heart function, even when ejection fraction is preserved," he said. "Numerous publications have reached conclusions that strain improves the prognostic and diagnostic accuracy of echocardiography in a wide variety of cardiac pathologies causing LV dysfunction."

Dr. Matsubara noted that the coronary arteries were mostly unaffected in the acute stage of MIS-C, as only one patient in their MIS-C cohort had coronary artery involvement, which normalized during early follow-up. "On the other hand, 20% of our classic KD patients had coronary abnormalities, including two with aneurysms."

By using positive troponin I or elevated brain natriuretic peptide (BNP) to assess cardiac injury, they found a "high" (60%) incidence of myocardial injury in their MIS-C cohort. During early follow-up, most of the MIS-C patients showed normalization of systolic function, although diastolic dysfunction persisted.

When compared with the classic KD group, MIS-C patients had higher rates of mitral regurgitation (46% vs. 15%, $P = .06$), more pericardial effusion (32% vs. 15%, $P = .46$), and more pleural effusion (39% vs. 0%, $P = .004$). MIS-C patients with suspected myocardial injury show these findings more frequently than those with actual myocardial injury.

Compared with the healthy controls, the MIS-C patients showed both LV systolic and diastolic dysfunction as well as significantly lower LA strain and peak RV free-wall longitudinal strain.

"In addition to the left ventricle, two other chambers of the heart, the LA and the RV that are often labeled as the 'forgotten chambers' of the heart, were also affected by MIS-C," Dr. Matsubara said. "Both LA and RV strains were markedly reduced in MIS-C patients, compared to normal and KD patients."

The study also indicates that elevated troponin I levels may not be as dire in children as they are in adults. Dr. Matsubara cited a study of more than 2,700 adult COVID-19 patients that found that even mild increases in troponin I level were associated with increased death during hospitalization (J Am Coll Cardiol. 2020;76:533-46).

However, most of the patients in the CHOP study, even those with elevated troponin I levels, recovered systolic function quickly. "We speculate that the elevation in cardiac troponins may have less dire implications in children, likely due to a more transient type of cardiac injury and less comorbidities in children," he said. "Clearly further studies are needed before a definitive statement can be made."

Dr. Matsubara added that recovered COVID-19 patients may be able to participate in sports as some schools reopen. "We are not saying restrict sport participation, but we are merely urging caution."

Comprehensive LV evaluation needed

The findings reinforce that myocardial involvement is more frequent and sometimes more severe in MIS-C than previously thought, said Kevin G. Friedman, MD, a pediatrician at Harvard Medical School, Boston, and an attending physician in the department of cardiology at Boston Children's Hospital. "We are underestimating it by using just traditional measures like ejection fraction. It requires a comprehensive evaluation of left ventricular function; it really affects all aspects of the ventricle, both the systolic function and the diastolic function."

This study supports that MIS-C patients should have a more detailed analysis than EF on echocardiography, including strain imaging. "Probably these patients should all be followed at centers where they can evaluate a more detailed analysis of the LV and RV function," he said. Patients with ongoing CA enlargement and LV dysfunction should have follow-up cardiac care indefinitely. Patients who have no cardiac symptoms during the acute phase probably don't need long-term follow-up.

"We're just trying to learn more about this disease, and it's certainly concerning that so many kids are having cardiac involvement," Dr. Friedman said. "Fortunately they're getting better; we're just trying to find out what this means for the long term."

Dr. Matsubara and Dr. Friedman have no relevant financial disclosures.

chestphysician@chestnet.org

SOURCE: Matsubara D et al. J Am Coll Cardiol. 2020 Sep 2. doi: 10.1016/j.jacc.2020.08.056.

Continued from previous page

The investigators found that the frequency of both alcohol and cannabis use increased during social isolation, and that, although about half of respondents reported solitary substance use, 32% reported using substances with peers via technology, and 24% reported using substances face to face, despite social distancing mandates, reported Tara M. Dumas, PhD, from Huron University College, London, Ont. (J Adolesc Health. 2020 Sep;67[3]:354-61).

E-cigarettes and COVID-19

A recent survey of 4,351 adolescents and young adults in the United States showed that a COVID-19 diagnosis was five times more likely among those who had ever used e-cigarettes, seven times more likely among conventional cigarette and e-cigarette uses, and nearly seven times more likely among those who had used both within the past 30 days (J Adolesc Health. 2020 Oct;67[4]:519-23).

Perhaps not surprisingly, adolescents and young adults with asthma who also vape may be at especially high risk for COVID-19, but the exact effect may be hard to pin down with current levels of evidence.

Dr. King said, "There is an emerging body of science that does indicate that there could be some respiratory risks related to e-cigarette use, particularly among certain populations. ... [But] there's no conclusive link between e-cigarette use and specific disease outcomes, which typically requires a robust body of different science conducted in multiple settings."

An ounce of prevention

"When it comes to cessation, we do know that about 50% of youth who are using tobacco products including e-cigarettes, want to quit, and about the same proportion make an effort to quit, so there's certainly a will there, but we don't clearly have an evidence-based way," Dr. King said.

Combinations of behavioral interventions including face-to-face consultations and digital or telephone support can be helpful, Dr. Cataletto said, but she said that prevention is the most effective method of reducing e-cigarette use among teens and young adults, including peer support and education efforts.

Dr. Cataletto and Dr. King reported no relevant conflicts of interest. Dr. Cataletto serves on the editorial advisory board for *CHEST Physician*.

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Annual rate estimate: BREZTRI 1.08 (n=2137); LAMA/LABA 1.42 (n=2120); ICS/LABA 1.24 (n=2131).[1]

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

ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.
*Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death.

Study 1 was a 52-week, Phase 3, randomized, double-blind, parallel-group, multicenter study of 8588 patients with moderate to very severe COPD that compared BREZTRI MDI 320/18/9.6 (n=2157) with budesonide/glycopyrrolate/formoterol fumarate MDI 160/18/9.6 (n=2137), glycopyrrolate/formoterol fumarate MDI 18/9.6 (n=2143), and budesonide/formoterol fumarate MDI 320/9.6 (n=2151), each administered as 2 inhalations twice daily. Patients were current or former smokers with a smoking history of ≥10 pack-years, aged 40-80 years, with symptomatic COPD despite receiving 2 or more inhaled maintenance therapies, and a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the estimated annual rate of moderate or severe COPD exacerbations.[1]

BREZTRI is administered as 2 inhalations twice daily.

Reference: 1. BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

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

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

Please see Brief Summary of Prescribing Information on adjacent pages.

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

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

AstraZeneca

BREZTRI AEROSPHERE™

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

BRIEF SUMMARY of PRESCRIBING INFORMATION.

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

The safety and efficacy of BREZTRI AEROSPHERE in patients with asthma have not been established. BREZTRI AEROSPHERE is not indicated for the treatment of asthma.

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

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

Deterioration of Disease and Acute Episodes

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

BREZTRI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREZTRI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREZTRI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of BREZTRI AEROSPHERE should not be increased beyond the recommended dose.

Avoid Excessive Use of BREZTRI AEROSPHERE and Avoid Use with other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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

Oropharyngeal Candidiasis

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

Pneumonia

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

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

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

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

Immunosuppression and Risk of Infections

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

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

Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

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

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

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

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

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

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

Corticosteroid Withdrawal Symptoms

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

Hypercorticism and Adrenal Suppression

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

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

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

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm

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

Hypersensitivity Reactions including Anaphylaxis

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

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

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

Reduction in Bone Mineral Density

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

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

Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

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

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

Worsening of Urinary Retention

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

Coexisting Conditions

BREZTRI AEROSPHERE, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. $Beta_2$-agonist therapies may produce transient hyperglycemia in some patients.

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

Additional Adverse Reactions

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

DRUG INTERACTIONS

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

Inhibitors of Cytochrome P450 3A4

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of $beta_2$-adrenergic agonists such as formoterol, a component of BREZTRI AEROSPHERE.

Non-Potassium Sparing Diuretics

The hypokalemia and/or ECG changes that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BREZTRI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and BREZTRI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

OVERDOSAGE

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

Budesonide

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

Glycopyrrolate

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

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Issued: 07/20 US-42033 7/20

Insomnia + COPD linked to more outpatient, ED visits

BY CHRISTINE KILGORE
MDedge News

Insomnia is "highly prevalent" in veterans with chronic pulmonary obstructive disease and is significantly associated with greater COPD-related health care utilization, according to an analysis of national Veterans Health Administration data.

"The study highlights the importance of exploring potential sleep disturbances and disorders in this population and suggests that a targeted treatment for insomnia may help to improve COPD outcomes in veterans with COPD and insomnia," said Faith Luyster, PhD, assistant professor at the University of Pittsburgh, in an interview after the virtual annual meeting of the Associated Professional Sleep Societies, where she presented the findings.

Dr. Luyster and coinvestigators used an administrative database from the Veterans Affairs Corporate Data Warehouse to identify more than 1.5 million patients with COPD who used VHA services over a 6-year period (fiscal years 2011-2017). Insomnia was defined by ICD-9/10 diagnostic codes and/or a sedative-hypnotic prescription for at least 30 doses during any of these years.

Insomnia with COPD was prevalent in this sample of veterans at 37.3%. Compared with veterans without comorbid insomnia, those who had both COPD and insomnia (575,539 of the total 1,542,642) were older (69 vs. 64 years), more likely to be female (6.3% vs. 3.7%), more likely to be Black (14% vs. 11%), and more likely to be a current smoker (46.1% vs. 35.5%).

Those with both COPD and insomnia were also more likely to have a service-connected disability rating of 50% of greater; use supplemental oxygen; be divorced, widowed, or separated; have a higher body mass index; or have other medical or psychiatric conditions – in particular obstructive sleep apnea (39% vs. 7%), depression (21% vs. 5%), and PTSD (33% vs. 3%).

P values were < .001 for all of these demographic and clinical variables, Dr. Luyster reported at the meeting.

Comorbid insomnia clearly impacted health care utilization, she said. Veterans with insomnia in addition to COPD had more outpatient and ED visits (10.5 vs 6.9, and 1.6 vs. 1.4, respectively) and more hospitalizations (2.2 vs. 1.8) with a primary diagnostic code for COPD or COPD exacerbation ($P < .001$).

A negative binomial regression analysis ($P < .001$) showed that "even after controlling for demographic and other medical conditions, COPD patients with insomnia had greater rates of health care utilization relative to COPD patients without insomnia," Dr. Luyster said in the interview.

"Regardless of the etiology [of insomnia in veterans with COPD]," Dr. Luyster said, "it's important that [insomnia] be addressed and treated appropriately, whether that be through pharmacological treatment, or probably more ideally through [cognitive behavioral therapy] for insomnia."

The study did not control for COPD severity, she said, because of the difficulty of extracting this data from the VA Corporate Data Warehouse. The study was funded by the VA Competitive Career Development Fund.

Dr. Luyster had no disclosures.

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VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, FCCP, comments: The criteria used to define insomnia – unadjudicated ICD diagnoses as well as sedative-hypnotic prescriptions – may explain part of the reported prevalence of insomnia. Even so, the findings add to existing literature demonstrating that COPD and insomnia are both common disorders among VHA patients, and that their frequent coexistence could have adverse consequences on the overall health, functional status, long-term outcomes, and quality of life of these patients. Questions of causation are yet to be answered. Is it that uncontrolled or severe airflow obstruction causing frequent nocturnal arousals, dyspnea, orthopnea, overuse of inhaled sympathomimetics and heightened anxiety leads to insomnia? Or is it that insomnia – possibly in a cluster with other affective disorders such as depression, anxiety disorders, or PTSD – elicits more frequent or more severe symptoms of shortness of breath in those with smoking-induced airway and parenchymal lung disease, making the latter diagnosis more overt than in others? My bet is on a bidirectional causal relationship.

Obesity-related hypoventilation linked to increased morbidity risk after bariatric surgery

BY CHRISTINE KILGORE
MDedge News

Patients with obesity-associated sleep hypoventilation had a heightened risk of postoperative morbidities after bariatric surgery, according to a retrospective study.

Reena Mehra, MD, director of sleep disorders research for the Sleep Disorders Center at the Cleveland Clinic, led the team and reported the findings at the virtual annual meeting of the Associated Professional Sleep Societies. Her research team examined the outcomes of 1,665 patients who underwent polysomnography prior to bariatric surgery performed at the Cleveland Clinic from 2011 to 2018.

More than two-thirds, 68.5%, had obesity-associated sleep hypoventilation as defined by body mass index (BMI) of ≥30 kg/m^2 and either polysomnography-based end-tidal CO_2 ≥45 mm Hg or serum bicarbonate ≥27 mEq/L.

These patients represent "a subset, if you will, of obesity hypoventilation syndrome – a subset that we were able to capture from our sleep studies [because] we do CO_2 monitoring during sleep studies uniformly," Dr. Mehra said in an interview after the meeting.

Pornprapa Chindamporn, MD, a former fellow at the center and first author on the abstract, presented the findings. Patients in the study had a mean age of 45.2 ± 12.0 years and a BMI of 48.7 ± 9.0. Approximately 20% were male and 63.6% were White.

Those with obesity-associated sleep hypoventilation were more likely to be male and have a higher BMI and higher hemoglobin A_{1c} than those without the condition. They also had a significantly higher apnea-hypopnea index (17.0 vs. 13.8) in those without the condition, she reported.

A number of outcomes (ICU stay, intubation, tracheostomy, discharge disposition, and 30-day readmission) were compared individually and as a composite outcome between those with and without obesity sleep hypoventilation syndrome (OHS). While some of these postoperative morbidities were more common in patients with the condition, the differences between those with and without OHS were not statistically significant for intubation (1.5% vs. 1.3%, $P = .81$) and 30-day readmission (13.8% vs. 11.3%, $P = .16$).

More than two-thirds of these patients, 68.5%, had obesity hypoventilation syndrome (OHS) as defined by BMI of ≥30 kg/m^2 and either polysomnography-based end-tidal CO_2 ≥45 mm Hg or serum bicarbonate ≥27 mEq/L.

However, the composite outcome was significantly higher: 18.9% vs. 14.3% ($P = .021$), including in multivariable analysis that considered age, gender, BMI, Apnea Hypopnea Index, and diabetes.

All-cause mortality was not significantly differ-

Continued on page 34

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Screening algorithm safely selects patients for OSA treatment before bariatric surgery

BY CHRISTINE KILGORE
MDedge News

A novel algorithm for selecting patients who require treatment for obstructive sleep apnea (OSA) before undergoing bariatric surgery proved safe in a prospective cohort study of 1,103 patients.

Screening for OSA is recommended before bariatric surgery. OSA has been associated in several meta-analyses with increased risk for postoperative complications – not limited to bariatric surgery – and some studies have suggested that this increased risk may be limited to severe OSA, said Frédéric Series, MD, of Université Laval, Quebec City, at the virtual annual meeting of the Associated Sleep Societies.

The preoperative screening algorithm, which utilizes the results of nocturnal home oximetry and morning capillary gas measurements, effectively stratified patients for the risk of postoperative adverse events and "safely selected patients who don't need [continuous positive airway pressure] before bariatric surgery," he said. "The risk of postoperative adverse events following bariatric surgery was not increased in untreated OSA patients with low or moderate risk of severe OSA and hypoventilation."

The study also demonstrated, he said, that patients with severe OSA with or without hypoventilation, even when correctly treated, remain at higher risk for complications.

The algorithm utilizes an oxygen desaturation index (ODI) corresponding to 3% drops in SaO_2 and the percent of the total recording time with an SaO_2 below 90%, as well as capillary gas measurements (PCO_2). Treatment was initiated for those with severe OSA (ODI ≥ 25/hr, < 10% of recording time with a SaO_2 below 90%) or OSA with hypoventilation (PCO_2 ≥ 45).

The study also demonstrated that patients with severe OSA with or without hypoventilation, even when correctly treated, remain at higher risk for complications.

"When the ODI was less than 25 per hour, and when the total recording time spent below 90% SaO_2 was less than 10%, with PCO_2 < 45 mmHg, we expected no need for CPAP treatment," Dr. Series said. For analysis, the investigators considered part of the untreated group – those with an ODI < 10/hr (no or mild OSA) – as a control group.

Treated patients underwent CPAP/BiPAP for a mean duration of 1.5 months. Good treatment compliance was mandatory for surgery, and treatment was continued immediately after extubation, in the recovery room, in nearly all patients, Dr. Series reported.

The analysis covered 1,103 patients: 447 controls (40.8%), 358 untreated (32.7%), 289 treated for OSA (26.4%) and 9 (0.8%) treated for OSA + hypoventilation. Patients with OSA, particularly those with severe OSA and those with hypoventilation, were older and heavier and significantly more likely to have hypertension and diabetes than controls.

There were no differences between the four groups in 10-day reoperation or 30-day readmission occurrence, and postoperative complications were "particularly infrequent in the control and OSA-untreated groups, with no differences between these two groups," Dr. Series said.

Cardiac arrhythmia (mainly atrial fibrillation) occurred more frequently in the OSA-treated group (2.4%) and the OSA/hypoventilation patients (11%) than in the other groups (0.5%-0.6%).

Respiratory failure occurred in about one-third of patients with hypoventilation, and admission to the ICU was "dramatically higher" in patients with hypoventilation (67%), because of respiratory failure, arrhythmia, or other unstable medical conditions, Dr. Series said.

There were no differences between the groups in the duration of surgery or the amount of anesthetic used, but the length of stay in the recovery room was significantly longer in the OSA-treated and hypoventilation groups. The length of hospital stay was also longer in these groups. Sleeve gastrectomy was the most frequent bariatric surgical procedure across all groups, including 100% of patients with hypoventilation, he noted.

Dr. Series reported that he has no relevant disclosures.

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ent between the groups, likely because of its low overall rate (hazard ratio, 1.39; 95% confidence interval, 0.56-3.42).

"In this largest sample to date of systematically phenotyped obesity-associated sleep hypoventilation in patients undergoing bariatric surgery, we identified increased postoperative morbidity," said Dr. Chindamporn, now a pulmonologist and sleep specialist practicing in Bangkok.

Dr. Mehra said in the interview that patients considering bariatric surgery are typically assessed for obstructive sleep apnea, but "not so much obesity hypoventilation syndrome or obesity-associated sleep-related hypoventilation syndrome." The findings "support the notion that we should be closely examining sleep-related hypoventilation in these patients."

At the Cleveland Clinic, "clinically, we make sure we're identifying these individuals and communicating the findings to bariatric surgery colleagues and to anesthesia," said Dr. Mehra, also professor of medicine at Case Western Reserve University, Cleveland.

OHS is defined, according to the 2019 American Thoracic Society clinical practice guideline on evaluation and management of OHS, by the combination of obesity, sleep-disordered breathing, and awake daytime hypercapnia, after excluding other causes for hypoventilation (Am J Respir Crit Care Med. 2019;200[3]:e6-24).

A European Respiratory Society task force has proposed severity grading for OHS, with early stages defined by sleep-related hypoventilation and the highest grade of severity defined by morbidity-associated daytime hypercapnia (Eur Respir Rev. 2019;28:180097). However, Dr. Mehra said she is "not sure that we know enough [from long-term studies of OHS] to say definitively that there's such an evolution."

Patients considering bariatric surgery are typically assessed for obstructive sleep apnea, but "not so much OHS or obesity-associated sleep-related hypoventilation syndrome."

Certainly, she said, future research on OHS should consider its heterogeneity. It is possible that a subset of patients with OHS, "maybe these individuals with sleep-related hypoventilation," are most likely to have adverse postsurgical outcomes.

Atul Malhotra, MD, professor of medicine at the University of California, San Diego, who was asked to comment on the study, said that OHS is understudied in general and particularly in the perioperative setting. "With the obesity pandemic, issues around OHS are likely to be [increasingly] important. And with increasing [use of] bariatric surgery, strategies to minimize risks are clearly needed," he said, adding that the potential risks of nonbariatric surgery in patients with OHS require further study.

He noted that mortality rates in good hospitals "have become quite low for many elective surgeries, making it hard to show mortality benefit to most interventions."

The ATS guideline on OHS states that it is the most severe form of obesity-induced respiratory compromise and leads to serious sequelae, including increased rates of mortality, chronic heart failure, pulmonary hypertension, and hospitalization caused by acute-on-chronic hypercapnic respiratory failure.

Dr. Chindamporn said in her presentation that she had no disclosures. Dr. Mehra's research program is funded by the National Institute of Health, but she has also procured funding from the American College of Chest Physicians, American Heart Association, Clinical Translational Science Collaborative, and Central Society of Clinical Research. Dr. Malhotra disclosed that he is funded by the NIH and has received income from Merck and LIvanova related to medical education.

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E-cigarettes may be linked to sleep deprivation

BY RICHARD FRANKI
MDedge News

Current and former users of e-cigarettes are more likely to report sleep deprivation, compared with those who have never used e-cigarettes, according to the first study to evaluate the association in a large, nationally representative population of young adults.

"The e-cigarette use and sleep deprivation association seems to have a dose-response nature as the point estimate of the association increased with increased exposure to e-cigarette," Sina Kianersi, DVM, and associates at Indiana University, Bloomington, said in Addictive Behaviors.

Sleep deprivation was 49% more prevalent among everyday users of e-cigarettes, compared with nonusers. Prevalence ratios for former users (1.31) and occasional users (1.25) also showed significantly higher sleep deprivation, compared with nonusers, they reported based on a bivariate analysis of data from young adults aged 18-24 years who participated in the 2017 and 2018 Behavioral Risk Factor Surveillance System surveys

After adjustment for multiple confounders, young adults who currently used e-cigarettes every day were 42% more likely to report sleep deprivation than those who never used e-cigarettes, a difference that was statistically significant.

The prevalence of sleep deprivation among those who used e-cigarettes on some days was not significantly higher (prevalence ratio, 1.08), but the ratio between former users and never users was a significant 1.17, the investigators said.

"The nicotine in the inhaled e-cigarette aerosols may have negative effects on sleep architecture and disturb the neurotransmitters that regulate sleep cycle," they suggested, and since higher doses of nicotine produce greater reductions in sleep duration, "those who use e-cigarette on a daily basis might consume higher doses of nicotine, compared to some days, former, and never users, and therefore get fewer hours of sleep."

Nicotine withdrawal, on the other hand, has been found to increase sleep duration in a dose-dependent manner, which "could explain the smaller [prevalence ratios] observed for the association between e-cigarette use and sleep deprivation among former and some days e-cigarette users," Dr. Kianersi and associates added.

The bivariate analysis involved 18,945 survey respondents, of whom 16,427 were included in the fully adjusted model using 12 confounding factors.

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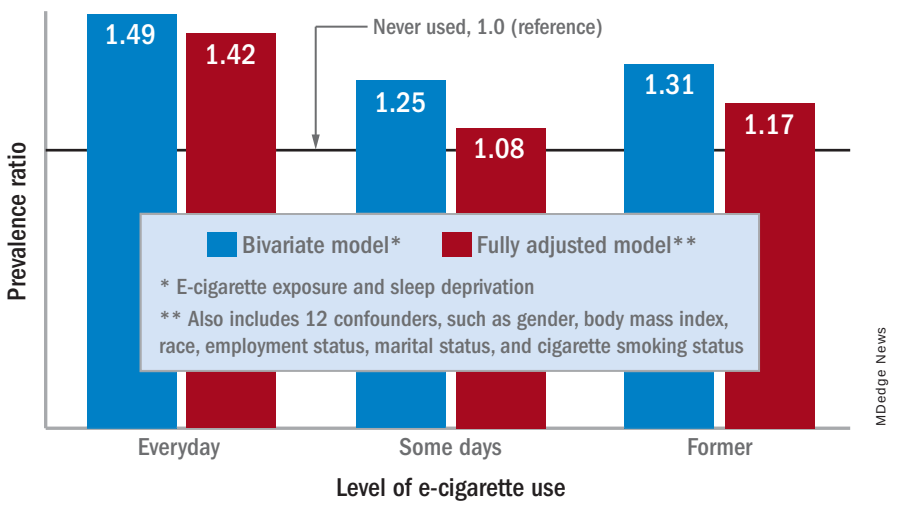
SOURCE: Kianersi S et al. Addict Behav. 2020 Sep 6. doi: 10.1016/j.addbeh.2020.106646.

Sleep deprivation more common in e-cigarette users



Note: Based on data for 18,945 (bivariate) and 16,427 (fully adjusted) young adults who responded to the 2017 and 2018 Behavioral Risk Factor Surveillance System surveys.
Source: Addict Behav. 2020 Sep 6. doi: 10.1016/j.addbeh.2020.106646

OSA may affect pain threshold in young adults

BY DOUG BRUNK
MDedge News

Sleep specialists might want to take a closer look at the connections between obstructive sleep apnea, chronic pain, and reported pain intensity in younger patients. Young adults with a diagnosis of obstructive sleep apnea (OSA) are more likely to report moderate to severe pain intensity, compared with their peers who do not have the diagnosis, results from a large cross-sectional analysis showed.

"Because of the high burden of chronic pain conditions in younger adults, this study highlights the need to understand the impact of OSA diagnosis and treatment on pain intensity," researchers led by Wardah Athar, a graduate student at Yale University, New Haven, Conn., and Lori A. Bastian, MD, MPH, a professor of internal medicine at Yale, wrote in an article published in Annals of the American Thoracic Society. "This understanding would then help inform the development of interventions to promote screening for OSA among young adults with chronic pain and pain management among those with diagnosed OSA."

The study looked at data from young adult veterans, who frequently report significant musculoskeletal pain. "The specific link between OSA and pain remains unclear, but one hypothesis posits that patients with OSA become hyperalgesic because of fragmented sleep, thereby enhancing sensitivity to pain, promoting inflammation, and advancing spontaneous pain. It is also believed that this association may be bidirectional, with an increase in pain and opioid use shown to be associated with sleep-disordered breathing. In addition, OSA is associated with the development and progression of headaches. Most studies examining the association of OSA and pain intensity have included older (age 50 years and above) patients, so there is a need to understand the relationship between OSA and pain among younger adults and to examine for potential sex differences."

Dr. Lori A. Bastian

Wardah Attar

In an effort to assess whether young adults with diagnosed OSA are more likely to report higher pain intensity, compared with those without OSA, the researchers drew from a sample of 858,226 veterans from Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn who had at least one visit to a VA clinic between 2001 and 2014. They used ICD-9 codes to identify OSA and assessed self-reported responses to pain measures on a 0-10 numeric scale which were recorded in each veteran's EMR. Next, they averaged pain intensity responses over a 12-month period and categorized them as none (0), mild (1-3), and moderate/severe (4–10). Covariates included age, sex, education, race, mental health diagnoses, headache diagnoses, pain diagnoses, hypertension, diabetes, body mass index, and smoking status. The researchers used multivariate logistic regression models and multiple imputation to generate values for missing variables.

The mean age of the patients was 30 years, 64% were White, 17% were Black, 12% were Hispanic, and remainder were other/unknown race/ethnicity. Ninety percent were male, and 20% had greater than a high school education. Of the 858,226 patients, 91,244 (11%) had a diagnosis of OSA. Compared with patients who had no diagnosis of OSA, the unadjusted odds of reporting moderate/severe pain was 48% higher among those with OSA (odds ratio, 1.48; $P < .0001$). After the researchers adjusted for all covariates in the model, the association between OSA and moderate/severe pain remained significant though attenuated, with an adjusted odds ratio of 1.09 ($P < .0001$).

Several characteristics were different between those who had a diagnosis of OSA and those who did not, including age (a mean of 36 vs. 26 years, respectively) and having the following diagnoses: pain (36% vs. 16%), headache (28% vs. 14%), diabetes (12% vs. 2%), hypertension (40% vs. 12%), and a body mass index of 30 kg/m^2 or greater (69% vs. 35%). Certain psychiatric disorders were also common among patients with OSA, including major depressive disorder (20% vs. 10%), posttraumatic stress disorder (50% vs. 30%), and substance use disorder (26% vs. 17%). Patients with OSA were also more likely to have been prescribed benzodiazepines or opioids within 90 days of their OSA diagnosis. Although men were more likely to have a diagnosis of OSA, no differences related to sex in the association of OSA and pain were observed in sex-based stratified analyses.

"Based on these results, we suggest more thorough and more frequent pain intensity screening in patients with OSA, particularly in those patients who are younger than 60 years old without significant comorbid illness," the researchers concluded. "Furthermore, we also recommend increased OSA screening for patients with moderate/severe pain intensity and pain diagnoses." One tool they recommend is the STOP-Bang (Snoring, Tiredness, Observed Apnea, Blood Pressure, Body Mass Index, Age, Neck Circumference, and Gender) questionnaire, which has been validated in multiple settings (PLoS One. 2015;10:e0143697).

The study was supported by the Health Services Research & Development in the Department of Veterans Affairs of the Veterans Health Administration, the Yale School of Medicine Medical Student Fellowship, and the U.S. National Institutes of Health.

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SOURCE: Athar W et al. Ann Am Thorac Soc. 2020;17(10):1273-48.

VIEW ON THE NEWS

Krishna M. Sundar, MD, FCCP, comments: One of the problems with sleep apnea studies is that there are always confounding effects, especially from BMI. This is a population that has a significant medical burden of disease, but I think this is a well-done study to look at the relationship between pain and OSA in a younger population. The authors tried to adjust for all these confounders and they still found a significant association. This indicates that sleep affects one's pain threshold. And sleep apnea, by mechanisms still yet to be defined, also alters that pain threshold. It may also affect the expression of pain or management of pain, making treatment more problematic in this population. A key limitation of the study was the fact it evaluated only one aspect of sleep: OSA. They didn't look at duration of sleep, comorbid insomnia, or fragmentation of sleep from apnea or from other causes. We have multiple ways of treating sleep apnea. Clearly, we need studies of treating sleep apnea with continuous positive airway pressure and how that affects the occurrence of pain. The relevant practical aspect of this is that there are pain clinics all over the country that should screen for sleep apnea. Along the same lines, sleep practitioners should be aware that pain has an important association with sleep apnea.

COLCOT: The earlier the better for colchicine post MI

BY PATRICE WENDLING

The earlier the anti-inflammatory drug colchicine is initiated after a myocardial infarction the greater the benefit, a new COLCOT analysis suggests.

The parent trial was conducted in patients with a recent MI because of the intense inflammation present at that time, and added colchicine 0.5 mg daily to standard care within 30 days following MI.

As previously reported, colchicine significantly reduced the risk of the primary end point – a composite of cardiovascular (CV) death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization – by 23% compared with placebo.

This new analysis shows the risk was reduced by 48% in patients receiving colchicine within 3 days of an MI (4.3% vs. 8.3%; adjusted hazard ratio, 0.52; 95% confidence interval, 0.32-0.84; *P* = .007).

Risk of a secondary efficacy end point – CV death, resuscitated cardiac arrest, MI, or stroke – was reduced by 45% over an average follow-up of 22.7 months (3.3% vs 6.1%; adjusted HR, 0.55; 95% CI, 0.32-0.95; *P* = .031).

"We believe that our results support an early, in-hospital initiation of adjunctive colchicine for post-MI prevention," Nadia Bouabdallaoui, MD, Montreal Heart Institute,said during an online session devoted to colchicine at the European Society of Cardiology Congress 2020.

Session moderator Massimo Imazio, MD, professor of cardiology at the University of Turin (Italy), said the improved outcomes suggest that earlier treatment is better – a finding that parallels his own experience using colchicine in patients with pericarditis.

"This substudy is very important because this is probably also the year in cardiovascular applications [that] early use of the drug could improve outcomes," he said.

Positive data have been accumulating for colchicine from COLCOT, LoDoCo, and, most recently, the LoDoCo2 trial, even as another anti-inflammatory drug, methotrexate, flamed out as secondary prevention in the CIRT trial.

The new COLCOT substudy included 4,661 of the 4,745 original patients and examined treatment initiation using three strata: within 0-3 days (n = 1,193), 4-7 days (n = 720), and 8-30 days (n = 2,748). Patients who received treatment within 3 days were slightly younger, were more likely to be smokers, and had a shorter time from MI to randomization (2.1 days vs 5.1 days vs. 20.8 days, respectively).

In the subset receiving treatment within 3 days, those assigned to colchicine had the same number of cardiac deaths as those given placebo (2 vs. 2) but fewer resuscitated cardiac arrests (1 vs. 3), MIs (17 vs. 29), strokes (1 vs. 5), and urgent hospitalizations for angina requiring revascularization (6 vs. 17).

"A larger trial might have allowed for a better assessment of individual endpoints and subgroups," observed Bouabdallaoui.

Although there is growing support for colchicine, experts caution that the drug may not be for everyone. In COLCOT, 1 in 10 patients were unable to tolerate the drug, largely because of gastrointestinal (GI) issues.

Experts caution that colchicine may not be for everyone. In COLCOT, 1 in 10 patients were unable to tolerate the drug, largely because of gastrointestinal issues.

Pharmacogenomics substudy

A second COLCOT substudy aimed to identify genetic markers predictive of colchicine response and to gain insights into the mechanisms behind this response. It included 767 patients treated with colchicine and another 755 treated with placebo – or about one-third the patients in the original trial.

A genomewide association study did not find a significant association for the primary CV endpoint, although a prespecified subgroup analysis in men identified an interesting region on chromosome 9 (variant: rs10811106), which just missed reaching genomewide significance, said Marie-Pierre Dubé, PhD, director of the Université de Montréal Beaulieu-Saucier Pharmacogenomics Centre at the Montreal Heart Institute.

In addition, the genomewide analysis found two significant regions for GI events: one on chromosome 6 (variant: rs6916345) and one on chromosome 10 (variant: rs74795203).

For each of the identified regions, the researchers then tested the effect of the allele in the placebo group and the interaction between the genetic variant and treatment with colchicine. For the chromosome 9 region in males, there was no effect in the placebo group and a significant interaction in the colchicine group.

For the significant GI event findings, there was a small effect for the chromosome 6 region in the placebo group and a very significant interaction with colchicine, Dr. Dubé said. Similarly, there was no effect for the chromosome 10 region in the placebo group and a significant interaction with colchicine.

Additional analyses in stratified patient populations showed that males with the protective allele (CC) for the chromosome 9 region represented 83% of the population. The primary CV endpoint occurred in 3.2% of these men treated with colchicine and 6.3% treated with placebo (HR, 0.46; 95% CI, 0.24-0.86).

For the gastrointestinal events, 25% of patients carried the risk allele (AA) for the chromosome 6 region and 36.9% of these had GI events when treated with colchicine versus 18.6% when treated with placebo (HR, 2.42; 95% CI, 1.57-3.72).

Similarly, 13% of individuals carried one or two copies of the risk allele (AG+GG) for the chromosome 10 region and the risk of GI events in these was nearly four times higher with colchicine (47.1% vs. 18.9%; HR, 3.98; 95% CI 2.24-7.07).

Functional genomic analyses of the identified regions were also performed and showed that the chromosome 9 locus overlaps with the SAXO1 gene, a stabilizer of axonemal microtubules 1.

"The leading variant at this locus (rs10811106 C allele) correlated with the expression of the HAUS6 gene, which is involved in microtubule generation from existing microtubules, and may interact with the effect of colchicine, which is known to inhibit microtubule formation," observed Dr. Dubé.

Also, the chromosome 6 locus associated with gastrointestinal events was colocalizing with the Crohn's disease locus, adding further support for this region.

"The results support potential personalized approaches to inflammation reduction for cardiovascular prevention," Dr. Dubé said.

This is a post hoc subgroup analysis, however, and replication is necessary, ideally in prospective randomized trials, she noted.

The substudy is important because it provides further insights into the link between colchicine and microtubule polymerization, affecting the activation of the inflammasome, session moderator Dr. Imazio said.

"Second, it is important because pharmacogenomics can help us to better understand the optimal responder to colchicine and colchicine resistance," he said. "So it can be useful for personalized medicine, leading to the proper use of the drug for the proper patient."

COLCOT was supported by the government of Quebec, the Canadian Institutes of Health Research, and philanthropic foundations. Bouabdallaoui has disclosed no relevant financial relationships. Dr. Dubé reported grants from the government of Quebec; personal fees from DalCor and GlaxoSmithKline; research support from AstraZeneca, Pfizer, Servier, Sanofi; and minor equity interest in DalCor. Dr. Dubé is also coauthor of patents on pharmacogenomics-guided CETP inhibition, and pharmacogenomics markers of response to colchicine.

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

G. Hossein Almassi, MD, FCCP, comments: This is an interesting study on an old drug finding new use in patients with myocardial infarction. The pharmacogenomic studies opens new avenues for personalized medicine in cardiac patients.

Outgoing President's final report

BY STEPHANIE M. LEVINE, MD, FCCP

As I am writing this report, my presidential year is coming to a close. It was certainly not what I could have anticipated, but an incredible opportunity for my personal and professional growth, and a year in which CHEST adapted and grew, as well. We accomplished a great deal during this unprecedented year, and I will take this opportunity for a year-in-review!

In the winter, as COVID-19 appeared across the globe, we established a COVID-19 Task Force led by then incoming President, Dr. Steve Simpson, with the goal of keeping our members updated on the latest research and clinical management of COVID-19 illness, as well as distilling and delivering the latest COVID-19–related information quickly to those on the front lines. We have held weekly COVID-19 webinars, disseminated infographics, and developed an interactive COVID-19 quiz. CHEST also published several COVID-19-related guideline statements and expert panel reports on bronchoscopy, tracheostomy, lung nodule management, and venous thromboembolism in the setting of COVID-19.

Knowing the stress that our health-care workers were under, we also established a CHEST Wellness Center. This longitudinal, webinar-based curriculum, led by Dr. Alex Niven, had its impetus with COVID-19 but will continue and be extended to general wellness topics.

In March, we joined forces with NAMDRC, under the CHEST umbrella, and a combination of our board members and their former board members now make up our Health Policy and Advocacy Committee (HPAC), led by Drs. Neil Freedman and Jim Lamberti, with CHEST Past-President, Dr. John Studdard, also actively involved. Our HPAC is already focusing on home ventilation and competitive bidding, oxygen prescribing, education and access, pulmonary rehabilitation, and tobacco and vaping. The monthly *Washington Watchline* online publication features the latest on advocacy-related issues of interest to our membership. Last month, the HPAC held a multiorganizational technical expert panel meeting on nocturnal noninvasive ventilation, with plans to submit a manuscript on outcomes from the meeting to the journal *CHEST*. These activities are an answer to our member's requests and needs in the areas of advocacy.

With the onset of the pandemic, we pivoted the delivery of our signature education to virtual platforms beginning with a successful global congress in Bologna in June with 3,500 registered attendees. This was a wonderful way to provide education to our global audience. I want to thank co-chairs Dr. Bill Kelly and Dr. Girolamo Pelaia, and Dr. Francesco de Blasio from our Italian Delegation, for their innovative leadership. In August, we held our first virtual board review courses in pulmonary medicine, critical care medicine, and pediatric pulmonary medicine, attended by 775 registered attendees complete with didactic sessions, audience response sessions, SEEK sessions, and live Q&A with the faculty. The on-demand versions of these courses are also available.

Knowing the stress that our health-care workers were under, we also established a CHEST Wellness Center. This longitudinal, webinar-based curriculum, led by Dr. Alex Niven, had its impetus with COVID-19 but will continue and be extended to general wellness topics.

The *CHEST* journal, in its second year with Dr. Peter Mazzone at the helm, continues to be a leading source of clinically relevant research and patient management guidance for pulmonary, critical care, and sleep medicine clinicians worldwide. The year 2020 has been a year like no other – submission rates have doubled since the start of the pandemic, with nearly 5,000 manuscript submissions so far, this year. The journal has rapidly built a robust and growing COVID-19 topic collection, with relevant original research, guidelines, commentaries, and more, published online, within days of acceptance. The journal will continue to seek innovative ways to meet the needs of its readers and contributors during this time when our members and their patients urgently need current and high-quality information.

This year, CHEST hit a publishing milestone, with the publication of *CHEST SEEK™ Critical Care Medicine: 30th Edition* and the SEEK program is celebrating 30 years! Those who registered for CHEST 2020 by October 15 received the access announcement regarding the commemorative 30 Years of SEEK collection in the CHEST SEEK Library.

Dr. Levine

Our Guidelines Oversight Committee has continued to publish evidence-based guidelines in the areas of cough and cryobiopsy, with a guideline on hypersensitivity pneumonitis and updated guidelines in our core topics of lung cancer and venous thromboembolism in the works.

Under the leadership of Dr. Aneesa Das, the NetWorks Task Force started work to accomplish the goal of increasing member engagement and reach by developing pilot projects focusing on infographics interviews with key opinion leaders and social media communications. Additionally, the Digital Strategy Task Force launched a redesigned website for the CHEST Foundation, which you can see at chestfoundation.org, and look for exciting changes coming to the CHEST website in the very near future.

We have continued our collaborative partnerships with our sister societies. We established the volunteer clinician matching program with the American Thoracic Society (ATS) to send clinicians to areas of need during the pandemic, and partnered on other COVID-19 related activities. We held a virtual fellows' graduation with ATS and the Association of Pulmonary and Critical Care Medicine Program Directors. CHEST leadership attended the Asian Pacific Respiratory Society in Vietnam in November, the Society of Critical Care Medicine, and Forum of International Respiratory Societies in February and the recent virtual meetings of ATS, European Respiratory Society, and the Brazilian Thoracic Society.

The CHEST Foundation has continued on their mission to champion lung health and make a difference through their successful fundraising. This was highlighted with a tremendous foundation gala in San Antonio in December, The Golden Era of Erin Popovich, attended by more than 500 people. Since COVID-19, the foundation held several creative virtual fundraising events ranging from wine tastings to poker night to bingo night to a recent trivia night, as well as actively participating in COVID-19-related campaigns, such as the partnership with ATS for COVID-19 public service announcements directed to those affected by COVID-19, and other fundraising campaigns, such as the Buy-A-Mask, Give-A-Mask campaign. In addition, the foundation has continued with their support for clinical research grants, community service grants, and patient education resources and toolkits. For example, they have developed an oxygen tool kit to provide access and empowerment to patients in need.

Thank you to all our donors for continuing to support these CHEST Foundation initiatives. The foundation couldn't continue to do this amazing work to create an impact and raise awareness for lung health without you.

As the movement to combat racism and racial disparity swept across our nation, we issued a statement of equity in early June. In September, the CHEST Foundation launched the first of a series of listening tours to hear community needs in the areas of trust, access, and equity. Information from these tours will be used to launch a designated fund to have the power to transform these needs into action. CHEST is now actively developing a strategic plan focusing on how CHEST can make an impactful difference in this arena. We want to ensure we take this essential time to listen, reflect, and make appropriate plans for ways we can truly make a difference. Expect more to come on this in the coming year.

The year concluded with CHEST 2020. CHEST 2020 had the highest number of case reports and abstracts ever submitted to a CHEST Annual Meeting, and a total registration of more than 4,000. At CHEST 2020, you had an opportunity to see a reimagined virtual annual meeting with combinations of interactive live and prerecorded didactic sessions, audience response sessions, live Q&A with the faculty, educational games at the CHEST Gaming Hub, CHEST Challenge Championship, networking opportunities, narrated abstracts, case reports, original research presentations, COVID-19 update sessions, industry-sponsored programs, a virtual exhibit hall, and surprises, to deliver the in-person CHEST experience virtually. In addition, this came with the greatest number of CME/MOC credits we have ever offered! And, CHEST 2020 education will continue throughout the year with ongoing postgraduate courses creating the ultimate longitudinal educational experience. While nothing can replace the opportunity to connect with our community in person, I hope you found that this year's meeting provided a wealth of learning, connection, and fun.

My sincere thanks to the CHEST 2020 Program Chair, Dr. Victor Test, to the entire Scientific Program Committee, and to our incredible CHEST staff, for the immense amount of hard work over the past year to reimagine CHEST 2020 and make it a reality. Little did Victor know that he would be planning three meetings: a live meeting, a hybrid meeting, and, ultimately, a virtual meeting. Thank you for all you did to make CHEST 2020 a meeting to remember. We plan to continue our efforts to maintain and grow educational innovation year-round through more e-learning, virtual learning, and, hopefully soon, live learning, both locally, nationally, and internationally.

As my year closes, you are in excellent hands with Dr. Steven Simpson, your 83rd President, who will lead the organization forward. You will hear more from him, but you are in the hands of a thoughtful and dedicated leader with a long history of CHEST experience, strong expertise in critical care, and a thought leader in the COVID-19 pandemic, including serving on the NIH COVID-19 Treatment Guidelines Panel.

There are so many people to thank! I want to thank my family: my husband and children, and my work family, the faculty and fellows of my division, for their unwavering support. I also want to thank my Co-President lineage group for their counsel and wisdom, several Past Presidents who I have called on over this past year for advice, Drs. John Studdard, Gerard Silvestri, and Darcy Marciniuk among others, the board (who I only saw face-to-face once!); our CHEST leadership and educators; the incredible CHEST staff; the Executive Leadership team; and our superb, hard-working CEO/EVP Bob Musacchio. Last, and most importantly, I would like to thank our members for being in the trenches this year as we all dealt with COVID-19. You are the heroes! At the beginning of my term last year, I told you that my goal was to be "the welcoming home" for interprofessional health-care team members seeking to obtain the best possible educational experiences and patient outcomes. I had no idea how absolutely needed this would be for our chest medicine family this year. CHEST has always been your connection to relevant clinical information and late-breaking updates in our field – but this year, our CHEST community has been even more than that. Through this year of crisis and change, you all have shown resilience: a resilience molded by being flexible. Not only have you embodied flexibility at your home institutions, you've embodied flexibility in your learning, teaching, and connecting. You've joined us as we've reimagined what learning at CHEST is all about – I sincerely thank you for that!

Through this year of crisis and change, you all have shown resilience: a resilience molded by being flexible. Not only have you embodied flexibility at your home institutions, you've embodied flexibility in your learning, teaching, and connecting. You've joined us as we've reimagined what learning at CHEST is all about – I sincerely thank you for that!

SLEEP STRATEGIES

Sleep-disordered breathing in neuromuscular disease

BY MEREDITH KENDALL GREER, MD; AND NANCY A. COLLOP, MD, MASTER FCCP

Sleep-disordered breathing (SDB) is a common sleep disturbance in neuromuscular disease (NMD) affecting 36% to 53% of diagnosed adults (Arens R, et al. Paediatr Respir Rev. 2010;11[1]:24). Disturbances in sleep may serve as the earliest sign of muscle weakness in these patients, at times being detected before their underlying neuromuscular disease is diagnosed. This is of paramount importance to sleep medicine and pulmonary physicians who may be among the first specialists to evaluate these patients and can play a vital role in the recognition and diagnosis of neuromuscular disease. Herein, we will provide a guide to aid the reader in recognizing the early signs and symptoms of NMD as it pertains to sleep, as earlier diagnosis may lead to improved quality of life or possibly even survival, in some cases.

Dr. Greer

Dr. Collop

Pathophysiology

To begin, it is important to understand the pathophysiology of NMD and how it is altered during the sleep state. Sleep-related physiologic changes in healthy humans include reduction in upper airway muscle tone, blunting of chemoreceptors associated with pharyngeal dilator augmentation, and sleep stage-specific changes in skeletal muscle tone. In patients with NMD, these changes may not be adequately compensated for, leading to sleep-disordered breathing that can present as sleep apnea, hypoventilation, or hypoxia (Govindarajan R, et al. Sleep Issues in Neuromuscular Disorders: A Clinical Guide. Springer International Publishing AG, Springer Nature 2018).

Central respiratory control

The respiratory centers in the pons and medulla are generally spared from the primary effects of most NMD; however, over time, they may be affected secondarily. Similar to obesity hypoventilation syndrome (OHS), untreated chronic sleep-related hypoventilation from NMD can impair the sensitivity of respiratory chemoreceptors leading to worsening hypoventilation.

Upper airway resistance

Pharyngeal muscle tone is key to maintaining a patent airway during sleep. In some NMD, bulbar muscle weakness with pharyngeal dilator muscle hypotonia leads to increased upper airway resistance, especially during REM sleep, which can result in obstructive sleep apnea (OSA). In addition to weakness affecting the upper airway musculature, anatomical changes may also contribute toSDB. In Pompe disease, for example, macroglossia and fibro-fatty replacement of tongue muscles may occur, leading to the development of OSA.

Diaphragm weakness

In NMD that affects the diaphragm, there is an increased reliance on the skeletal muscles of respiration to maintain adequate ventilation as the underlying disease progresses. Generally, weakness of the diaphragm will cause disturbances in REM sleep first as, during REM, ventilation predominately depends on the diaphragm and patients lose the assistance of their skeletal muscles. However, over time, the progressive weakening of the diaphragm will progress to involve NREM sleep as well, clinically manifesting with frank sleep apnea, hypoventilation, and, ultimately, chronic hypercapnic respiratory failure.

Inspiratory muscle weakness

As noted above, there are many other muscles used in inspiration in addition to the diaphragm. Other primary muscles include the intercostal and scalene muscles, and accessory muscles include the sternocleidomastoid, pectoralis, latissimus dorsi, erector spinae, and trapezius muscles. While sleep and breathing problems may begin early in the course of a neuromuscular disease, the complex restrictive lung disease pattern that we see in these patients may not develop until the respiratory muscles of the chest wall are involved. This restriction, which corresponds to lower lung volumes, leads to a fall in the caudal traction force of the airways which can lead to reduction in the pharyngeal airway cross section. Because these issues are worsened in the supine position, their pathophysiologic effects on respiration are most notable during sleep, putting patients at higher risk of OSA.

Cardiac abnormalities

Lastly, it should be noted that diseases such as the muscular dystrophies, myotonic dystrophy, mitochondriopathies, and nemaline myopathy can be associated with a cardiomyopathy, which can lead to central sleep apnea in the form of Cheyne-Stokes breathing.

Sleep-disordered breathing in specific NMDs

In amyotrophic lateral sclerosis (ALS), up to 75% of patients may have SDB, the majority of which is central sleep apnea (CSA) and hypoventilation although they still have a higher prevalence of OSA than the general population. Whether the diaphragm or the pharyngeal muscles are predominantly affected may have something to do with the type of apnea a patient experiences; however, studies have shown that even in bulbar ALS, CSA is most common. It should be noted, that this is not Cheyne-Stokes CSA, but rather lack of chest wall and abdominal movement due to weakness. (David WS, et al. J Neurol Sci. 1997;152[suppl 1]:S29-35).

In myasthenia gravis (MG), about 40% to 60% of patients have SDB, and about 30% develop overt respiratory weakness, generally late in the course of their disease. Many of these patients report excessive daytime sleepiness, often attributed to myasthenic fatigue requiring treatment with corticosteroids. It is important to evaluate for sleep apnea, given that if diagnosed and treated, their generalized fatigue may improve and the need for steroids may be reduced or eliminated altogether. It is also important to note that the respiratory and sleep issues MG patients face may not correlate with the severity of their overall disease, such that patients well-controlled on medications from a generalized weakness standpoint may still require home noninvasive ventilation (NIV) for chronic respiratory failure due to weakness of the respiratory system muscles.

Pharyngeal muscle tone is key to maintaining a patent airway during sleep. In some NMD, bulbar muscle weakness with pharyngeal dilator muscle hypotonia leads to increased upper airway resistance, especially during REM sleep, which can result in obstructive sleep apnea.

Duchenne muscular dystrophy (DMD), an X-linked disease associated with dysfunction of dystrophin synthesis, is often diagnosed in early childhood and gradually progresses over years. Their initial sleep and respiratory symptoms can be subtle and may start with increased nighttime awakenings and daytime somnolence. Generally, these patients will develop OSA in the first decade of life and progress to hypoventilation in

Continued on page 42

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References: **1.** Corren J. *J Allergy Clin Immunol Pract*. 2019;7(5):1394-1403. **2.** Lambrecht BN, Hammad H, Fahy JV. *Immunity.* 2019;50(4):975-991. **3.** Lambrecht BN, Hammad H. *Nat Immunol.* 2015;16(1):45-56.

Continued from page 40

their second decade and beyond. These patients are especially important to recognize, as studies have shown appropriate NIV therapy may significantly prolong their life (Finder JD, et al; American Thoracic Society. Am J Respir Crit Care Med. 2004(Aug 15);170[4]:456-465).

In addition to the well-known motor neuron and neuromuscular diseases mentioned above, neuropathic diseases can lead to sleep disturbances, as well. In Charcot-Marie-Tooth (CMT), pharyngeal and laryngeal neuropathy, as well as hypoglossal nerve dysfunction, lead to OSA. Similar to ALS and MG, there is a significant amount of CSA and hypoventilation, likely related to phrenic neuropathy. In contrast to MG, in CMT, the severity of neuropathic disease does correlate to the severity of sleep apnea.

Testing

Testing can range from overnight oximetry to polysomnogram (PSG) with CO_2 monitoring. Generally, all patients with a rapidly progressive neuromuscular disease should get pulmonary function testing (PFT) (upright and supine) to evaluate forced vital capacity (FVC) every 3 to 6 months to monitor for respiratory failure. Laboratory studies that can be helpful in assessing for SDB are the $PaCO_2$ (> 45 mm Hg) measured on an arterial blood gas and serum bicarbonate levels (> 27 mmol/L or a base excess >4 mmol/L). Patients can qualify for NIV with an overnight SaO_2 less than or equal to 88% for greater than or equal to 5 minutes in a 2-hour recording period, $PaCO_2$ greater than or equal to 45 mm Hg, FVC < 50% of predicted, or maximal inspiratory pressure (MIP) < 60 cm H_2O. For ALS specifically, sniff nasal pressure < 40 cm H_2O and orthopnea are additional criteria that can be used. It is worth noting that a PSG is not required for NIV qualification in neuromuscular respiratory insufficiency. However, PSG is beneficial in patients with preserved PFTs but suspected of having early nocturnal respiratory impairment.

Generally, all patients with a rapidly progressive neuromuscular disease should get pulmonary function testing (upright and supine) to evaluate forced vital capacity every 3 to 6 months to monitor for respiratory failure.

Therapy

NIV is the mainstay of therapy for SDB in patients with NMD and has been associated with a slower decline in FVC and improved survival in some cases, as demonstrated in studies of patients with DMD or ALS. Generally, a bi-level PAP mode is preferred; the expiratory positive airway pressure prevents micro-atelectasis and improves V/Q matching and the inspiratory positive airway pressure reduces inspiratory muscle load and optimizes ventilation. As weakness progresses, patients may have difficulty creating enough negative force to initiate a spontaneous breath, thus a mode with a set respiratory rate is preferred that can be implemented in bilevel PAP or more advanced modes such as volume-assured pressure support (VAPS) modality. For patients who are unable to tolerate NIV, particularly those with severe bulbar disease and difficult to manage respiratory secretions, tracheostomy with mechanical ventilation may ultimately be needed. This decision should be made as part of a multidisciplinary shared decision-making conversation with the patient, their family, and their team of providers.

Summary

Sleep is a particularly vulnerable state for patients with NMD, and in many patients, disturbances in sleep may be the first clue to their ultimate diagnosis. It is important that sleep medicine and pulmonary specialists understand the pathophysiology and management of NMD as they can play a vital role in the interdisciplinary care of these patients.

Dr. Greer is a sleep medicine fellow, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine. Dr. Collop is Professor of Medicine and Neurology, Director, Emory Sleep Center; Emory University, Atlanta, Georgia.

Confronting health disparities: A virtual listening tour

BY RUDY ANDERSON
Executive Director, CHEST Foundation

How do we discuss race and lung health issues that impact our most deserving, underserved communities? Continuously and uncomfortably. As the Executive Director of the CHEST Foundation and as a young Black man, I am hopeful that we, as CHEST, can lead these uncomfortable conversations to better our communities. Our ability to listen and deliver support to our most-deserving communities is critical in how we fulfill our mission. CHEST continues to be a leader in lung health because we choose to give a voice and a platform in support of better lung health – especially to those who are disproportionately affected by lung disease, specifically addressing the quality of care they receive and bringing to light the fact that too often these patients are forgotten by the rest of society.


Mr. Anderson

As cases of COVID-19 and civil unrest continue to swell across our nation, we, the CHEST Foundation, have launched a virtual listening tour. We are taking this pragmatic, and more importantly, passionate approach to addressing health disparities by identifying and addressing barriers and issues affecting our most deserving and disproportionately underserved communities. By bringing together these communities' patients and caregivers, local leaders, involved businesses, and our CHEST members in a virtual community gathering, we intend to clearly define the needs of each community, elevate those needs to a national level, and work to collaborate with and support these local communities and leaders to address their most-pressing issues.

Stories are what connect us and move us forward. We are confident that this virtual listening tour will be an opportunity for constituents to tell their own stories and learn from each other, while allowing the CHEST organization, through the CHEST Foundation, to act as the arbiter for pulmonary health and provide a path forward to create equity for those suffering from chronic lung disease.

We need your support to challenge these long-standing disparities in chest medicine. Help us advance these critical conversations and move the needle toward equality by contributing today at chestfoundation.org/donate.

CHEST and American Thoracic Society respond to proposed fee schedule

CHEST and the American Thoracic Society (ATS) submitted joint comments regarding the proposed Medicare Physician Fee Schedule for 2021 to CMS Administrator Seema Verma on topics of direct interest to members. The letter focuses on:

Medicare payment for critical care services: Further to the joint letter from CHEST, ATS, and the Society of Critical Care Medicine to Department of Health and Human Services Secretary Azar (see article in September 2020 *Washington Watchline*), the concerns related to the proposed 8% reduction in reimbursement for critical care services are explained, particularly relating to the role of critical care providers during the pandemic. They call for waiving budget neutrality or utilizing the public health emergency declaration to ensure appropriate patient care.

ATS and CHEST voice support for the proposed changes to E/M office visits and the increased reimbursement for the cognitive component of E/M medicine.

E/M payment changes: ATS and CHEST voice support for the proposed changes to evaluation and management (E/M) office visits and the increased reimbursement for the cognitive component of E/M medicine. They urge CMS to use its authority to waive the budget neutrality requirements while implementing the E/M changes.

Adoption of RUC-recommended values for pulmonary services: They urge CMS to finalize values for specific pulmonary services while acknowledging thanks for the adoption of the Relative Value Scale Update Committee (RUC)-recommended physician work values for a range of Current Procedural Terminology codes.

Telehealth services: While commending CMS for actions related to telehealth to provide care during the pandemic, they suggest it is now appropriate to sunset the telehealth listing for critical care services as providers have acquired additional experience in treating COVID-19.

GPC1X descriptors and utilization projections: They urge CMS to clarify the descriptors and seek additional comments on primary and ongoing health-care services.

Watch for reports of ongoing efforts from CHEST as the fee schedule process continues. Details of other activities in support of CHEST members appear in the November issue of Washington Watchline.

Reprinted from the November 2020 issue of *Washington Watchline*.

This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

International Perspective on the New 2019 IDSA/ATS CAP Guideline: A Critical Appraisal by a Global Expert Panel. *By Dr. Mathias Pletz, et al.*

Development of an Accurate Bedside Swallowing Evaluation Decision Tree Algorithm for Detecting Aspiration in Acute Respiratory Failure Survivors. *By Dr. Marc Moss, et al.*

How I Do It: Managing Fatigue in Patients With Interstitial Lung Disease. *By Dr. Marlies Wijsenbeek, et al.*

Life-Threatening and Non-Life-Threatening Complications Associated With Coughing: A Scoping Review. *By Dr. Richard S. Irwin, Master FCCP, et al.*

Obstructive Sleep Apnea in Professional Transport Operations: Safety, Regulatory, and Economic Impact. *By Dr. Indira Gurubhagavatula, et al.*

In memoriam

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

Hassan M. Alkhouli, MD, FCCP (2019)
Doros Michaelides, MD, FCCP (2019)
Clive Kearon, MBBCh, PhD (2020)
Joseph J. Costa, MD (2020)

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1. Novosad SA, Sapiano MR, Grigg C, et al. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. MMWR Morb Mortal Wkly Rep 2016;65:864–869.
2. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Filmarray® Pneumonia (PN) Panel.
3. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Blood Culture Identification 2 (BCID2) Panel.

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