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.

New tech promises better blood oxygen readings on dark skin

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 hasn’t 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
BREATHE EASY WHEN DIAGNOSING RESPIRATORY INFECTIONS.

Results from our respiratory solutions provide clarity, enabling clinicians to know earlier, intervene sooner, and improve patient outcomes.

**BIOFIRE RESPIRATORY 2.1 PANEL**
1 Test. 22 Targets. ~45 Minutes.
FDA cleared
Sample Type: Nasopharyngeal swab
Identifies 22 of the most common respiratory viruses and bacteria.

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1 Test. 33 Targets. ~1 Hour.
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Sample Type: BAL-like (including mini-BAL) Sputum-like (including ETA)
Identifies 26 of the most common respiratory viruses and bacteria, and 7 antimicrobial resistance genes.

**VIDAS® B-R-A-H-M-S PCT™**
1 Test. ~20 Minutes.
FDA cleared
Sample Type: Serum or plasma
Measures procalcitonin (PCT), a specific marker of severe bacterial infection in patients with lower respiratory tract infections.

Product availability varies by country. Consult your bioMérieux representative.
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. 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. 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 management or 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 oximeter.
Minimal Practice Changes, Major Patient Impact

Experience and patient feedback tell us patients are more compliant and have better outcomes when they feel understood. Getting to know your patients in the short window of time you have is challenging. Try these free, self-paced learning modules designed to help you nurture connections faster and more meaningfully.

Building Patient Trust Fundamentals
Quickly create rapport, respond with empathy, and build your relationship.

Building Patient Trust Skills Practice
Apply your empathetic communication skills by conversing with a simulated patient.

The First 5 Minutes® program consists of evidence-based skills to establish trust with your patients in the first 5 minutes of your interactions. With improved communication, you’ll see that it takes less effort to help your patients more.

“...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).

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 IPF 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 (Advances in 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.”

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 device 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.
T he 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/glycopyrronium triad) 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/4jp2bpjr).

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.

BY LUCY HICKS

**FDA warns AstraZeneca over ‘misleading claims’ about COPD drug**

**AI continued from previous page**

press release from Lenum, 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 (BMJ 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. “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.”

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. pdg.000198). 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 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 supplanting 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 algorithmic 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. Tseng envisioned how AI would work in the clinic. “I personally think that, at some time in the not too distant 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-Barre 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-particle matter (PM2.5).

“Our findings provide evidence that reducing exposure to both extreme temperatures and fine-particle 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:

- The risk of fatal MI was 18% higher during 2-day heat waves with heat indexes at or above the 90th percentile (ranging from 92.6° 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 104.4°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/m3. 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/m3).
- 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-particle 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.

FOR PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA, YOU CAN REDUCE:

**EOSINOPHILS**

FASENRA targets and provides near complete depletion of blood eosinophils in 24 hours.†2,3,4

The relationship between the pharmacologic properties and clinical efficacy has not been established.

**EXACERBATIONS**

FASENRA significantly reduced patients’ exacerbations.‡5,6

**ORAL STEROIDS**

FASENRA significantly reduced patients’ need for OCS use.§7

Do not abruptly discontinue corticosteroids. Dose reductions, if appropriate, should be gradual and may be associated with withdrawal symptoms and/or unmask previously controlled conditions.

Scan here or visit www.FasenraOptions.com to see if FASENRA is appropriate for your patients.

Results May Vary.

*Based on IQVIA data from July 2021 to June 2022.†

†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 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.¶

‡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).¶

§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).¶

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.
IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)
Acute Asthma Symptoms or Deteriorating Disease
FASENRA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dosage should 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 pretreatment helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA, and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥ 5%) include headache, nasopharyngitis.

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.

STUDY DESIGNS
SIROCCO AND CALIMA (Trials 1 and 2)5,6
SIROCCO (48-week) and CALIMA (56-week) were two randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing FASENRA 30 mg SC Q4W for the first 3 doses, then Q8W thereafter, with 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 and LABA 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 usual dosing in the previous year. At the end of treatment, EOT, end of treatment; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, standard of care.

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, with 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.

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.motherstobaby.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.
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, 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 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 it is a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by keeping at room temperature for at least 20 minutes. Usually inject FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few transparent 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.

The prefilled syringe is for administration by a healthcare provider.

Autoadminister FASENRA® (benralizumab) PEN
FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject the patient 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

| Needle guard activation clips | Needle guard cover | Needle guard | Flange | Syringe body | Label | Plunger | Syringe plunger | Needle cover |

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 use 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 the plunger head 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.

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

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

4. 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.

5. 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 can occur up to several hours after the last dose. In the event of a hypersensitivity reaction, FASENRA should be discontinued [see Contraindications (4) in the full Prescribing Information].

Acute Asthma Flare Following Determining 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 be monitored closely for asthma that is 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 controlled by corticosteroids.

Parasitic (Helminth) Infection
Eosinophilia may be involved in the immunological response to some helminth infections, patients with active helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient’s response against helminth infections.

History of Infections or Inflammation Related to Malignant Cells
Infections or inflammation related to malignant cells have been observed pre-existing infections before initiation with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-infection treatment, discontinue treatment with FASENRA until infection resolves.

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
This drug has been evaluated in patients conducting under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other drugs and may not reflect the rates observed in practice.

3192 adults and 1,108 children 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 3092 patients (1585 reported for at least 14 weeks and 1307 exposed at least 48 weeks). The safety exposure for FASENRA is derived from two Phase 3 placebo-controlled studies (Trials 1 and 2) from 46 weeks duration (FASENRA every 4 weeks or placebo) or 4 weeks (FASENRA every 4 weeks or placebo). While a dosing regimen of FASENRA every 4 weeks was used in clinical trials, a dosing regimen of every 8 weeks is recommended (see Dosage and Administration (2.1) in the full Prescribing Information). The population studied was 12 to 75 years of age, at which 66% 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 in Patients with FASENRA for Particular Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FASENRA (N=3092)</th>
<th>Placebo (N=3047)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis*</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

*Pharyngitis was defined in the following terms: Pharyngitis, Pharyngitis sicca, Viral pharyngitis.

Adverse Reactions

3039 (57%) of patients treated with FASENRA and 2930 (54%) of patients treated with placebo experienced adverse 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.

Incapacitation
As with all therapeutic proteins, there is potential for immunogenicity. The detection of anti-benralizumab antibodies on the sensitivity and specificity of FASENRA. Additional, the observed incidence of antibody (including neutralizing antibody) positivity is in an assay may be influenced by several including assay methodology, sample handling, stability of antibody collection, status of the patient prior to testing. 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 12% 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 clinical outcomes or adverse events following initiation with FASENRA.

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 reported 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 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 [see Use in Specific Populations (8.1) in the full Prescribing Information].

Infants

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SLEEP MEDICINE

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.

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.

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 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 Payor+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.

"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.

BY MEGAN BROOKS

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**PULMONARY MEDICINE**

**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 a basis for diagnosis (data = .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.

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**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, Gigamesh Eamer, MD, MSc, FRCS(C), 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 neg.

The authors stated, They observed further that the analysis revealed that 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 the ICER [incremental cost-effectiveness ratio] was lower for observation than for aspiration (0.77 for CT, 0.79 for aspiration, and 0.82 for observation). The authors 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 McShane, MD, a pulmonologist on line clinicians generally assume that hospitalizations, or other signs of a 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 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 FEV₁ 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 FEV₁.

“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.

Nontuberculous 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
BRONCHIECTASIS continued from previous page

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, 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

<table>
<thead>
<tr>
<th>OPSUMIT® (macitentan) tablets</th>
<th>OPSUMIT® (macitentan) tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNING: EMBRYO-FOetal TOXICITY</strong></td>
<td><strong>Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study</strong></td>
</tr>
<tr>
<td>• Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see Contraindications, Warnings and Precautions, Use in Specific Populations].</td>
<td></td>
</tr>
<tr>
<td>• Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception [see Pregnancy Testing in Females of Reproductive Potential (2.2) in Full Prescribing Information, Use in Specific Populations].</td>
<td></td>
</tr>
<tr>
<td>• For all female patients, OPSUMIT is available only through a restricted program called the Macienten Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions].</td>
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</tbody>
</table>

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo.

Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated [see Adverse Reactions].

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant alanine aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Fluid Retention

Peripheral edema and fluid retention are known clinical consequences of PAH and known effects of ERAs. In the placebo-controlled study of OPSUMIT in PAH, the incidence of edema was 21.9% in the OPSUMIT 10 mg group and 20.5% in the placebo group.

Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of OPSUMIT in patients with pulmonary hypertension because of left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations because of worsening heart failure compared to those randomized to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported [see Adverse Reactions].

Monitor for signs of fluid retention after OPSUMIT initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause, such as OPSUMIT or underlying heart failure, and the possible need to discontinue OPSUMIT.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline of up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 9.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see Adverse Reactions].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

OPSUMIT, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility [see Use in Specific Populations and Nonclinical Toxicology].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

• Embryo-fetal Toxicity [see Warnings and Precautions]

• Hepatotoxicity [see Warnings and Precautions]

• Fluid Retention [see Warnings and Precautions]

• Decrease in Hemoglobin [see Warnings and Precautions]

Clinical Trial 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 clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 424 patients with PAH (SERAPHIN study) [see Clinical Studies (14) in Full Prescribing Information].

The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).
the disease course, the data provide a basis for questioning whether rou-
tine cultures are needed, according to the discussion that followed Dr. McShane's presentation.

Expert opinion
Several of the experts at the pre-
sentation 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 infec-
tion is suspected of exacerbating the disease.

Of this latter group, which seemed
to be dominant, Juzar Ali, MD, pro-
fessor of medicine, Louisiana State
University, New Orleans, said that
he has not been ordering fungal cul-
tures 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 com-
mon clinical issue.

Dr. McShane reports no rele-
vant financial relationships. Dr. Ali
reports a financial relationship with
Insmed.
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) (Benjafied 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 trouble-shoot 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.
updated polysomnography if a recent study is not offered to examine upper airway anatomy. When available. If the polysomnography reveals central the total AHI, patients are referred to ENT Sleep and mixed apneas comprising less than 25% of MPH, FCCP

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

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*Albuterol-Budesonide Pressur-ized Metered-Dose Inhaler in Patients With Mild-to-Moderate Asthma
By Bradley E. Chippys, MD, et al.

Cardiovascular and Pulmonary Responses to Acute Use of Electronic Nicotine Delivery Systems and Combustible Cigarettes in Long-Term Users
By Matthew C. Tattersall, DO, et al.

Complications and Practice Variation in the Use of Peripherally Inserted Central Venous Catheters in People With Cystic Fibrosis
By Alex H. Gifford, MD, et al.

Exercise Testing in the Risk Assessment of Pulmonary Hypertension
By Lindsay M. Forbes, MD, et al.

*Impaired Spirometry and COPD Increase the Risk of Cardiovascular Disease
By Saurya 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

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/ m² (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 maxillo-mandibular 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 tolerated 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 HGNSs 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.
changes on the airway in patients hyperreactive. Cold air can remove moisture and humidity, which can be impactful on our patients. Asthmatics may have been especially sensitive to the extreme weather changes in the region in which we live.

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 sensitized. Cold air can remove airway moisture. Similarly, 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 (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

**References**


**CRITICAL CARE NETWORK**

**Palliative and End-of-Life Section**

PalliPulm: Time to expand our arsenal


Palliative care is associated with a number of benefits, including improved symptom burden, quality of life, and patient satisfaction (Vermeylen 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 (Dueck 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).

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). 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 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).

Amaraja Kanitkar, MD, MBBS
Guest Author

References
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 POCUS Diagnosis, PulmMemory, Peer Pressure, and more

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.

“The strength of peer-reviewed, expert-written content has remained the same, but modalities such as digital flash cards and behind-the-scenes peer review discussions have enhanced this enduring product in ways that help it stand the test of time.”

Based on CHEST evaluation data, more than 90% of SEEK learners said their practice will change based on content found in the library. Plus, more than 95% of SEEK learners agreed that SEEK question authors are effective instructors.

“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.
Attend a Bronchiectasis Learning Theater at the CHEST Annual Meeting 2023

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

The Learning Theater is a non-CME event and does not qualify for CME, CE, or MOC credit. This event is not part of the official CHEST Annual Meeting 2023 conference sessions. This event is not an endorsement by CHEST and does not reflect the views or opinions of CHEST.

Learn more about bronchiectasis at Insmed’s Booth #1001 or visit RethinkNCFBE.com

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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 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 known 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. ■

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IMPORTANT SAFETY INFORMATION (continued)

DOSEAGE AND ADMINISTRATION

Recommended Dosage

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

Patients With Hepatic Impairment

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

Co-administration With Moderate CYP2C8 Inhibitors

When co-administered with moderate CYP2C8 inhibitors (eg, clopidogrel, deferriox and teriflunomide), reduce the dosing of UPTRAVI® to once daily.

Dosage Strengths

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

Additional Important Safety Information for UPTRAVI® IV

Use UPTRAVI® for injection in patients who are temporarily unable to take oral therapy. Administer UPTRAVI® for injection in patients who are temporarily unable to take oral therapy. Administer UPTRAVI® for injection at a dose that corresponds to the patient’s current dose of UPTRAVI® Tablets (see Table 1 in full Prescribing Information). Administer UPTRAVI® for injection as an 80-minute intravenous infusion.

Adverse Reactions: Infusion-site reactions (infusion-site erythema/redness, pain and swelling) were reported with UPTRAVI® for injection. Additional adverse reactions more frequent compared to placebo (≥3%) seen with UPTRAVI® Tablets are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

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


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MDEDGE.COM/CHESTPHYSICIAN • SEPTEMBER 2023 • 23
BY MARCUS A. BANKS

Generic inhalers for COPD support hold their own

S 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 Indhuf (the combination corticosteroid/long-acting beta2 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.
The study authors compared Wixela’s effectiveness in controlling symptoms of COPD with that of the brand name inhaler Advair Diskus (fluticasone-salmeterol; GlaxoSmithKline), 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 the 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 proliferation 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 based on asthma but not also COPD – 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.

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 FEV₁ and FVC, resulting in the normal ratio of FEV₁ 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 wrote 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.
**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 before initiating SUNOSI. SUNOSI is not a substitute for those 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.

**MORE DAYTIME WAKEFULNESS AT SUNOSIHC.com**

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.

**MOST COMMON ADVERSE REACTIONS**
The most common adverse reactions (incidence ≥5% and greater than placebo) reported more frequently with SUNOSI were headache, nausea, decreased appetite, anxiety, and insomnia.

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

**CONTRAINDICATIONS**

SUNOSI is contraindicated in patients receiving concurrent treatment with monoamine oxidase (MAO) inhibitor, 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 or 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, one or more risk factors, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

**Periodically reassess blood pressure and heart rate with treatment with SUNOSI. If 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 of 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 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 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)**

**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 (75 mg and 150 mg)**
times the MRHD based on mg/m² body surface area. Solriamfetol at ≥4 times the background risks of major birth defects and miscarriage in clinically recognized pregnancies. The estimated background risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, solriamfetol was teratogenic at ≥19 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥0.4 times the human MRHD, it caused fetal skeletal malformation (sight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for maternal and fetal toxicity is approximately 2 times and for maternal toxicity is approximately 5 times the MRHD based on mg/m² body surface area. Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 in an toxicokinetic studies. The safety profile of solriamfetol was characterized by maternal toxicity similar to that observed in humans following oral and IV administration. 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.

LACTATION

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. Preclinical studies have demonstrated 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 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.

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 use of SUNOSI was evaluated in two during the two weeks safety follow-up periods in the Phase 3 study. There was no evidence that abrupt discontinuation 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 is not recommended. Treatment of overdose should be symptomatic and supportive. Instruct patients to contact their healthcare provider if they experience anxiety, agitation, insomnia, akathisia, or signs of psychosis or parkinsonian symptoms.

Instruct patients to contact their healthcare provider if they experience, anxiety, insomnia, akathisia, or signs of psychosis or parkinsonian symptoms.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
<th>Placebo</th>
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<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
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<td>3.5</td>
<td>1</td>
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<td>3.5</td>
<td>3.4</td>
<td>2.9</td>
<td>2.4</td>
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<tr>
<td>HR</td>
<td>n</td>
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<td></td>
<td>1.8</td>
<td>1.7</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Table 6: Blood Pressure and Heart Rate by 24-Hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 6**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
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<td>46</td>
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<td>-3.1</td>
<td></td>
<td>0.5</td>
<td>-2.7</td>
<td>-1.9</td>
<td>-1.9</td>
</tr>
<tr>
<td>HR</td>
<td>n</td>
<td>46</td>
<td>-0.2</td>
<td>0.1</td>
<td></td>
<td>0.3</td>
<td>-0.2</td>
<td>0.4</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg **</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>n</td>
<td>46</td>
<td>0.1</td>
<td>-2.0</td>
<td></td>
<td>0.8</td>
<td>-0.7</td>
<td>-0.8</td>
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</tr>
<tr>
<td>HR</td>
<td>n</td>
<td>46</td>
<td>0.4</td>
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<td>2.4</td>
<td>1.7</td>
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<td>2.6</td>
</tr>
</tbody>
</table>
AI scribes: Just how good are they?

LORRAINE L. JANECZKO, MPH

A ndrea 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.

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.”

“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.

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.
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 conversations with patients 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.”

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