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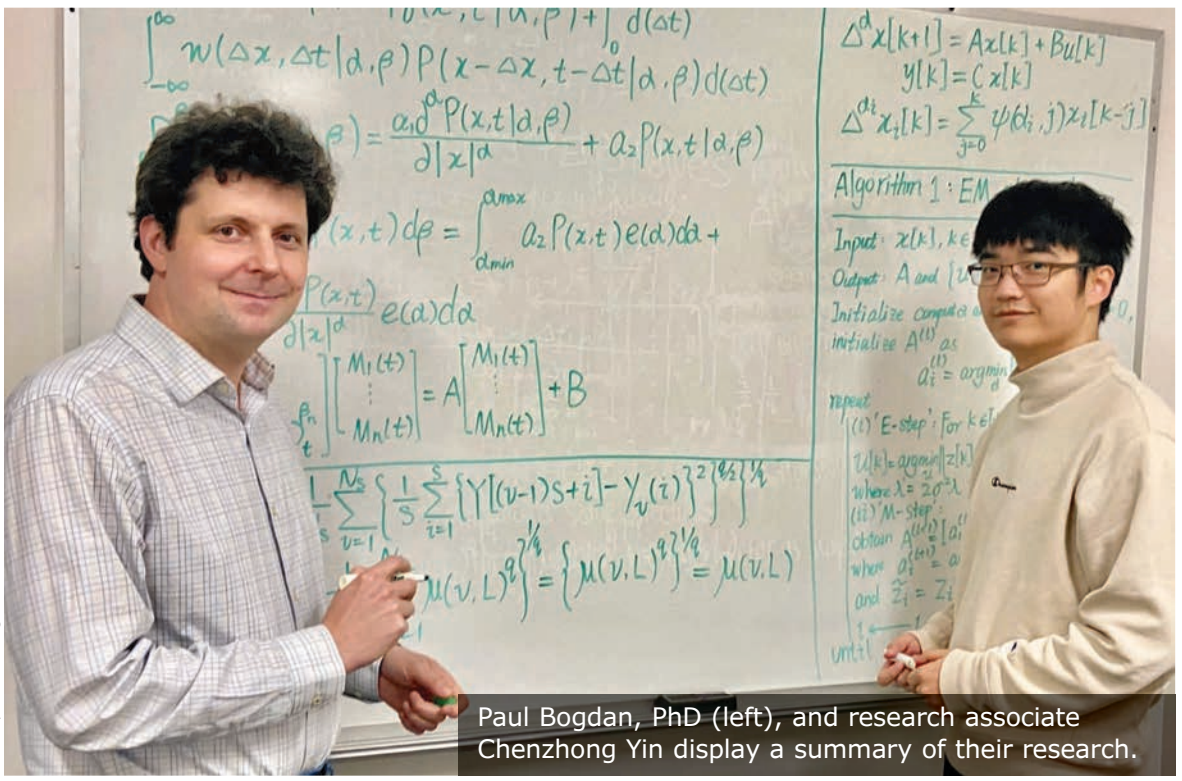

Courtesy Dr. Paul Bogdan

Paul Bogdan, PhD (left), and research associate Chenzhong Yin display a summary of their research.

AI in pulmonary medicine – imaging and beyond

BY RICHARD MARK KIRKNER
MDedge News

The utility of artificial intelligence in pulmonology has focused mainly on using image datasets to detect and diagnose lung malignancies, but now a growing number of AI models are emerging that apply machine learning to improve predictability for other pulmonary conditions, including pulmonary infections, pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD).

These applications are moving beyond the traditional AI model of collecting data from a multitude of images to cast a wider data net that includes electronic health records.

Also on the horizon, ChatGPT technology is poised to have an impact. But pulmonologists and their practices have a number of barriers to clear before they feel a meaningful impact from AI.

The imperative, said AI researcher Ishanu Chattopadhyay, PhD, is to create transformative models that can detect lung disease early on. Dr. Chattopadhyay, an assistant professor of medicine at the University of Chicago and its Institute for Genomics and Systems Biology, and fellow researchers developed an AI algorithm that uses comorbidity signatures in electronic health records to screen for idiopathic pulmonary fibrosis (IPF) (Nature Med. 2022 Sep 29. doi: 10.1038/s41591-022-02010-y).

AI // *continued on page 4*

New tech promises better blood oxygen readings on dark skin

BY DAVID WARMFLASH, MD

Researchers in Texas are developing a "green light" technology they hope will solve a crucial problem highlighted by the pandemic: the limits of pulse oximeters in patients with darker skin.

A recent study adds weight to earlier findings that their device works.

"It is a new, first-in-class technology," said Sanjay Gokhale, MD, the bioengineer who is leading this research at the University of Texas at Arlington. "The team conducted extensive preclinical work and carried out phase 1 studies in human volunteers, demonstrating sensitivity and accuracy."

It's one of several projects underway to update pulse oximetry, a technology based on research in lighter-skinned people that has not changed much in 50 years.

The pulse oximeter, or "pulse ox," measures the saturation of oxygen in your hemoglobin (a protein in red blood cells). But it tends to

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INSIDE HIGHLIGHT

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NEW TECH

// *continued from page 1*

overestimate the oxygen saturation in patients with darker skin by about 2%-3%. That may not sound like a lot, but it's enough to delay major treatment for respiratory issues like COVID-19.

"Falsely elevated readings from commercial oximeters have delayed treatment of Black COVID-19 patients for hours in some cases," said Divya Chander, MD, PhD, an anesthesiologist in Oakland, Calif., and chair of neuroscience at The Singularity Group. (Dr. Chander was not involved in the UT Arlington research.)

"The team conducted extensive preclinical work and carried out phase 1 studies in human volunteers, demonstrating sensitivity and accuracy."

Early research happening separately at Brown University and Tufts University aims to redesign the pulse oximeter to get accurate readings in patients of all skin tones. University of California, San Diego, researchers are looking into a method that measures blood oxygen using sound in combination with light. Other solutions try to correct for skin tone with algorithms.

The device from UT Arlington uses an algorithm too, but its main innovation is that it replaces red light with green light.

Red light, green light

Traditional oximetry devices, which typically clip on to the patient's fingertip, use LEDs to beam light through the skin at two wavelengths: one in the red part of the spectrum, the other in the infrared. The light transmits from one side of the clip to the other, passing through arterial blood as it pulses.

The device calculates a patient's oxygenation based on how much light of each wavelength is absorbed by hemoglobin in the blood. Oxygenated hemoglobin absorbs the light differently than deoxygenated hemoglobin, so oxygenation can be represented as a percentage; 100% means all hemoglobin is completely oxygenated. But the melanin in skin can interfere with the absorption of light and affect the results.

The green-light strategy measures not absorption but reflectance – how much of the light bounces back. As with traditional oximetry, the green-light method uses two wavelengths. Each is a different shade of green, and the two forms of hemoglobin reflect them differently.

Using an algorithm developed by the researchers, the device can capture readings in patients of all skin tones, the researchers say. And because it works on the wrist rather than a finger, the device also eliminates issues with cold fingers and dark nail polish – both known to reduce accuracy in traditional oximetry.

In the latest experiments, the researchers tested the technology on synthetic skin samples with varying amounts of melanin, Dr. Gokhale said. The device picked up changes in blood oxygen saturation even in samples with high melanin levels.

In a study published last year, the technology was tested in 16 people against an invasive handheld blood analyzer and a noninvasive commercial pulse oximeter, and found to be comparable to the invasive method.

A drawback

The green-light approach could be "game changing," Dr. Chander said. But there is a drawback.

Since green light doesn't penetrate as deeply, this approach measures blood oxygen saturation in capillary beds (small blood vessels very close to the skin surface). By contrast, traditional oximetry measures oxygen saturation in an artery as it pulses – thus the name pulse oximetry. Valuable information can be obtained from an arterial pulse.

The green-light method may be useful as an adjunct, not a full replacement, to a standard pulse oximeter.

Changes in arterial pulse, known as the waveforms, "can tell us about a patient's hydration status [for instance]," Dr. Chander said. "In a mechanically ventilated patient, this variation with a patient's respiratory cycle can give us feedback about how responsive the patient will be to fluid resuscitation if their blood pressure is too low."

Given such considerations, the green light method may be useful as an adjunct, not a full replacement, to a standard pulse ox, Dr. Chander noted. ■

AI

// *continued from page 1*

"If you could do this when somebody walks into a primary care setting and they are barely suspecting something is going on with them or when they don't have the typical risk factors, there is a certain fraction of these people who do have IPF and they will almost invariably be diagnosed late and/or misdiagnosed," Dr. Chattopadhyay said, citing a study that found 55% of patients with IPF have had at least one misdiagnosis and 38% have two or more misdiagnoses (BMC Pulm Med. 2018 Jan 17. doi: 10.1186/s12890-017-0560-x).


Dr. Tseng

Harnessing massive data sets

AI models cull data sets, whether banks of radiographic images or files in an EHR, to extract telltale signatures of a disease state. Dr. Chattopadhyay and his team's model used three databases with almost 3 million participants and 54,247 positive cases of IPF. Hospitals in Scotland have deployed what they've claimed are the first AI models to predict COPD built with 55,000 patient records from a regional National Health Service database. Another AI model for staging COPD, developed by researchers in the United States and Romania, used more than 18,000 medical records from 588 patients to identify physiological signals predictive of COPD (Advanced Sci. 2023 Feb 19. doi: 10.1002/advs.202203485).

Said Dr. Chattopadhyay: "If I can bring in AI which doesn't just look at radiological images but actually gets it back where someone walks into primary care using only the information that is available at that point in the patient files and asking for nothing more, it raises a flag reliably that gets you a pulmonary referral that will hopefully reduce the misdiagnosis and late diagnosis."

Victor Tseng, MD, medical director for pulmonology at Ansible Health in Mountain View, Calif., who's researching the potential of AI in pulmonology, speculated on what functions AI can perform in the clinic. "I think you will start to see much more interventional sort of clinically patient care–facing applications," he said. That would include acting as a triage layer to direct patient queries to a nurse, physician, or another practitioner, providing patient instructions, serving as therapeutic software, coordinating care, integrating supply chain issues," he said.

AI vs. spirometry for COPD

Researchers in the United States and Romania, led by Paul Bogdan, PhD, at the University of Southern California Viterbi School of Engineering, developed a model that predicted COPD with an accuracy of almost 99% (98.66%) and avoids many of the shortcomings of spirometry, Dr. Bogdan said.

The models developed by Dr. Bogdan and collaborators use a different principle than existing AI platforms, Dr. Bogdan said. They analyze the properties of the data. As he explained it, they exploit what he called the "geometry of these data" to make inferences and decisions on a patient's risk for COPD.

"Deep learning is very good for images, for videos, but it doesn't work that well for signals," said Mihai Udrescu, PhD, one of the Romanian collaborators. "But if we process the data with the technique brought up by Paul [Bogdan] and his team at USC, deep learning also works well on physiological signals."


Dr. Udrescu

Said Dr. Bogdan, "Nobody thought about using physiological signals to predict COPD before this work. They used spirometry, but spirometry is cumbersome and several steps have to be performed in order to have an accurate spirometry." His team's AI models extract and analyze risk data based on 10 minutes of monitoring.

This technology also has the potential to improve accessibility of COPD screening, Dr. Udrescu said. "It can democratize the access to the health care because you don't need to travel for 100 or 200 miles to see a specialist," he said. "You just send an app to the mobile phone of a patient, the person puts on a smart watch and wears it for a couple of minutes, and the data is either recorded locally or is transmitted and it is analyzed." The computations can be done locally and in a matter of minutes, he said.

In Scotland, a 12-month feasibility study is underway to evaluate an AI model to identify COPD patients at greatest risk for adverse events. A

AI *continued on following page*

FDA warns AstraZeneca over 'misleading claims' about COPD drug

BY LUCY HICKS

The U.S. Food and Drug Administration has issued a warning letter to AstraZeneca over the pharmaceutical company's advertising of the efficacy of a treatment for chronic obstructive pulmonary disease (COPD).

Promotional materials for the drug Breztri (budesonide/formoterol fumarate/glycopyrrolate inhaled) suggest that the drug has a positive effect on all-cause mortality for COPD patients, but the referenced clinical trial does not support that claim, the letter states. The FDA issued the warning letter on Aug. 4 and published it online on Aug. 15. (https://tinyurl.com/4jpzbprj).

The sales aid highlights a 49% observed relative difference in time to all-cause mortality (ACM) over 1 year between Breztri and long-acting muscarinic antagonist/long-acting beta agonist (LAMA/LABA) inhalers.

Because of "statistical testing hierarchy failure" as well as confounding factors such as the removal of patients from inhaled corticosteroids (ICS) prior to entering the treatment arm of the trial, "no conclusions about the effect of Breztri on ACM can be drawn from the [clinical] trial," the FDA wrote.

"To date, no drug has been shown to improve ACM in COPD," the FDA added.

The Breztri sales aid also states that there was a 20% reduction of severe exacerbations in patients using Breztri compared with patients using ICS/LABA. However, in the cited clinical trial, "the reduction in severe exacerbations was not statistically significant for patients treated with Breztri relative to comparator groups," according to the FDA.

AstraZeneca was given 15 working days from the receipt of the letter to respond in writing with "any plan for discontinuing use of such communications, or for ceasing distribution of Breztri," the agency wrote. ■

AI *continued from previous page*

press release from Lenus, the company developing the technology, said the study will use a COPD multidisciplinary team to consider real-time AI model outputs to enable proactive patient encounters and reduce emergency care visits.

Researchers in Paris built an AI model that showed a 68% accuracy in distinguishing people with asthma from people with COPD in administrative medical databases (BMC Pulmon Med. 2022 Sep 20. doi: 10.1186/s12890-022-02144-2). They found that asthma patients were younger than those with COPD (a mean of 49.9 vs. 72.1 years) and that COPD occurred mostly in men (68% vs. 33%). And an international team of researchers reported that an AI model that used chest CT scans determined that ever-smokers with COPD who met the imaging criteria for bronchiectasis were more prone to disease exacerbations (Radiology. 2022 Dec 13. doi: 10.1148/radiol.221109).

AI in idiopathic pulmonary fibrosis

The AI model that Dr. Chattopadhyay and collaborators developed had an 88% accuracy in predicting IPF. The model, known as the zero-burden comorbidity risk score for IPF (ZCoR-IPF), identified IPF cases in adults age 45 and older 1-4 years sooner than in a variety of pulmonology practice settings.

The model accounted for about 700 different features of IPF, Dr. Chattopadhyay said, but it deviated from standard AI risk models in that it used a machine learning algorithm to extract disease features that aren't well understood or even known. "We do not know what all the risk factors of IPF are," he said. "People who don't have all the risk factors still get IPF. So we have to step back from the raw EHR data from where the features are being generated automatically, and then you can apply standard ML tools."

The AI model that Dr. Chattopadhyay and collaborators developed had an 88% accuracy in predicting IPF.

Researchers at Nagoya University in Japan also reported on an AI algorithm for predicting IPF that used 646,800 high-resolution CT images and medical records data from 1,068 patients. Their algorithm had an average diagnostic accuracy of 83.6% and, they reported, demonstrated good accuracy even in patients with signs of interstitial pneumonia or who had surgical lung biopsies (Respirology. 2022 Dec 13. doi: 10.1111/resp.14310).

ChatGPT: The next frontier in AI

Dr. Tseng last year led a group of researchers that fed questions from the United States Medical Licensing Exam to a ChatGPT model, which found it answered 60%-65% of questions correctly (PLOS Digit Health. 2023 Feb 9. doi: 10.1371/journal.pdig.0000198). As Dr. Tseng pointed out, that's good enough to get a medical license.

It may be a matter of time before ChatGPT technology finds its way into the clinic, Dr. Tseng said. A quick ChatGPT query of how it could be used in medicine yielded 12 different answers, from patient triage to providing basic first aid instructions in an emergency.

Dr. Tseng, who's pulmonology practice places an emphasis on virtual care delivery, went deeper than the ChatGPT answer. "If you're a respiratory therapist and you're trying to execute a complicated medical care plan written by a physician, there's a natural disconnect between our language and their language," he said. "What we have found is that GPT has significantly harmonized the care plan. And that's amazing because you end up with this single-stream understanding of the care plan, where the language is halfway between a bedside clinician, like the respiratory therapist or nurse, and is also something that a physician can understand and take the bigger sort of direction of care from."

Barriers to AI in clinic

Numerous barriers face widespread adoption of AI tools in the clinic, Dr. Tseng said, including physician and staff anxiety about learning new technology.

"AI tools, for all purposes, are supposed to allay the cognitive burden and the tedium burden on clinicians, but end up actually costing more time," he said.

Health care organizations will also need to retool for AI, a group of medical informatics and digital health experts, led by Laurie Lovett Novak, PhD, reported (JAMIA Open. 2023 May 3. doi: 10.1093/jamiaopen/ooad028). But it's coming nonetheless, Dr. Novak, an associate professor of biomedical informatics at Vanderbilt University Medical Center in Nashville, Tenn., said in an interview.

"In the near future, managers in clinics and inpatient units will be overseeing care that involves numerous AI-based technologies, including predictive analytics, imaging tools, language models, and others," she said. "Organizations need to support managers by implementing capabilities for algorithmo-vigilance."

That would include dealing with what she called "algorithmic drift" – when the accuracy of an AI model wanes because of changes in the underlying data – and ensuring that models are unbiased and aren't used in a way that contributes to inequities in health care. "These new organizational capabilities will demand new tools and new competencies," she said. That would include policies and processes drawing guidance from medical societies for legal and regulatory direction for managers, staff training, and software documentation.

Dr. Novak

Dr. Tseng envisioned how AI would work in the clinic. "I personally think that, at some time in the near future, AI-driven care coordination, where the AI basically handles appointment scheduling, patient motivation, patient engagement and acts as their health navigator, will be superior to any human health navigator on the whole, only for the reason that AI is indefatigable," Dr. Tseng said.

"It doesn't get tired, it doesn't get burned out, and these health navigation care coordination roles are notoriously difficult."

The physicians and researchers interviewed for this report had no relevant relationships to disclose. ■

CDC offers guidance on RSV vaccines for adults

BY MARCIA FRELLICK

Two newly approved respiratory syncytial virus (RSV) vaccines for adults aged 60 years and older may be able to prevent illness in those at risk for severe RSV disease.

Most adult RSV illness occurs among the older age group and results in an estimated 60,000-160,000 hospitalizations and 6,000-10,000 deaths per year among people aged at least 65 years.

Older adults deciding whether to get the vaccines should weigh risks and their own preferences and decide in consultation with their clinicians, said authors of a Centers for Disease Control and Prevention report.

Michael Melgar, MD, with the Coronavirus and Other Respiratory Viruses Division at the CDC, was lead author on the report, published in the Morbidity and Mortality Weekly Report (2023 Jul 21;72[29]:793-801).

Two new vaccines

In May, the U.S. Food and Drug Administration approved the first of two vaccines for preventing RSV lower respiratory–tract disease for adults aged at least 60 years.

On June 21, the Advisory Committee on Immunization Practices (ACIP) recommended that people in that age group receive a single dose of RSV vaccine using shared decision-making.

The recommendation for shared decision-making makes the ACIP decision different from routine and risk-based vaccine recommendations.

Rather than targeting all in a particular age group or risk group, the decision calls for consideration of a patients' risk for disease and their characteristics, preferences, and values; the health care professional's clinical discretion; and performance of the vaccine.

Dr. Melgar and colleagues reported that vaccination with one dose of the GSK or Pfizer RSV vaccines has proved moderately to highly effective in preventing symptomatic RSV-associated lower respiratory tract disease over two consecutive RSV seasons among people aged 60 and older.

The trials that led to approval weren't powered to gauge efficacy against RSV-associated hospitalization and death. However, the authors wrote, the prevention of lower respiratory tract disease, including medically attended illness, suggests that the shots might prevent considerable morbidity from RSV disease among those aged 60 and older.

Both vaccines were generally well tolerated with a good safety profile. However, six cases of inflammatory neurologic events (including Guillain-Barré Syndrome, acute disseminated encephalomyelitis, and others) were reported in clinical trials after RSV vaccination.

"Whether these events occurred due to chance, or whether RSV vaccination increases the risk for inflammatory neurologic events, is currently unknown," they wrote.

Postmarketing surveillance may help clarify the existence of any potential risk, but until those results are clearer, the CDC researchers said, RSV vaccinations should be targeted to older adults at highest risk for severe RSV and those most likely to benefit from the shots.

At higher risk

Some adults with certain medical conditions have a higher risk for RSV-associated hospitalization, according to the report.

Those conditions include chronic obstructive pulmonary disease, asthma, heart failure, coronary artery disease, cerebrovascular disease, diabetes mellitus, and chronic kidney disease. People who are frail and of advanced age also are at higher risk for RSV hospitalization. That risk increases with age and the highest risk is for people aged at least 75 years.

The researchers added that RSV can cause severe disease in those with compromised immunity, including people who have received hematopoietic stem cell transplants and patients taking immunosuppressive drugs such as those used with solid-organ transplants, cancer treatment, or other conditions.

For the 2023-2024 season, the report states, clinicians should offer RSV vaccination to adults aged at least 60 years using shared clinical decision-making as early as vaccine supply is available and should continue to offer vaccination to eligible adults who remain unvaccinated.

RSV vaccines can be administered with other adult vaccines during the same visit, the authors confirmed. ■

Heat waves plus air pollution tied to doubling of fatal MI

BY MEGAN BROOKS

The combination of heat waves and poor air quality is associated with double the risk of fatal myocardial infarction (MI), with women and older adults at greatest risk, according to a new study. Researchers estimate that up to 3% of all deaths due to MI could be attributed to the combination of extreme temperatures and high levels of ambient fine-particulate matter (PM2.5).

"Our findings provide evidence that reducing exposure to both extreme temperatures and fine-particulate pollution may be useful to prevent premature deaths from heart attack," senior author Yuewei Liu, MD, PhD, with Sun Yat-sen University in Guangzhou, China, said in a statement. The study was published online in Circulation (2023 Jul 24. doi: 10.1161/CIRCULATIONAHA.122.063504).

There is "long-standing evidence" of the harmful cardiovascular effects of air pollution, Jonathan Newman, MD, MPH, cardiologist at NYU Langone Heart in New York, who wasn't involved in the study, said in an interview. However, this study found an interaction between extreme hot temperatures and air pollution, "which is worrisome with global warming," said Dr. Newman. Data was analyzed on 202,678 adults (mean age, 77.6 years; 52% male) who suffered fatal MI between 2015 and 2020 in Jiangsu province, a region with four distinct seasons and a wide range of temperatures and ambient PM2.5. They evaluated the association of exposure to extreme temperature events, including both hot and cold spells, and PM2.5 with MI mortality, and their interactive effects. Among the key findings:

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- The risk of fatal MI was 18% higher during 2-day heat waves with heat indexes at or above the 90th percentile (ranging from 82.6° to 97.9° F) and 74% higher during 4-day heat waves with heat indexes at or above the 97.5th percentile (ranging from 94.8° to 109.4° F), compared with control days.
- The risk of fatal MI was 4% higher during 2-day cold snaps with temperatures at or below the 10th percentile (ranging from 33.3° to 40.5° F) and 12% higher during 3-day cold snaps with temperatures at or below the 2.5th percentile (ranging from 27.0° to 37.2° F).
- The risk of fatal MI was twice as high during 4-day heat waves that had PM2.5 above 37.5 mcg/m^3. Days with high levels of PM2.5 during cold snaps did not have an equivalent increase in the risk of fatal MI.
- Up to 2.8% of MI deaths during the 5-year study period may be attributable to the combination of extreme temperature exposure and PM2.5 at levels exceeding World Health Organization air-quality guidelines (37.5 mcg/m^3).
- The risk of fatal MI was generally higher among women than men during heat waves and was higher among adults 80 years old and older than in younger adults during heat waves, cold snaps, or days with high levels of PM2.5.

The finding that adults over age 80 are particularly susceptible to the effects of heat and air pollution and the interaction of the two is "notable and particularly relevant given the aging of the population," Dr. Newman said.

"To improve public health, it is important to take fine-particulate pollution into consideration when providing extreme temperature warnings to the public," Dr. Liu added in the statement.

The authors and Dr. Newman reported having no financial conflicts. ■

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 or for the relief of acute bronchospasm or status asthmaticus.

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† The pharmacodynamic response (blood eosinophil depletion) following repeat subcutaneous (SC) dosing was evaluated in asthma patients in a 12-week phase 2 trial. Patients received 1 of 3 doses of benralizumab [25 mg (n=6), 100 mg (n=6), or 200 mg (n=6) SC] or placebo (n=6) every 4 weeks for a total of 3 doses. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of median blood eosinophil levels, which was maintained throughout the dosing period.[2,3,4]

‡ In SIROCCO (48 weeks), a 51% reduction in annual asthma exacerbation rate was observed in patients treated with FASENRA + SOC (n=267) vs placebo + SOC (n=267) (0.74 vs 1.52, $P<0.0001$). In CALIMA (56 weeks), a 28% reduction in annual asthma exacerbation rate was observed in patients treated with FASENRA + SOC (n=239) vs placebo + SOC (n=248) (0.73 vs 1.01, $P=0.019$).[5,6]

§ In ZONDA (28 weeks), a 75% reduction in median final OCS dose was observed in patients treated with FASENRA + SOC (n=73) vs 25% reduction with placebo + SOC (n=75) ($P<0.001$).[7]

See Study Designs on next page.

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 full Prescribing Information on following pages.

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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.

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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 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.

STUDY DESIGNS

SIROCCO AND CALIMA (Trials 1 and 2)[5,6]

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 prebronchodilator FEV_1 and total asthma symptom score at Week 48 (SIROCCO) and Week 56 (CALIMA) in the same population.

ZONDA (Trial 3)[7]

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.

EOT, end of treatment; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, standard of care.

References: 1. Data on File, US-68618, AZPLP. **2.** FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2021. **3.** Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med.* 2016;111:21-29. **4.** Data on File, REF-28001, AZPLP. **5.** Bleecker ER, FitzGerald JM, Chanez P, et al; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting $ß_2$-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115-2127. **6.** FitzGerald JM, Bleecker ER, Nair P, et al; CALIMA study investigators. 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. **7.** 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.

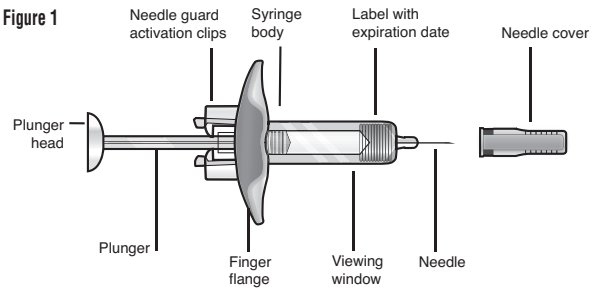
Autoinjector (FASENRA PEN™)

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.

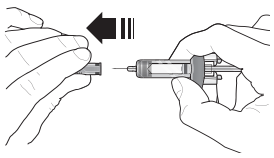
Figure 1



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

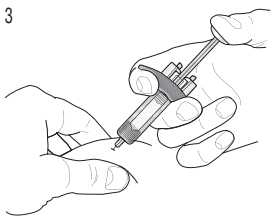
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



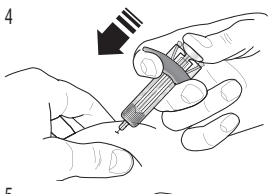
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without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

3



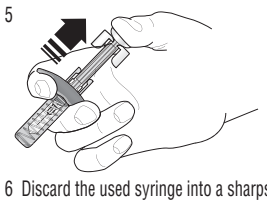
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

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 anti-body 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,<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]*.

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Smart-bed technology reveals insomnia, flu risk link

BY MEGAN BROOKS

Insomnia may increase vulnerability to influenza-like illness, a novel finding that was revealed by the passive collection of biometric data from a smart bed.

The study of smart-bed sleepers found that there was a statistically significant correlation between a higher number of episodes of influenza-like illnesses (ILI) per year with longer duration compared with people without insomnia.

However, more research is needed to determine causality and whether insomnia may predispose to ILI or whether ILI affects long-term sleep behavior, the researchers noted.

"Several lines of evidence make me think that it's more likely that insomnia makes one more vulnerable to influenza through pathways that involve decreased immune function," study investigator Gary Garcia-Molina, PhD, with Sleep Number Labs, San Jose, Calif., said in an interview.

Sleep disorders, including insomnia, can dampen immune function and an individual's ability to fight off illness, he noted.

The findings were presented at the annual meeting of the Associated Professional Sleep Societies.

Smart, connected devices

Pathophysiological responses to respiratory viral infection affect sleep duration and quality in addition to breathing function. "Smart" and "connected" devices that monitor biosignals over time have shown promise for monitoring infectious disease.

Data from both 2019 and 2021 show that smart sleepers with insomnia had significantly more and longer ILI episodes per year, compared with peers without insomnia.

In an earlier study presented at SLEEP 2021, Dr. Garcia-Molina and colleagues found that real-world biometric data obtained from a smart bed can help predict and track symptoms of COVID-19 and other respiratory infections. They showed that worsening of COVID-19 symptoms correlated with an increase in sleep duration, breathing rate, and heart rate and a decrease in sleep quality.

In the new study, the researchers evaluated vulnerability to ILI in people with insomnia.

They quantified insomnia over time using the insomnia severity index (ISI). They quantified ILI vulnerability using an established artificial intelligence model they developed that estimates the daily probability of ILI symptoms from a Sleep Number smart bed using ballistocardiograph sensors.

Smart-bed data – including daily and restful sleep duration, sleep latency, sleep quality, heart rate, breathing rate, and motion level – were queried from 2019 (pre-COVID) and 2021.

A total of 1,680 smart sleepers had nearly constant ISI scores over the study period, with 249 having insomnia and 1,431 not having insomnia.

Data from both 2019 and 2021 show that smart sleepers with insomnia had significantly more and longer ILI episodes per year, compared with peers without insomnia.

For 2019, individuals without insomnia had 1.2 ILI episodes on average, which was significantly less ($P < .01$) than individuals with insomnia, at 1.5 episodes. The average ILI episode duration for those without insomnia was 4.3 days, which was significantly lower ($P < .01$) in those with insomnia group, at 6.1 days.

The data for 2021 show similar results, with the no-insomnia group having significantly fewer ($P < .01$) ILI episodes (about 1.2), compared with the insomnia group (about 1.5).

The average ILI episode duration for the no-insomnia group was 5 days, which was significantly less ($P < .01$) than the insomnia group, at 6.1 days.

The researchers said their study adds to other data on the relationship between sleep and overall health and well-being. It also highlights the potential health risk of insomnia and the importance of identifying and treating sleep disorders.

"Sleep has such a profound influence on health and wellness, and the ability to capture these data unobtrusively in such an easy way and with such a large number of participants paves the way to investigate different aspects of health and disease," Dr. Garcia-Molina said.

Rich data source

In a comment, Adam C. Powell, PhD, president of Payer+Provider Syndicate, a management advisory and operational consulting firm, said "smart beds provide a new data source for passively monitoring the health of individuals."

"Unlike active monitoring methods requiring self-report, passive monitoring enables data to be captured without an individual taking any action. These data can be potentially integrated with data from other sources, such as pedometers, smart scales, and smart blood pressure cuffs, to gain a more holistic understanding of how an individual's activities and behaviors impact their well-being," said Dr. Powell, who wasn't involved in the study.

There are some methodological limitations to the study, he noted.

"While the dependent variables examined were the duration and presence of episodes of influenza-like illness, they did not directly measure these episodes. Instead, they calculated the daily probability of influenza-like illness symptoms using a model that received input from the ballistocardiograph sensors in the smart beds," Dr. Powell noted.

"Unlike active monitoring methods requiring self-report, passive monitoring enables data to be captured without an individual taking any action."

"The model used to calculate daily probability of influenza-like illness was created by examining associations between individuals' smart-bed sensor data and population-level trends in influenza-like illness reported by the Centers for Disease Control and Prevention," he explained.

Nonetheless, the findings are "consistent with the literature. It has been established by other researchers that impaired sleep is associated with greater risk of influenza, as well as other illnesses," Dr. Powell said.

Funding for the study was provided by Sleep Number. Dr. Garcia-Molina and five coauthors are employed by Sleep Number. Dr. Powell reported no relevant financial relationships. ■

Neutropenia affects clinical presentation of pulmonary mucormycosis

BY HEIDI SPLETE

FROM THE JOURNAL CHEST® ▪ Neutropenia and radiological findings affected the presentation and diagnosis of pulmonary mucormycosis in adult patients, based on data from 114 individuals.

Diagnosis of pulmonary mucormycosis (PM), an invasive and potentially life-threatening fungal infection, is often delayed because of its variable presentation, wrote Anne Coste, MD, of La Cavale Blanche Hospital and Brest (France) University Hospital, and colleagues.

Improved diagnostic tools including molecular identification and image-guided lung biopsies are now available in many centers, but relations between underlying conditions, clinical presentations, and diagnostic methods have not been described, they said.

In a study published in the journal Chest (2023 Jul 5. doi: 10.1016/j.chest.2023.06.039), the researchers reviewed data from all cases of PM seen at six hospitals in France between 2008 and 2019. PM cases were based on European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Diabetes and trauma were included as additional host factors, and positive serum or tissue PCR (serum qPCR) were included as mycological evidence. Participants also underwent thoracic computed tomography (CT) scans.

The most common underlying conditions among the 114 patients were hematological malignancy (49%), allogeneic hematopoietic stem cell transplantation (21%), and solid-organ transplantation (17%). Among the 40% of the cases

Among the 40% of the cases that involved dissemination, the most common sites were the liver (48%), spleen (48%), brain (44%), and kidneys (37%).

that involved dissemination, the most common sites were the liver (48%), spleen (48%), brain (44%), and kidneys (37%).

A review of radiology findings showed consolidation in a majority of patients (58%), as well as pleural effusion (52%). Other findings included reversed halo sign (RHS, 26%), halo sign (24%), vascular abnormalities (26%), and cavity (23%).

Bronchoalveolar lavage (BAL) was present in 46 of 96 patients (50%), and transthoracic lung biopsy was used for diagnosis in 8 of 11 (73%) patients with previous negative BALs.

Seventy patients had neutropenia. Overall, patients with neutropenia were significantly more likely than were those without neutropenia to show an angioinvasive presentation that included both RHS and disease dissemination ($P < .05$).

In addition, serum qPCR was positive in 42 of 53 patients for whom data were available (79%). Serum qPCR was significantly more likely to be positive in neutropenic patients (91% vs. 62%, $P = .02$). Positive qPCR was associated with an early diagnosis ($P = .03$) and treatment onset ($P = .01$).

Possible reasons for the high rate of disseminated PM in the current study may be the large number of patients with pulmonary involvement, use of body CT data, and availability of autopsy results (for 11% of cases), the researchers wrote in their discussion.

Neutropenia and radiological findings influence disease presentation and contribution of diagnostic tools during PM. Serum qPCR is more contributive in neutropenic patients and BAL examination in nonneutropenic patients. Lung biopsies are highly contributive in case of noncontributive BAL.

The findings were limited by several factors including the retrospective design, the inability to calculate sensitivity and specificity of diagnostic methods, and lack of data on patients with COVID-19, the researchers noted. However, the results provide real-life information for clinicians in centers with current mycological platforms, they concluded.

The study received no outside funding. Dr. Coste had no financial conflicts to disclose. ■

Observation recommended as first-line therapy in select cases of primary spontaneous pneumothorax

BY WALTER ALEXANDER

FROM THE JOURNAL CHEST® ▪ Observation should be considered the first-line treatment of choice in appropriately selected primary spontaneous pneumothorax patients, according to a recent review.

Observation was the dominant choice, based on economic modeling showing it to offer both the highest utility and the lowest cost, according to the review published in the journal CHEST (2023 May 18. doi: 10.1016/j.chest.2023.05.017), which encompassed 20 years of relevant publications.

While current guidelines are shifting toward either aspiration or observation and away from recommending chest tube placement, chest tube placement remains quite common in physicians' clinical practices, Gilgamesh Eamer, MD, MSc, FRCSC, of Children's Hospital of Eastern Ontario, Ottawa, and colleagues wrote. While prior systematic reviews have examined various primary spontaneous pneumothorax management techniques, no reviews encompass more recently published high-quality studies comparing aspiration to other interventions such as observation or Heimlich valve devices.

The authors identified 22 articles for systematic review and meta-analysis after screening an initial list of 5,179 potentially relevant articles (Jan. 1, 2000, to April 10, 2020). They compared observation, needle aspiration, and chest tube placement, and created an economic model for these three treatment pathways based on Canadian medical cost data. The primary outcome measure was resolution following the initial intervention. Secondary outcomes included primary spontaneous pneumothorax recurrence, length of hospital stay, and treatment complications.

The analysis revealed that, compared with observation, chest tube and aspiration had higher resolution without additional intervention (relative risk for chest tube, 0.81; $P < .01$; RR for aspiration, 0.73; $P < .01$). Compared with a chest tube, observation and aspiration had shorter length of stay (mean difference for observation, 5.17; $P < .01$); (MD for aspiration, 2.72; $P < .01$).

Two-year recurrence rates did not differ between management strategies. Cost utility modeling found a cost of $14,658 (Canadian dollars [CAD] with 1.2535 = 1 U.S. dollar) for chest tube placement, $13,126 CAD for aspiration, and $6,408 CAD for observation.

The utility (a measure including both quantity and quality of life) for each management arm was 0.77 for CT placement, 0.79 for aspiration, and 0.82 for observation. "The observation arm dominates the other two arms meaning it results in a more desirable (higher) utility with lower cost and results in a negative ICER [incremental cost-effectiveness ratio]," the authors stated.

They observed further that it is not typical for a medical intervention to improve patient outcomes, compared with standard care, and at the same time to bring costs down. "Given this, and the increasing evidence that observation is safe and effective in appropriately selected patients presenting with primary spontaneous pneumothorax," they concluded that "observation should be considered in all patients presenting with primary spontaneous pneumothorax who meet predefined criteria." They added that, because aspiration is favored over chest tube placement, it should be considered second-line therapy in well-selected primary spontaneous pneumothorax patients presenting with recurrence or who have failed a trial of observation.

"This review sheds light on 'less is better' for primary spontaneous pneumothorax management," commented Dharani K. Narendra, MD, of the department of medicine, Baylor College of Medicine, Houston.

Neither Dr. Eamer nor Dr. Narendra reported any conflicts. ■

Bronchiectasis fungal cultures don't predict outcome

BY TED BOSWORTH

The presence of a positive fungal culture in patients with bronchiectasis does not appear to correlate with disease severity or any increased risk of an adverse outcome, according to data pulled from the Bronchiectasis and NTM Registry and presented at the 6th World Bronchiectasis & NTM Conference.

"The question we were asking is whether there is some signal that suggests we need to take care of these patients differently, and the answer is no," reported Pamela J. McShane, MD, a pulmonologist on the faculty at the University of Texas Health Science Center at Tyler.

When compared for outcome over time, those with a positive fungal culture at initial evaluation did not have more exacerbations, more hospitalizations, or other signs of a more severe disease or more complex course than did those without a positive fungal culture.

When fungal infections are detected in an initial microbiologic evaluation of patients with bronchiectasis or other lung diseases, first-line clinicians generally assume that coverage is needed. Dr. McShane noted that many of the patients referred to her with bronchiectasis and a positive fungal culture were already on an antifungal.

These data are not supportive of treatment in the absence of fungal-related complications. Dr. McShane suggested they even raise questions about the value of culturing beyond bacterial pathogens in the absence of suspicion that fungal organisms are playing a role in symptoms. She cautioned, however, that more studies specifically studying this possibility are needed.

Study details

The data were drawn in December 2022 from the U.S.-based Bronchiectasis and NTM Registry, which at that time had 22 participating sites. Of the more than 5,000 patients enrolled, the study looked at 2,230 after several exclusions, such as a diagnosis of allergic bronchopulmonary aspergillosis (ABPA).

Of these 2,230 patients, 949 had a fungal infection at the time of diagnosis and 1,281 did not. Those with a fungal infection were further subdivided into those with an aspergillosis (331 patients) and those with a nonaspergillosis fungal infection (751 patients). The total of these two numbers is greater than the total number of fungal infections because these were not mutually exclusive.

At enrollment into the registry, there were no statistical differences between groups for age. Some statistical differences were observed among groups stratified by race, but Dr. McShane doubted that these were clinically significant with the exception of a potential disparity among Asians that might deserve further analysis.

Infection results

Of clinical features evaluated for their association with fungal infection, there was no correlation with either body mass index or history of asthma. Eosinophilia was associated

significantly with positive fungal cultures.

Baseline FEV_1 was slightly lower among those with a positive fungal culture even if the difference was highly significant ($P = .0006$). Again, Dr. McShane questioned the clinical significance of values that varied by only a few percentage points, even though she was willing to acknowledge that higher is always preferable to a lower FEV_1.

In the context of other pathogens, "generally speaking, those with a positive bacterial culture were more likely to have a fungal infection," Dr. McShane reported, although there was some variation when looking at pathogenicity of the bacteria and other variables.

"Whether this [higher rate of fungal infection] just involves the environment or our antibiotics are driving the opportunity to permit the fungi to exist, we do not have the answer," she added.

Nontuberculosis mycobacteria (NTM) infection was similarly represented in those with or without a fungal infection, according to Dr. McShane. Noting the high use of antibiotics in an NTM population, Dr. McShane conceded that this challenges the theory that antibiotic use is driving the risk of fungal

BRONCHIECTASIS *continued on following page*

6MWD=6-minute walk distance; CI=confidence interval; FC=Functional Class; HPAH=heritable PAH; HR=hazard ratio; IPAH=idiopathic PAH; IV=intravenous; PAH-CHD=PAH associated with congenital heart disease; PAH-CTD=PAH associated with connective tissue disorders; PAH-HIV=PAH associated with human immunodeficiency virus; PDE-5=phosphodiesterase type 5; SC=subcutaneous; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve CliNical Outcome; WHO=World Health Organization.

References: 1. OPSUMIT® [prescribing information]. Actelion Pharmaceuticals US, Inc. **2.** Pulido T, Adzerikho I, Channick RN, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818 and Suppl 1-21. **3.** Center for Drug Evaluation and Research, US Food and Drug Administration. OPSUMIT® (macitentan) NDA 204410. Accessed July 19, 2023. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf

infection, but these are what the data say.

Steroid use was associated with a statistically significant risk of fungal infection, but Dr. McShane said it is unclear whether steroid use drives the risk or is an epiphenomenon.

"We looked at this a lot of different ways: oral vs. inhaled and oral vs. inhaled and oral, and it did not make much difference. Generally speaking, the fungal cultures were more likely to be positive in patients on any kind of steroid," she said.

Finally, with the exception of the slightly lower FEV_1 in patients with fungal infections, Dr. McShane said that there was no discernible relationship between the presence of a fungal infection and severity of bronchiectasis.

Because of this evidence, Dr. McShane concluded that the presence of fungus in the culture of patients with bronchiectasis does not appear to correlate with outcome or severity. Since completing the study, she said she is now using these data to reassure patients who have a positive fungal culture.

While these data do not affect the need to diagnosis fungal infections in patients who are not responding typically to therapy or otherwise have an abnormal course of bronchiectasis, raising suspicion that fungal infection is participating in

the disease course, the data provide a basis for questioning whether routine cultures are needed, according to the discussion that followed Dr. McShane's presentation.

Expert opinion

Several of the experts at the presentation provided an opinion. Some reported that they would continue to order fungal cultures on a routine basis, while others said that they now, on the basis of these data, plan to order cultures only at the first visit or when fungal infection is suspected of exacerbating the disease.

Of this latter group, which seemed to be dominant, Juzar Ali, MD, professor of medicine, Louisiana State University, New Orleans, said that he has not been ordering fungal cultures on every visit. Rather, he has been doing so selectively. Examples include those who are on steroids or those with an unusual pattern of exacerbations.

"The value of these data is that they have now provided some data to support this approach," Dr. Ali said in an interview. Noting that this is the first large study to address this question in a systematic way, he considers this to be a valuable contribution for approaching a common clinical issue.

Dr. McShane reports no relevant financial relationships. Dr. Ali reports a financial relationship with Insmed. ■

SLEEP STRATEGIES

Enacting a hypoglossal nerve stimulation program

BY KIRAT GILL, MD

It is estimated that almost one billion people globally are affected by obstructive sleep apnea (OSA) (Benjafield A, et al. *Lancet Respir Med*. 2019;7[8]:687-98). Despite such high prevalence, the treatment options for OSA are somewhat limited. Continuous positive airway pressure (CPAP), the gold standard therapy, is not viable for many due to difficulties tolerating the device or mask, and thus may not be a realistic long-term solution. As per certain estimates, nearly 50% of CPAP users discontinue treatment by the fifth year (Schoch O, et al. *Respiration*. 2014;87[2]:121-8). Furthermore, alternative options such as mandibular advancement devices, positional therapy, weight loss, and maxillofacial or palate surgery, also have unique challenges and limitations.

First described in 2001, hypoglossal nerve stimulation (HGNS) is a relatively new and emerging technology for the treatment of OSA (Schwartz A, et al. *Arch Otolaryngol Head Neck Surg*. 2001 Oct;127[10]:1216-23). HGNS therapy was approved by the U.S. Food and Drug Administration in 2014 for the treatment of moderate to severe OSA. The therapy involves surgical implantation of the HGNS device, optimization of device settings, and evaluation for treatment response. A physician-led multidisciplinary Hypoglossal Nerve Stimulation Clinic involves collaboration from essential stakeholders, most importantly sleep medicine providers, clinic staff, sleep technologists, and ENT sleep surgeons. Goals of the multidisciplinary program are to ensure timely follow-up, optimization of device settings, and maximizing treatment efficacy. This review describes steps involved in developing a successful multidisciplinary HGNS program within a sleep medicine practice.

Patient selection and evaluation

There is growing interest in HGNS relative to conventional CPAP therapy, with many patients presenting to clinic to inquire about this therapy. However, not all patients are candidates for HGNS therapy. Prioritizing appropriate patient selection and education are key first steps. The initial assessments usually occur with a sleep medicine specialist. It begins with confirmation of the diagnosis of OSA in all patients and a concerted effort to troubleshoot and address any barriers to CPAP use before consideration of surgery. Patients who are unwilling to use or unable to tolerate CPAP therapy undergo further evaluation for HGNS therapy. It is important to ensure that patients are also screened for other sleep disorders,

PROGRAM *continued on following page*

This month in the journal *CHEST*®

Editor's picks

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

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By Lindsay M. Forbes, MD, et al.

***Impaired Spirometry and COPD Increase the Risk of Cardiovascular Disease**
By Suurya Krishnan, MD, et al.

Making Progress in Clinical Trials in Sarcoidosis
By Kerry M. Hena, MD, and Karen C. Patterson, MD

Outcomes in Patients Perceived as Receiving Excessive Care by ICU Physicians and Nurses: Differences Between Patients < 75 and ≥ 75 Years of Age?
By Ruth D. Piers, MD, PhD, et al.

Procalcitonin-Guided Antibiotic Prescription in Patients With COVID-19
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Reducing Pulmonary Capillary Wedge Pressure During Exercise Exacerbates Exertional Dyspnea in Patients With Heart Failure With Preserved Ejection Fraction: Implications for V_E/Q_E Mismatch
By Bryce N. Balmain, PhD, et al.

PROGRAM *continued from previous page*

such as insomnia or restless leg syndrome, to rule out their contribution to daytime (or nighttime) symptoms.

Other salient inclusion criteria include an apnea-hypopnea index (AHI) between 15 and 100 events per hour (previously 65), at least 18 years of age, and a body mass index (BMI) less than 40 kg/m^2 (previously 32). Qualifying patients undergo an updated polysomnography if a recent study is not available. If the polysomnography reveals central and mixed apneas comprising less than 25% of the total AHI, patients are referred to ENT Sleep Surgery, and drug-induced sleep endoscopy is offered to examine upper airway anatomy. When a complete concentric collapse of the soft palate is seen on drug-induced sleep endoscopy, surgery is contraindicated. Prior palate surgery or maxillomandibular advancement (MMA) are not contraindications to HGNS therapy.

The patients receive comprehensive information on the nature of the surgery, expected recovery course, and device activation timeline. Perhaps most importantly, the patients receive structured education on HGNS therapy and potential outcomes to set realistic expectations. In the STAR trial, patients experienced a reduction in the AHI of approximately 70% (Strollo P, et al. *N Engl J Med*. 2014;370[2]:139-49). It is important to note that a response to therapy was defined as a reduction in the AHI by at least 50% and a value less than 20 events/hour (Strollo P, et al. *Sleep*. 2015;38[10]:1593-8). Therefore, patients who are expecting complete resolution of snoring and/or OSA may not be ideal candidates for surgery. Furthermore, patients who continue to experience fatigue and sleepiness on CPAP despite control of OSA may not experience amelioration of these symptoms with HGNS therapy.

Surgery and device management

The surgery, performed under general anesthesia, lasts approximately 3 hours, and may be followed by an overnight hospital stay depending on patient's comorbidities. The device implantation involves placement of an implantable pulse generator (IPG) in the chest wall and leads to the hypoglossal nerve. The IPG is similar to a pacemaker and functions to stimulate the ipsilateral hypoglossal nerve innervating the tongue during sleep. The most common postoperative complications noted in the STAR trial data include incision site pain and swelling as well as temporary tongue weakness or paresthesia. Postoperative restrictions are minimal and include no heavy lifting for 1 month after surgery.

One week postsurgery, patients return to the ENT Sleep Surgery Clinic for follow-up, at which time the incisions, as well as tongue strength and sensation are evaluated. In a subsequent visit, between 4 and 6 weeks postsurgery, patients are evaluated in a joint Sleep Medicine and ENT clinic. They undergo device education and activation of the IPG using a dedicated programmer obtained from the device manufacturer. Device comfort features such as start delay and pause time are also programmed. Furthermore, appropriate tongue movement, lead placement, and voltage range settings are assessed during the visit. The ENT surgery team reevaluates the incision sites and assesses for tongue function and sensation. Patients are instructed to increase the voltage incrementally every week as tolerated with the goal of using the device nightly for the entirety of sleep. If patients tolerate the therapy well during the 2- to 3-month follow-up, a sleep study is scheduled to evaluate treatment effectiveness at the peak tolerable voltage. For those struggling with the therapy, adjustments to electrode configurations should be considered, pulse width, and rate. Occasionally, patients may require awake endoscopy and/or an advanced HGNS titration while asleep to determine the most appropriate settings to optimally control sleep apnea.

Until recently, patients implanted with an early version of the HGNS were limited to magnetic resonance imaging (MRI) scans of the head, neck, and extremities only. However, patients with the latest model IPGs can now undergo full-body MRI scans. It is important to note that the MRI's Tesla cannot exceed 1.5T, necessitating specific imaging centers. Other constraints include the inability to adjust device settings remotely, which could mean long travel for minor setting adjustments such as altering start delay or pause times. Furthermore, provider education on operating and managing the device can be time consuming and may also be a barrier to implementation in a clinic. Also challenging may be the availability of an ENT surgery, which plays a critical role in the implantation of the devices and follow-up.

Currently, Inspire Medical Systems is the only FDA-approved hypoglossal nerve stimulation device available in the United States, and globally, more than 45,000 patients have had implants. However, the field of neurostimulation is rapidly growing. Companies like LivaNova have secured Investigational Device Exemption for their HGNS device. The Genio system by Nyxoah is evaluating the use of bilateral hypoglossal nerve stimulation in patients with OSA and complete concentric collapse of the palate. A multidisciplinary Hypoglossal Nerve Stimulation Clinic is an important component of a comprehensive sleep medicine clinic for patient care and medical education. In the appropriate patient, this emerging technology may provide improvement in OSA severity and symptoms. ■

Dr. Gill is Clinical Associate Professor, Division of Sleep Medicine, Stanford (Calif.) University.

NETWORKS

Asthma/COPD, sepsis cardiomyopathy, and more....

AIRWAYS DISORDERS NETWORK
Asthma & COPD Section
Hot or cold – impact on asthma and COPD

Many of us may have experienced the extreme weather and climate patterns in the past year, depending on the region in which we live. These extreme weather changes are not unusual, but their recent occurrences may have been especially impactful on our patients.

Earlier works investigating effects of temperature and humidity changes on the airway in patients with asthma are insightful (Strauss, et al. 1978). Heat can irritate asthmatic airways that are already hyperreactive. Cold air can remove airway moisture. Similar mechanisms with warm/hot air can affect airway inflammation in COPD. In addition, poor air quality often occurs during extreme heat events and can affect patients with COPD.

Seasonal variation in COPD exacerbations was demonstrated by the TORCH study, where a two-fold increase in COPD exacerbations and hospitalizations was noted during the winter months in both northern and southern regions of the world. This trend was not observed in tropical countries with average annual temperatures of >18 °C (64 °F). Factors accounting for this variation may include greater risk of viral infections, increased host susceptibility, and more time spent indoors, along with impact of temperature variation on lung function (Jenkins, et al. 2012). This effect was accompanied by variation in the treatment choices with antibiotics alone or in combination with steroids. A trend towards combined antibiotics and steroids was noted during winters.

Ideal conditions for patients with COPD to minimize risk for exacerbation would be home humidity between 30% and 50% with indoor temperature of 21°C at least 9 hours per day in living areas.

Ideal conditions for patients with COPD to minimize risk for exacerbation would be home humidity between 30% and 50% with indoor temperature of 21°C at least 9 hours per day in living areas (Osman, et al. 2008).

Outdoor activities during extreme temperatures should be avoided. Air conditioning and/or humidifiers can be helpful in modifying influences.

Maria Azhar, MD
Section Fellow-in-Training
Richard George Barbers, MD, FCCP
Section Chair

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CRITICAL CARE NETWORK
Palliative and End-of-Life Section
PalliPulm: Time to expand our arsenal

Symptoms at the end of life in patients with COPD are just as severe as in patients with advanced cancer (Solano JP, et al. *J Pain Symptom Manage*. 2006;31[1]:58-69). However, despite the high symptom burden, palliative care is less common in patients with COPD (Gore J, et al. *Thorax*. 2000;55[12]:1000-6).

Palliative care is associated with a number of benefits, including improved symptom burden, quality of life, and patient satisfaction (Vermylen JH, et al. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1543-51). The majority of pulmonologists report that palliative care for patients with COPD is desirable, but about half of pulmonologists indicate that they do not use the palliative care guidelines and many were not even aware they existed (Duenk RG, et al. *Int J Chron Obstruct Pulmon Dis*. 2017;12:299-311). Patients with COPD often have unmet needs, and the majority of patients with COPD do not have access to palliative care at their end of life (Gore JM, et al). Unfortunately, the supply of palliative care specialists is too low to meet demand, especially in outpatient settings (Kamal AH, et al. *Am J Med*. 2017;130:113-4).


Dr. Winter

The ATS released a multisociety policy statement in 2022 that established a framework for early palliative care in the care in patients with respiratory illnesses (Sullivan DR, et al. *Am J Respir Crit Care Med*. 2022;206[6]:e44-e69). However, given the paucity of specialists and the aging population, the needs of patients and their loved ones cannot be met exclusively by palliative care specialists. Pulmonologists must expand their practice to include guideline-based palliative care in order to truly serve our patients to the best of our abilities. It is incumbent on training programs to train future pulmonologists with these palliative skills, and upon medical organizations to supply time and resources to ensure the pulmonologist is able to use these skills.

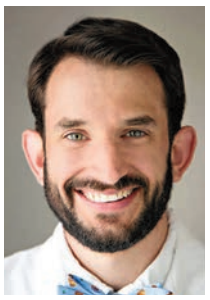
Gretchen Winter, MD
Section Member-at-Large

PULMONARY VASCULAR & CARDIOVASCULAR NETWORK
Cardiovascular Medicine and Surgery Section
Sepsis-induced cardiomyopathy: Is it time to establish a standard of care?

Sepsis and septic shock still carry high morbidity and mortality in patients in the ICU despite recent improvements in care. Sepsis-induced cardiomyopathy (SICM), which complicates greater than 10% of sepsis and septic shock cases, carries a worse prognosis and is often underrecognized. Unfortunately, no universal definition of SICM exists, making diagnosis and evaluation of novel therapeutic options difficult. Initially described in the 1980s, common fundamental features of SICM include an acute and reversible decline in LVEF with typical resolution in days to weeks; RV, LV, or BiV dysfunction; LV dilation;

diminished response to fluid resuscitation or catecholamines; and absence of acute coronary syndrome (L'Heureux, Sternberg et al. 2020).


Dr. Kapoor


Dr. Petrilli

A definition of SICM based solely on LVEF is incomplete due to its reliance on cardiac loading conditions. Diagnostic advances using pulse contour analysis and echocardiographic measure of longitudinal strain hold promise in better characterizing cardiac dysfunction in sepsis (Beesley et al, 2018). SICM should further be distinguished from stress-induced cardiomyopathy or Takotsubo cardiomyopathy, which can also complicate cases of sepsis and is characterized by regional wall motion abnormalities, classically LV apical ballooning with preserved contractility of the basal segments. A movement toward a standard definition of SICM would allow a more rigorous evaluation of risk factors and future directions for therapy, including a potential role for mechanical circulatory support in patients who fail to improve with inotropic support.

Tarun Kapoor MD
Section Fellow-in-Training
Andrew Petrilli, MD
Guest Author

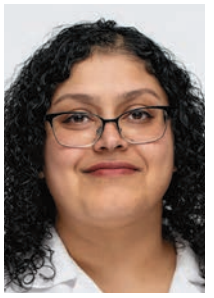
Looking for more information on sepsis? Visit CHEST's Sepsis Topic Collection Page at chestnet.org/Topic-Collections/Sepsis for research, infographics, and more developed by the CHEST Sepsis Resources Steering Committee.

THORACIC ONCOLOGY AND CHEST IMAGING NETWORK

Lung Cancer Section

Environmental and occupational risk factors for lung cancer

Lung cancer is the third most prevalent cancer in United States, with the highest mortality (Oliver, 2022)(Siegel et al, 2023). The factors contributing to its occurrence have become more complex due to increased industrialization and worsening environmental pollution. Air pollution is a well-established environmental risk factor for lung cancer (Lu et al. 2019). On average, a full-time worker spends around 90,000 hours at work over their lifetime. It is crucial to control environmental and occupational exposures to decrease the risk of developing lung cancer. Occupations like asbestos-related work, mining, and transportation are well-known to be at risk for lung cancer (Li et al. 2021). With worsening air pollution, occupations such as firefighters, outdoor delivery workers, and forest rangers are facing an increased risk as well. Many of these carcinogens independently increase lung cancer risk (Li et al. 2021). Smoking combined with these exposures, causes a synergistic effect on lung cancer incidence. They also have a cell subtype differential risk favoring squamous and small cell lung cancer (Christiani, 2020). It is essential for workers in these high-risk occupations to use proper PPE, have regular check-ups and screenings and follow occupational safety regulations and guidelines. As air pollution continues to worsen, individuals living in these areas should reduce outdoor activities during AQI alerts, and use air purifiers and masks. Public health efforts to decrease air pollution with cleaner transportation and energy production, and better local and national air quality regulations will decrease risk in the general population (Rice et al. 2021).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Are you ready for CHEST 2023 in Hawai'i?

Just a few weeks ahead of CHEST 2023, we're sharing the can't-miss opportunities available on site at the meeting.

With double the abstract submissions of previous meetings, CHEST 2023 – taking place October 8 to 11 in Honolulu – will offer the highest caliber of educational content covering pulmonary, critical care, and sleep medicine. Beyond the top-tier education, CHEST 2023 has a lot to offer attendees in the way of networking, development, and unique experiences that will all make for a memorable meeting.

We're sharing a preview of the many opportunities that will be available over the 4 days of the meeting. For more specifics on these events, including locations, scan the QR code to visit the CHEST 2023 website. You can also download the CHEST 2023 mobile app, which will be available in mid-September.

Networking and development

- For those who want to get more involved with the CHEST community, the **Networks Mixer (Monday, October 9, 4 PM HST)** is open to all who would like to learn more about the seven CHEST Networks and the 21 clinically-focused Sections within them.
- The annual **Women in Chest Medicine Luncheon (Monday, October 9, 12:45 PM HST)** will feature a panel of three women speaking about their experiences, their advice, how to support other women in the field, and more. This event is free, but preregistration is required.
- The first-ever **Ohana Mixer (Tuesday, October 10, 6 PM HST)** is an opportunity for CHEST attendees to celebrate the spirit of community that unites us across our differences. Attendees can network with each other, meet the members of our newly formed Interest Groups – including the leaders of our Women in Chest Medicine Interest Group and Respiratory Care Interest Group – and socialize with presenters from our three local CHEST Community Connections organizations.
- The Trainee Lounge will feature activities like **speed mentoring**, a **lunch and learn** with the Keynote Speaker, Dr. Cedric "Jamie" Rutland, **financial wellness** presentations, and more.

CHEST experiences

- The **Opening Session (Sunday, October 8, 3:15 PM HST)** will showcase traditional Hawaiian performances and the Keynote Address from Dr. Rutland. Immediately following, the **CHEST Welcome Reception** will feature live music and a traditional Hawaiian luau.
- For the second year, **CHEST After Hours (Monday, October 9, 3 PM HST)** will feature clinicians sharing stories of their personal triumphs, tribulations, and more experiences within medicine.
- Each year, the **CHEST Challenge Championship (Tuesday, October 10, 7 PM HST)** gives pulmonary and critical care medicine fellows-in-training an opportunity to compete in a live Jeopardy-style game – with bragging rights and cash prizes on the line.
- The **Wellness Zone** has a packed schedule of events, including beachy workouts, food demonstrations, meditation, and more.

Exhibit hall activities

- Opportunities to network with and hear presentations from local Hawaiian organizations, such as the Waianae Coast Comprehensive Health Center
- Hands-on, experiential education escape rooms
- Live educational games, including Hocus POCUS Diagnosis, PulmMemory, Peer Pressure, and more
- Simulation experiences, including Aspirated and Need for Speed – Airway Bleed

Mark your calendars now to participate in all that CHEST 2023 has to offer. We'll see you in Hawai'i! ■

CHEST SEEK releases key points feature and new print edition

Two exciting updates have come to the CHEST SEEK™ portfolio this summer.

The latest book, *CHEST SEEK™ Pulmonary Medicine: 33rd Edition*, was released in August. And in this newest book and certain CHEST SEEK Library collections, a feature called key points is included in the recently published 150 pulmonary medicine questions.

Key points are concise summaries of the most important takeaways of SEEK questions. Knowing the key point can help learners focus their studies.

"SEEK questions can be quite robust and intentionally detailed in their response as to why the answer options are correct or incorrect. But because of the level of detail, it can be difficult at times for the learner to correctly hone in on the author's teaching point," said CHEST Director, Product Strategy and Evaluation, Martha Zaborowski Pascale, CPM.

"Key points concisely summarize each question's most important details, potentially saving the learner study time."

CHEST SEEK™ Pulmonary Medicine: 33rd Edition was developed from the pulmonary medicine board subspecialty examination content blueprints. It tests recall, interpretation, and problem-solving skills.

Rationales provide thorough explanations and reasoning for the correct and incorrect answers. Key points are easy to find at the bottom of the pages and in a tab within SEEK Library questions.

For 3 decades, SEEK has been a trusted resource for chest medicine clinicians. From a printed booklet to the classic book and subscription-based library, learners have engaged with case-based questions in multiple ways. As SEEK has transformed through the years, it's continued to be a timeless, reliable study partner.

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"The success of SEEK in the past and the ability of this tool to be adapted to the changing needs of learners makes one excited about the editions to come," said Jesse B. Hall, MD, FCCP, SEEK Editor-in-Chief and Chair of *CHEST SEEK™ Pulmonary Medicine: 33rd Edition*.

Looking toward the future, SEEK will continue to develop and serve the needs of chest medicine clinicians.

"One of the joys of our professional lives is the constant new discoveries and trials that change the way we practice," said SEEK Pulmonary Medicine Vice-Chair and Deputy Editor, Jess Mandel, MD.

"However, with this comes the challenge of keeping up and staying current as the field evolves. SEEK is a terrific resource for keeping up with changes in practice and the underlying data that justify them."

Subscribe to the SEEK Library and find *CHEST SEEK™ Pulmonary Medicine: 33rd Edition* at chestnet.org/Learning-and-Events/Learning/Seek-App or by scanning the QR code at left. ■

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Navigating Bronchiectasis Exacerbations: An Expert Discussion

Colin Swenson, MD
Section Chief, Pulmonary & Critical Care
Medical Director, Respiratory Services
Emory St Joseph's Hospital

Wednesday, October 11 | **11:45 AM** | **Learning Theater 2**

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LAMA-LABA surpasses corticosteroid combination

BY HEIDI SPLETE
MDedge News

Use of inhalers with long-acting muscarinic antagonists and long-acting beta-agonists reduced COPD exacerbations and pneumonia hospitalizations compared with inhalers with corticosteroids and long-acting beta-agonists (LABAs), based on data from more than 30,000 individuals.

Current guidelines for COPD patients recommend inhalers with long-acting muscarinic antagonists (LAMAs) and LABAs over those with inhaled corticosteroids (ICSs) and LABAs, but data comparing the two formulations have been inconsistent, wrote William B. Feldman, MD, of Brigham and Women's Hospital, Boston, and colleagues.

In a study published in JAMA Internal Medicine (2023;183[7]:685-95), the researchers reviewed data from a commercial insurance claims database of individuals diagnosed with COPD who filled a new prescription for a LAMA-LABA inhaler or ICS-LABA inhaler between Jan. 1, 2014, and Dec. 31, 2019. Patients with asthma and those younger than 40 years were excluded. The study population included 137,833 individuals with a mean age of 70.2 years; 50.4% were female. Of the 107,004 ICS-LABA users and 30,829 LAMA-LABA users, 30,216 matched pairs were included in a 1:1 propensity score–matched study. The primary outcomes were effectiveness, based on the rate of first moderate or severe COPD exacerbation, and safety, based on the rate of first pneumonia hospitalization.

Use of LAMA-LABA inhalers was associated with an 8% reduction in the rate of first moderate or severe COPD exacerbation and a 20% reduction in the rate of first pneumonia hospitalization compared with use of ICS-LABA (hazard ratios 0.92 and 0.80, respectively). The absolute rate reductions with LAMA-LABA inhalers for first moderate or severe COPD exacerbations and for first pneumonia hospitalizations were was 43.0 events per 1,000 person-years and 91.8 events per person-years, respectively.

The overall rates of total moderate to severe COPD and pneumonia hospitalizations were 5% and 17% lower, respectively, among patients who used LAMA-LABA than those treated with ICS-LABA. The results were consistently robust in subgroup and sensitivity analyses, the researchers wrote in their discussion. However, the results must be interpreted cautiously in comparison to other large studies because of the significant differences in the cohorts of patients studied, notably that most patients in the current study had not received previous inhaler therapy.

The study findings were limited by several factors including the relatively short follow-up time and reliance on prescription fills as an indicator of medication use, the researchers noted. Other limitations included notable differences between the LAMA-LABA patients and ICS-LABA patients, such as

more severe COPD and less access to respiratory care, they wrote.

Although the current study is not the definitive answer to conflicting results from previous trials, it is the largest know to date to compare LAMA-LABA with ICS-LABA, and the results support LAMA-LABA as the preferred therapy for COPD patients, the researchers concluded.

"This study was required to provide clarity regarding the optimal choice of treatment for COPD given conflicting data from other recent trials," Suman Pal, MBBS, of the University of New Mexico, Albuquerque, said in an interview. "The study findings reinforce the benefits of combined LAMA-LABA in improving clinical outcomes in COPD in a real-world setting," and the data provide further support for choosing LAMA-LABA over ICS-LABA in COPD patients, said Dr. Pal, who was not involved in the study. Availability and affordability of LAMA-LABA inhalers may be barriers to expanding their use in clinical practice, he noted.

Dr. Feldman disclosed fees from Alosa Health and Aetion and serving as an expert witness in litigation against inhaler manufacturers. Dr. Pal had no financial conflicts to disclose. ■

Generic inhalers for COPD support hold their own

BY MARCUS A. BANKS

Sometimes we get what we pay for. Other times we pay too much. That's the message of a study published in Annals of Internal Medicine (2023 Aug 8. doi: 10.7326/M23-0615), which finds that a generic maintenance inhaler is as effective at managing symptoms of chronic obstructive pulmonary disorder (COPD) as a pricier branded alternative.

In 2019, the U.S. Food and Drug Administration approved Wixela Inhub (the combination corticosteroid/long-acting beta^2 adrenergic agonist fluticasone-salmeterol; Viatris) as a generic dry-powder inhaler for managing symptoms of COPD. This approval was based on evidence of the generic's effectiveness against asthma, although COPD also was on the product

label. The study authors compared Wixela's effectiveness in controlling symptoms of COPD with that of the brand name inhaler Advair Diskus (fluticasone-salmeterol; GlaxoSmith-Kline), which uses the same active ingredients.

The result: "The generic looks to be as safe and effective as the brand name. I don't see a clinical reason why one would ever need to get the brand name over the generic version," said study author William Feldman, MD, DPhil, MPH, a health services researcher and pulmonologist at Harvard Medical School and Brigham and Women's Hospital, both in Boston. Dr. Feldman and colleagues compared the records of 10,000 patients with COPD who began using the branded inhaler to the records of another 10,000 patients with COPD who opted for the generic alternative.

Participants in the two groups were evenly matched by age, sex, race, and ethnicity, region, severity of COPD, and presence of other comorbidities, according to the researchers.

Participants were all older than age 40. The average age in both groups was 72 years.

The researchers looked for a difference in a first episode of a moderate exacerbation of COPD, defined as requiring a course of prednisone for 5-14 days. They also looked for cases of severe COPD exacerbation requiring hospitalization in the year after people began using either the generic or brand name inhaler. And they looked for differences across 1 year in rates of hospitalization for pneumonia.

For none of those outcomes, however, did the type of inhaler appear to matter. Compared with the brand-name drug, using the generic was associated with nearly identical rates of moderate or severe COPD exacerbation (hazard ratio, 0.97; 95% confidence interval, 0.90-1.04. The same was true for the proportion of people who went to the hospital for pneumonia at least once (HR, 0.99; 95% CI, 0.86-1.15).

As a general matter, having a single generic competitor will not lower costs much, Dr. Feldman noted, pointing to 2017 research from Harvard that found a profusion of generic competitors is needed to significantly lower health care costs (N Engl J Med. 2017;377:2597-8)."I don't want to in any way underestimate the importance of getting that first generic onto the market, because it sets the stage for future generics," he added.

"There are very few generic options for patients with COPD," said Surya Bhatt, MD, director of the Pulmonary Function and Exercise Physiology Lab at the University of Alabama at Birmingham.

"The results are quite compelling," said Dr. Bhatt, who was not involved in the research. Dr. Bhatt noted that the FDA's 2019 approval – given that the agency requires bioequivalence studies between branded and generic products – was enough to cause him to begin prescribing the generic inhaler.

The fact that this approval was based on asthma but not also COPD is not a concern.

"There are so many similarities between asthma, COPD, and some obstructive lung diseases," Dr. Bhatt noted.

Dr. Feldman reported funding from Arnold Ventures, the Commonwealth Fund, and consulting relationships with Alosa Health and Aetion. Dr. Bhatt reported having no conflicts. ■

Study suggests protective role for vitamin D

BY WALTER ALEXANDER
MDedge News

A potentially protective role for vitamin D in the pathogenesis of chronic obstructive pulmonary disease (COPD) is suggested by the finding that serum 25-hydroxyvitamin D (25[OH]D) concentrations are inversely associated with COPD incidence and mortality. COPD risk was 23% higher in people within the lowest quintile vs. the fourth quintile of 25(OH)D concentrations, according to research appearing in BMJ Open Respiratory Research (2023 Jun 23. doi: 10.1136/bmjresp-2023-001684).

While low vitamin D status has been linked to increased inflammatory diseases risk and to the regulation of pathogenic mechanisms in COPD, epidemiological evidence regarding the associations of 25(OH)D concentrations with COPD incidence and survival remains inconclusive, Zheng Zhu, MD, of Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China, and colleagues wrote.

From UK Biobank data recorded from 403,648 participants (mean age 56.4 years; 54% women) who were free of COPD at baseline and had 25(OH)D measurements, researchers estimated hazard ratios and 95% confidence intervals for the associations of 25(OH)D concentrations with COPD risk and survival. After median follow-up of 12.3 years (ending Sept. 30, 2021), with 11,008 COPD cases recorded, beyond the COPD and mortality increase (HR, 1.23; 95% CI, 1.16-1.31) in the lowest quintile of 25(OH)D concentrations, risk for overall death was 38% higher, as well (HR, 1.38; 95% CI, 1.22-1.56). Serum concentrations were greater than 64.6 nmol/L in the highest (quintile 5) and less than 31.7 nmol/L in the lowest (quintile 1). Also, men and current smokers had higher COPD and mortality risk (*P* interaction for both: < .05).

While event rates tracked generally inversely with 25(OH)D concentrations, overall the event curves were non-linear. Dr Zhu and associates reported that the decreasing risk of COPD appeared to be lowest at 55 nmol/L of 25(OH)D within quintile 4 (51.8 to < 64.6 nmol/L). Furthermore, lower prediagnostic 25(OH)D concentrations were associated with a significant decrease in overall and COPD-specific survival.


Dr. Maselli

Smoking is the most commonly encountered risk factor for COPD, the researchers noted, and their findings indicated that 25(OH)D concentrations were inversely associated with COPD risk in both smokers and never-smokers. In a fully adjusted model, compared with quintile 4, the quintile 1 increase in COPD risk was 25% in never-smokers and 23% in smokers.

"Our findings imply that vitamin D might play a role in progression of COPD," the authors stated. They added, "Whether lower concentrations of 25(OH)D are causal or contributory to COPD risk may spur future long-duration and large-scale RCTs."

"Vitamin D has an important function in the immune system and lower serum levels have been implicated in a variety of inflammatory diseases," commented associate professor of medicine Diego J. Maselli, MD, FCCP, who is chief of the division of pulmonary diseases & critical care at UT Health San Antonio and a member of the CHEST Physician Editorial Board.

"Patients with COPD often have lower levels of vitamin D compared to healthy individuals. COPD patients with low serum levels of vitamin D may have a higher risk of exacerbations and worse lung function."

He added, "The research by Zhu and colleagues adds to the field of study and highlights the potential role of vitamin D in the pathophysiology of COPD. It is important to remember that these associations do not establish causality, as patients with chronic and debilitating diseases may have limited sunlight exposure, poor nutritional intake, and other behaviors that may affect vitamin D levels. There are mixed results in studies evaluating the role of supplementing vitamin D in COPD with regards to disease progression and exacerbation reduction. While there are some studies that report that supplementation of vitamin D can reduce COPD exacerbations, there is still a need for randomized controlled studies that explore if the supplementation of vitamin D can prevent the development of COPD, particularly in those who actively smoke. Yet, it is reasonable to evaluate the serum vitamin D levels in COPD patients who have had exacerbations and supplement when there is a severe deficiency."

No disclosures were reported by Dr. Zhu or by Dr. Maselli. ■

COPD plus PRISm may promote frailty progression

BY HEIDI SPLETE

FROM THE JOURNAL CHEST® ■
Chronic obstructive pulmonary disease and a new phenotype of lung function impairment predicted progression of frailty in older adults, based on data from more than 5,000 individuals.

Longitudinal data on the association of COPD with progression of frailty are limited, as are data on the potential association of preserved ratio impaired spirometry (PRISm) with frailty progression, wrote Di He, BS, of Zhejiang University, China, and colleagues.

PRISm has been defined in recent studies as "proportional impairments in FEV_1 and FVC, resulting in the normal ratio of FEV_1 and FVC." Individuals with PRISm may transition to normal spirometry or COPD over time, the researchers wrote.

In a study published in the journal CHEST (2023 Jul 20. doi: 10.1016/j.chest.2023.07.020), the researchers reviewed data from 5,901 adults aged 50 years and older who were participating on the English Longitudinal Study of Ageing (ELSA), a prospective cohort study. Of these, 3,765 were included in an additional analysis of the association between transitions from normal spirometry to PRISm and the progression of frailty. The mean age of the participants was 65.5 years; 54.9% were women.

The median follow-up period for analysis with frailty progression was 9.5 years for PRISm and COPD and 5.8 years for PRISm transitions. Lung function data were collected at baseline. Based on spirometry data, participants were divided into three lung function groups – normal spirometry, PRISm, and COPD – and each of these was classified based on severity. Frailty was assessed using the frailty index (FI) during the follow-up period.

Frailty progression based on FI was significantly accelerated in patients with PRISm and COPD, compared with individuals with normal spirometry, with additional annual increases of 0.301 and 0.172, respectively (*P* < .001 for both).

When stratified by severity, individuals with more severe PRISm and with more COPD had higher baseline FI and faster FI progression, compared with those with mild PRISm and COPD.

PRISm transitions were assessed over a 4-year interval at the start of the ELSA. Individuals with normal spirometry who transitioned to PRISm during the study had accelerated progression of frailty, as did those with COPD who transitioned to PRISm. However, no significant frailty progression occurred in those who changed from PRISm to normal spirometry.

The mechanisms behind the associations of PRISm and COPD with frailty remain unclear, but the results were consistent after controlling for multiple confounders, "suggesting PRISm and COPD had independent pathophysiological mechanisms for frailty," the researchers write in their discussion. Other recent studies have identified sarcopenia as a complication for individuals with lung function impairment, they noted. "Therefore, another plausible explanation could be that PRISm and COPD caused sarcopenia, which accelerated frailty progression," they say.

The findings were limited by several factors, including the observational design and the potential underestimation of lung function in participants with reversible airflow obstruction because of the use of prebronchodilator spirometry in the cohort study, the researchers noted.

However, the results were strengthened by the large sample size and high-quality data from the ELSA, as well as by the repeat measures of FI and lung function. The results were consistent after controlling for multiple confounders, and support the need for more research to explore the causality behind the association of PRISm and COPD with frailty, the researchers concluded.

The researchers reported having no relevant financial relationships. ■

SUNOSI® (solriamfetol) IV
75, 150 mg tablets

For adults with excessive daytime sleepiness (EDS) in obstructive sleep apnea (OSA) or narcolepsy

ARE YOUR PATIENTS READY TO

PULL AN ALL-DAYER?[1]

Once-daily SUNOSI is the first and only WPA proven to improve wakefulness through 9 hours at week 12[1]*

*The 75 mg dose showed a trend toward improvement; however, this change was not statistically significant for patients with narcolepsy.[1]

Proven results for patients with OSA taking SUNOSI 150 mg[1†]:

82% **Increase in minutes of wakefulness**
vs 0% on placebo at week 12[2,3‡]

Co-primary endpoint: LS mean change from baseline to week 12 in mean sleep latency during the MWT was 11.0 minutes for SUNOSI 150 mg vs 0.2 minutes for placebo.[2]

52% **Reduction in daytime sleepiness**
vs 15% on placebo at week 12[2,3‡]

Co-primary endpoint: LS mean change from baseline to week 12 in ESS scores was -7.7 for SUNOSI 150 mg vs -3.3 for placebo.[2]

90% **Of patients reported feeling better**
vs 49% on placebo at week 12[2§]

The most common adverse reactions
(incidence ≥5% and greater than placebo) reported more frequently with SUNOSI were headache, nausea, decreased appetite, anxiety, and insomnia[1]

SUNOSI is the first and only DNRI
approved for the treatment of EDS in OSA or narcolepsy[1,4]

DNRI=dopamine-norepinephrine reuptake inhibitor; ESS=Epworth Sleepiness Scale; LS=least squares; MWT=Maintenance of Wakefulness Test; PGIC=Patient Global Impression of Change; WPA=wake-promoting agent.

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INDICATION

SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or 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 the following pages.

SUN HCP aISI 05/2022

†As seen in a 12-week randomized, multicenter, double-blind, placebo-controlled, parallel-group study of adult patients with OSA (n=459).[1,2]

‡Median percent change from baseline to week 12 was calculated using the last observation carried forward and was not adjusted for covariates used in these primary endpoints. Seven patients were missing from baseline values and were not included in the calculations.[1,2,3]

§The percentage of patients improved on the PGIC scale includes those who reported very much, much, and minimal improvement.[2]

References: 1. SUNOSI (solriamfetol) [prescribing information]. New York, NY: Axsome Therapeutics, Inc. **2.** Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. *Am J Respir Crit Care Med.* 2019;199(11):1421-1431. **3.** Data on File (SOL-2020-086). New York, NY: Axsome Therapeutics, Inc. **4.** Baladi MG, Forster MJ, Gatch MB, et al. Characterization of the neurochemical and behavioral effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther.* 2018;366(2):367-376.

axsome

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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AI scribes: Just how good are they?

LORRAINE L. JANECZKO, MPH

Andrea Partida, DO, an obstetrician and gynecologist in Enid, Okla., loves her new assistant.

The 15 or 20 minutes she used to spend on documentation for each patient visit is now 3. The 2-3 hours she'd spend charting outside clinic hours is maybe 1.

All that time saved allows her to see two to five more patients a day, provide better care to each patient, and get more involved in hospital leadership at Integris Health, where she works.

"I have a better work-life balance with my family," Dr. Partida said. "I leave work at work and get home earlier."

You've probably figured out the plot twist: Dr. Partida's assistant is not a person – it's artificial intelligence (AI).

Dr. Partida uses IRIS, a tool from OnPoint Healthcare Partners, part of a fast-growing niche of AI medical scribes designed to automate onerous data entry. The evolution of generative AI – specifically, large language models, such as ChatGPT – has led to a rapid explosion of these tools. Other companies in the space include Abridge, Ambience Healthcare, Augmedix, DeepScribe, Nuance (part of Microsoft), and Suki. The newest kid on the block, Amazon Web Services, announced the launch of HealthScribe in July.

These tools – some of which are already on the market, with more on the way – record patient visits and generate notes for treatment and billing. Earlier iterations combine AI with offsite human scribes who provide quality control. But more and more are fully automated: no human required. Some also offer video recording and foreign language translation.

The promise is alluring: Ease your workload and reclaim hours in your day so you can spend more time with patients or try that "work-life balance" thing you've heard so much about.

But do these tools fulfill that promise?

According to Dr. Partida and other doctors who spoke with this news organization, the answer is a resounding yes.

A tech solution for a tech problem

"I believe a lot of doctors see patients for free. They get paid to do paperwork," said Anthony J. Mazzarelli, MD, JD, MBE, co-president and CEO of Cooper University Health Care, in Camden, N.J.

Indeed, for every hour U.S. clinicians spend with their patients, they may spend 2 more hours documenting in electronic health records (EHRs), estimates show. About half of doctors, especially those in primary care, report feeling burned out, and some 42% say they want to quit clinical practice.

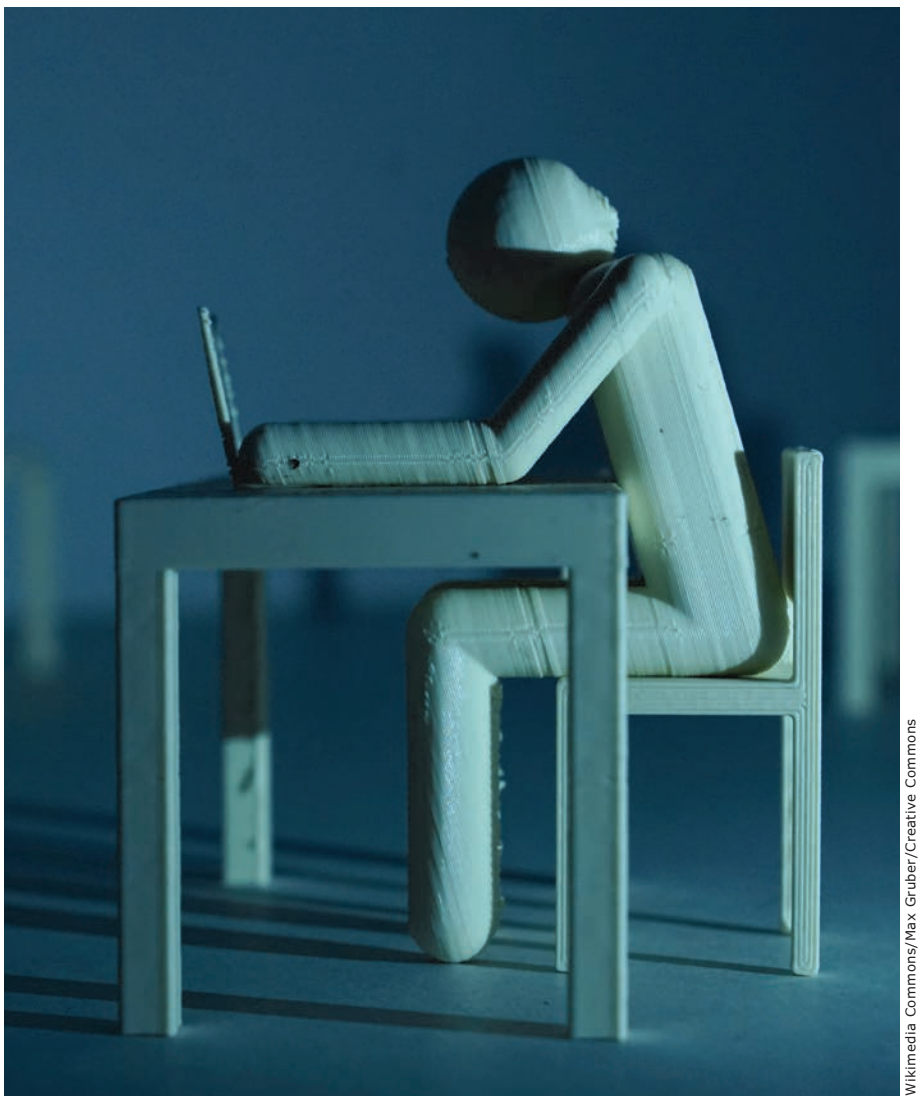
Enter AI scribes.

"The holy grail in medicine right now is improving burnout while also maintaining or improving productivity and quality," said Patricia Garcia, MD, associate clinical information officer for ambulatory care at Stanford (Calif.) Health Care. "These ambient digital scribes have the potential to do just that."

While anyone can buy these products, their use has been mostly limited to pilot programs and early adopters so far, said Dr. Garcia, who has been helping to pilot Nuance's digital scribe, DAX, at Stanford.

But that's expected to change quickly. "I don't think the time horizon is a decade," Dr. Garcia said. "I think within a matter of 2 or 3 years, these tools will be pervasive throughout health care."

Since introducing these tools at Cooper, "our doctors' paperwork burden is significantly lighter," said Dr. Mazzarelli, who decides which technologies Cooper should invest in and who monitors their results.



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In Cooper studies, physicians who used DAX more than half the time spent 43% less time working on notes.

"They spend more time connecting with their patients, talking with them, and looking them in the eye," Dr. Mazzarelli said. That, in turn, seems to improve patient outcomes, reduce doctor burnout and turnover, and lower costs.

The AI scribes, by virtue of eliminating the distraction of note taking, also allow doctors to give their full attention to the patient. "The patient relationship is the most important aspect of medicine," said Raul Ayala, MD, MHCM, a family medicine physician at Adventist Health, in Hanford, Calif., who uses Augmedix. The digital scribe "helps us strengthen that relationship."

What's it like to use an AI medical scribe?

The scribes feature hardware (typically a smartphone or tablet) and software built on automatic speech recognition, natural language processing, and machine learning. Download an app to your device, and you're ready to go. Use it to record in-person or telehealth visits.

In the first week, a company may help train you to use the hardware and software. You'll likely start by using it for a few patient visits per day, ramping up gradually. Dr. Partida said she was comfortable using the system for all her patients in 6 weeks.

Each day, Dr. Partida logs in to a dedicated smartphone or tablet, opens the app, and reviews her schedule, including details she needs to prepare for each patient.

At the start of each patient visit, Dr. Partida taps the app icon to begin recording and lays the device nearby. She can pause as needed. At the end of the visit, she taps the icon again to stop recording.

The AI listens, creates the note, and updates relevant data in the EHR. The note includes patient problems, assessment, treatment plan, patient history, orders, and tasks for staff, along with medications, referrals, and preauthorizations. A human scribe, who is also a physician, reviews the information for accuracy and edits it as needed. By the next morning, the data are ready for Dr. Partida to review.

Fully automated versions can generate notes much faster. Jack Shilling, MD, MBA, an orthopedic surgeon at Cooper University Health Care, in Voorhees, N.J., uses DAX. A new feature called DAX Express – which uses OpenAI's GPT-4 but no humans – provides him with a draft of his clinical notes in just seconds.

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How accurate are AI notes?

The accuracy of those notes remains an open question, Dr. Garcia said – mostly because accuracy can be hard to define.

"If you asked five docs to write a note based on the same patient encounter, you'd get five different notes," Dr. Garcia said. "That makes it hard to assess these technologies in a scientifically rigorous way."

Still, the onus is on the physician to review the notes and edit them as needed, Dr. Garcia said. How light or heavy those edits are can depend on your unique preferences.

Dr. Shilling said he may need to lightly edit transcripts of his conversations with patients. "When someone tells me how long their knee hurts, slight variability in their transcribed words is tolerable," he said. But for some things – such as physical exam notes and x-ray readings – he dictates directly into the device, speaking at a closer range and being less conversational, more exact in his speech.

Should you let patients know they're being recorded?

The federal Health Insurance Portability and Accountability Act (HIPAA) does not require providers to inform patients that their face-to-face conversations are being recorded, said Daniel Lebovic, JD, corporate legal counsel at Compliancy Group, in Greenlawn, N.Y., a company that helps providers adhere to HIPAA rules.

But make sure you know the laws in your state and the policies at your health care practice. State laws may require providers to inform patients and to get patients' consent in advance of being recorded.

All the doctors who spoke to this news organization said their patients are informed that they'll be recorded and that they can opt out if they wish.

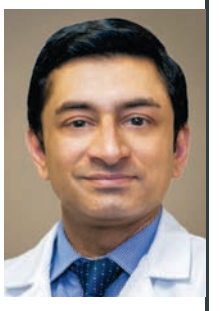
How much do AI scribes cost?

As the marketplace for these tools expands, companies are offering more products and services at different price points that target a range of organizations, from large health care systems to small private practices.

Price models vary, said Dr. Garcia. Some are based on the number of users, others on the number of notes, and still others on minutes.

Amazon's HealthScribe is priced at 10 cents per minute. For 1,000 consultation transcripts per month, with each call averaging 15 minutes, it would take 15,000 minutes at a total cost of $1,500 for the month.

In general, the rapidly growing competition in this space could mean prices become more affordable, Dr. Garcia said. "It's good that so many are getting into this game, because that means the price will come down and it will be a lot more accessible to everybody." ■



Humayun Anjum, MD, FCCP, comments: It has been highlighted multiple times in various studies that a lot of doctors and nurses quit their jobs due to high levels of burnout. The amount of time spent on documentation for electronic health records ranks highly among the grievances. This labor frequently extends into the evenings; doctors refer to this work as "pajama time." This piece focuses on the subtleties of AI scribes and gives a thorough overview of this innovative solution to a tiresome and time-consuming issue.

While there is no denying the advantages of AI-powered medical scribes, there are also difficulties and issues to take into account. The technology's underlying algorithms could be biased, to start. Health care inequities could result from this. The risk of data breaches and cybersecurity risks comes in second. Finally, a large initial investment in hardware, software, and training may be needed to implement AI medical scribes. These issues must be addressed by health care practices and organizations through appropriate security measures, training, and ethical considerations.

Together, medical professionals and technologists can create AI-powered medical scribes that are reliable, efficient, and secure. Artificial intelligence-powered medical scribes are just the beginning of a bright future for health care.

Dr. Anjum is a member of the CHEST Physician Editorial Board.

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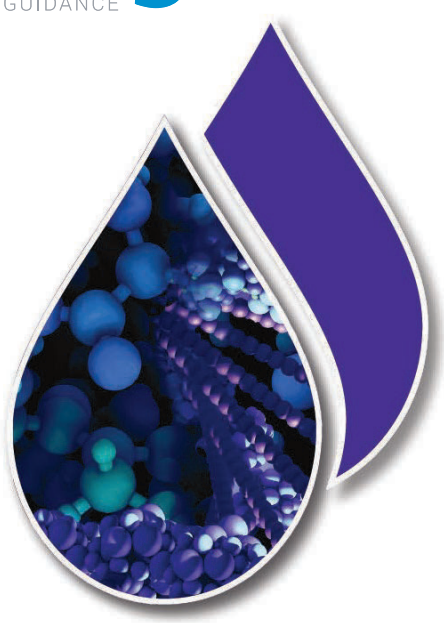

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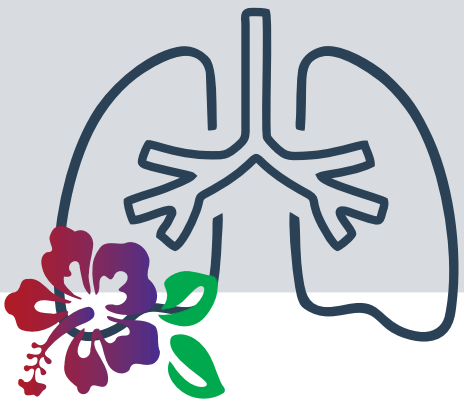

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