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CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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A risk analysis indicated that 19% of asthma cases could be prevented through improving sleep traits.

Can asthma incidence be reduced by attention to sleep disorders?

BY WALTER ALEXANDER

Early detection and management of sleep disorders could reduce asthma incidence, according to a large-scale prospective study that included nearly half a million participants. The study was published in BMJ Open Respiratory Research (2023. doi: 10.1136/bmjresp-2022-001535).

The population-attributable risk analysis indicated that 19% of asthma cases could be prevented through improving sleep traits. The investigators took into consideration polygenic risk scores (PRSs) for asthma and comprehensive sleep scores encompassing five sleep traits.

Sleep quality is generally recognized as a nongenetic driver of asthma. Poor sleep quality and obstructive sleep apnea have been reported particularly among those with severe disease. In addition, asthma is known to adversely affect sleep duration, sleep quality, napping, and daytime sleepiness.

The researchers suggest that the relationship between sleep and asthma is bidirectional, given that sleep disorders (sleep of short duration, insomnia, evening chronotype ["night owl"], snoring, excessive daytime sleepiness) are associated with specific chronic inflammatory reactions. It has remained unclear, however, whether poor sleep reflects a higher risk of early asthma progression.

ASTHMA // *continued on page 23*

SBRT seen as alternative to surgery for some in early-stage NSCLC

BY MEGAN BROOKS

Stereotactic body radiation therapy (SBRT) and surgery offer nearly equal overall survival rates for patients with stage I and II non–small cell lung cancer (NSCLC), according to population-based data from a German cancer registry.

"From a public health perspective, SBRT is a good therapeutic option in terms of survival, especially for elderly and inoperable patients," noted the study authors, led by Jörg Andreas Müller, MD, department of radiation oncology, University Hospital of Halle, Germany.

The analysis was published online in the journal Strahlentherapie Und Onkologie (2023 Mar 13. doi: 10.1007/s00066-023-02055-z).

Surgery remains the standard of care for early stage NSCLC. However, many patients are not eligible for surgery because of the tumor's location, age, frailty, or comorbidities.

Before the introduction of SBRT, conventional

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Sleep Strategies

Counting electric sheep

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- EXPLORE IN-DEPTH SCIENCE
- HEAR FROM EXPERTS
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References: 1. Flume PA, et al. *Lancet*. 2018;392(10150):880-890. **2.** Dente FL, et al. *Mediators Inflamm*. 2015;2015:642503. **3.** Effah CY, et al. *Front Immunol*. 2021;12:689866. **4.** Rosales C. *J Leukoc Biol*. 2020;108(1):377-396. **5.** Keir HR, Chalmers JD. *Semin Respir Crit Care Med*. 2021;42(4):499-512. **6.** Chalmers JD, et al. *Am J Respir Crit Care Med*. 2017;195(10):1384-1393.

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LUNG CANCER

New insight into timing of combination therapy

BY RANDY DOTINGA
MDedge News

Radiotherapy followed by immunotherapy within 1-12 months – but not sooner or later – may boost progression-free survival in patients with metastatic non–small cell lung cancer, according to a new study. However, patients still fared poorly on average since overall survival remained low and didn't change significantly.

While not conclusive, the new research – released at European Lung Cancer Congress 2023 – offers early insight into the best timing for the experimental combination treatment, study coauthor Yanyan Lou, MD, PhD, an oncologist at Mayo Clinic in Jacksonville, Fla., said in an interview.

The wide availability of radiation therapy could also allow the therapy to be administered even in regions with poor access to sophisticated medical care, she said. "Radiation is a very feasible approach that pretty much everybody in your community can get."

Radiotherapy is typically not added to immunotherapy in patients with non–small cell lung cancer. But "there has been recent interest in the combination: Would tumor necrosis from radiation enhance the immunogenicity of the tumor and thus

COMBINATION *continued on following page*

SBRT

// *continued from page 1*

radiation therapy was the only reasonable option for inoperable patients, with study data showing only a small survival improvement in treated vs. untreated patients.

High-precision, image-guided SBRT offers better tumor control with limited toxicity. And while many radiation oncology centers in Germany adopted SBRT as an alternative treatment for surgery after 2000, few population-based studies evaluating SBRT's impact on overall survival exist.

Using the German clinical cancer registry of Berlin-Brandenburg, Dr. Müller and colleagues assessed SBRT as an alternative to surgery in 558 patients with stage I and II NSCLC, diagnosed between 2000 and 2015.

More patients received surgery than SBRT (74% vs. 26%). Those who received SBRT were younger than those in the surgery group and had better Karnofsky performance status.

Among patients in the SBRT group, median survival was 19 months overall and 27 months in patients over age 75. In the surgery group, median survival was 22 months overall and 24 months in those over 75.

In a univariate survival model of a propensity-matched sample of 292 patients – half of whom received SBRT – survival rates were similar among those who underwent SBRT versus surgery (hazard ratio [HR], 1.2; $P = .2$).

Survival was also similar in the two treatment groups in a T1 subanalysis (HR, 1.12; $P = .7$) as well as in patients over age 75 (HR, 0.86; $P = .5$).

Better performance status scores were associated with improved survival, and higher histological grades and TNM (tumor/nodes/metastases) stages were linked to higher mortality risk. The availability of histological data did not have a significant impact on survival outcomes.

Overall, the findings suggest that SBRT and surgery offer comparable survival outcomes in early-stage NSCLC and "the availability of histological data might not be decisive for treatment planning," Dr. Müller and colleagues said.

Drew Moghanaki, MD, chief of the thoracic oncology service at UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, highlighted the findings on Twitter.

A thoracic surgeon from Germany responded with several concerns about the study, including the use of statistics with univariate modeling and undiagnosed lymph node (N) status.

Dr. Moghanaki replied that these "concerns summarize how we USED to think. It increasingly seems they aren't as important as our teachers once thought they were. As we move into the future we need to reassess the data that supported these recommendations as they seem more academic than patient centered."

The study authors reported no specific funding, and no relevant financial relationships. ■

Genetic analysis indicates a causal link between GERD and IPF

BY TERRY L. KAMPS, PHD

Jezperklauzen/ThinkStock

FROM CHEST ▪ Relationships between 22 unique comorbidities and idiopathic pulmonary fibrosis (IPF) were assessed by a bidirectional Mendelian randomization (MR) approach in a retrospective study. Three of the comorbidities that were examined appeared causally associated with an increased risk of IPF.

Researchers used summary statistics of large-scale genomewide association studies (GWAS) obtained from the IPF Genetics Consortium. For replication, they used data from the Global Biobank Meta-Analysis Initiative (GBMI).

Pulmonary or extrapulmonary illnesses are regularly observed to be comorbidities associated with IPF. Although randomized controlled trials can provide strong deductive evidence of causal relationships between diseases, they are also often subject to inherent practical and ethical limitations. MR is an alternative approach that exploits genetic variants of genes with known function as a means to infer a causal effect of a modifiable exposure on disease and minimizes possible confounding issues from unrelated environmental factors and reverse causation. Bidirectional MR extends the exposure-outcome association analysis of MR to both directions, producing a higher level of evidence for causality, Jiahao Zhu, of the Department of Epidemiology and Health Statistics, Hangzhou, China, and colleagues wrote.

In a study published in the journal *Chest* (2023 Mar 2. doi: 10.1016/j.chest.2023.02.038), the researchers reported on direction and causal associations between IPF and comorbidities, as determined by bidirectional MR analysis of GWAS summary statistics from five studies included in the IPF Genetics Consortium (4,125 patients and 20,464 control participants). For replication, they extracted IPF GWAS summary statistics from the nine biobanks from the GBMI (6,257 patients and 947,616 control participants). All individuals were of European ancestry.

The 22 comorbidities examined for a relationship to IPF were identified through a combination of a PubMed search limited to English-language articles concerning IPF as either an exposure or an outcome and having an available full GWAS summary statistic. The number of patients in these studies ranged from 3,203 for osteoporosis to a maximum of 246,363 for major depressive disorder.

To estimate causal relationships, single-nucleotide polymorphism selection for IPF and each comorbidity genetic instrument were based on a genomewide significance value and were clumped by linkage disequilibrium. Evidence from analysis associating each comorbidity with IPF was categorized as either convincing, suggestive, or weak. Follow-up studies examined the causal effects of measured lung and thyroid variables on IPF and IPF effects on blood pressure variables.

Convincing evidence

The bidirectional MR and follow-up analysis revealed "convincing evidence" of causal relationships between IPF and 2 of the evaluated 22 comorbidities. A higher risk of IPF was associated with gastroesophageal reflux disease (GERD). Importantly, a multivariable MR analysis conditioning for smoking continued to show the causal linkage between GERD and a higher risk of IPF. In contrast, the genetic liability of COPD appeared to confer a protective role, as indicated by an associated decrease in risk for IPF. The researchers suggest that this negative relationship may be caused by their distinct genetic architecture.

Suggestive evidence

"Suggestive evidence" of underlying relationships between IPF and lung cancer or blood pressure phenotype comorbidities was also found with this study. The MR results give support to existing evidence that IPF has a causal effect for a higher lung cancer risk. In contrast, IPF appeared to have a protective effect on hypertension and BP phenotypes. This contrasted with venous thromboembolism (VTE). Bidirectional MR analysis suggested that VTE was more likely to be a cause rather than a consequence of IPF. Evidence suggestive that genetic liability to hypothyroidism could lead to IPF was also found (International IPF Genetics Consortium analysis: $P < .040$; and GBMI analysis: $P < .002$).

The primary strength of the study was the ability of MR design to enhance causal inference, particularly when large cohorts for perspective investigations would be inherently difficult to obtain. Several noted limitations include the fact that causal estimates may not be well matched to observational or interventional studies and there was a low number of single-nucleotide polymorphisms available as genetic instruments for some diseases. In addition, it is unknown whether the results are applicable to ethnicities other than those of European ancestry.

The authors disclosed no relevant financial relationships. ■

COMBINATION *continued from previous page*

enhance the effect of immunotherapy?" oncologist Toby Campbell, MD, of University of Wisconsin–Madison, said in an interview.

Research has indeed suggested that the treatments may have a synergistic effect, he said, and it's clear that "strategies to try and increase immunogenicity are an important area to investigate."

But he cautioned that "we have a long way to go to understanding how immunogenicity works and how the gut microbiome, tumor, immunotherapy, and the immune system interact with one another."

For the new study, researchers retrospectively analyzed cases of 225 patients with metastatic non–small cell lung cancer (male = 56%, median age = 68, 79% adenocarcinoma) who were treated with immunotherapy at Mayo Clinic–Jacksonville from 2011 to 2022. The study excluded those who received targeted therapy or prior concurrent chemoradiotherapy and durvalumab.

The most common metastases were bone and central nervous system types (41% and 25%, respectively). Fifty-six percent of patients received radiotherapy before or during immunotherapy. Another 27% never received radiotherapy, and 17% received it after immunotherapy was discontinued.

Common types of immunotherapy included pembrolizumab (78%), nivolumab (14%), and atezolizumab (12%).

Overall, the researchers found no statistically significant differences in various outcomes between patients who received radiotherapy before or during immunotherapy compared with those who didn't get radiotherapy (progression-free survival: 5.9 vs. 5.5 months, $P = .66$; overall survival: 16.9 vs. 13.1 months, $P = .84$; immune-related adverse events: 26.2% vs. 34.4%, $P = .24$).

However, the researchers found that progression-free survival was significantly higher in one group: those who received radiotherapy 1-12 months before immunotherapy vs. those who received it less than 1 month before (12.6 vs. 4.2 months, hazard ratio [HR], 0.46; 95% confidence interval [CI] 0.26-0.83; $P = .005$) and those who never received radiotherapy (12.6 vs. 5.5 months, HR, 0.56; 95% CI, 0.36-0.89; $P = .0197$).

There wasn't a statistically significant difference in overall survival.

The small number of subjects and the variation in treatment protocols may have prevented the study from revealing a survival benefit, Dr. Lou said.

As for adverse effects, she said a preliminary analysis didn't turn up any.

It's not clear why a 1- to 12-month gap between radiotherapy and immunotherapy may be most effective, she said. Moving forward, "we need validate this in a large cohort," she noted.

In regard to cost, immunotherapy is notoriously expensive. Pembrolizumab, for example, has a list price of $10,897 per 200-mg dose given every 3 weeks, and patients may take the drug for a year or two.

Dr. Campbell, who didn't take part in the new study, said it suggests that research into radiation-immunotherapy combination treatment may be worthwhile.

No funding was reported. The study authors and Dr. Campbell reported no disclosures. ■

SUNOSI® (solriamfetol) IV
75, 150 mg tablets

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

ARE YOUR PATIENTS READY TO

PULL AN ALL-DAYER?[1]

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

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

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

82% **Increase in minutes of wakefulness**
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Co-primary endpoint: LS mean change from baseline to week 12 in mean sleep latency during the MWT was 11.0 minutes for SUNOSI 150 mg vs 0.2 minutes for placebo.[2]

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

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

90% **Of patients reported feeling better**
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The most common adverse reactions
(incidence ≥5% and greater than placebo) reported more frequently with SUNOSI were headache, nausea, decreased appetite, anxiety, and insomnia[1]

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

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

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INDICATION

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

LIMITATIONS OF USE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

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

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

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

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

Psychiatric Symptoms

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

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

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

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

MOST COMMON ADVERSE REACTIONS

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

Please see Brief Summary of full Prescribing Information on the following pages.

SUN HCP aISI 05/2022

†As seen in a 12-week randomized, multicenter, double-blind, placebo-controlled, parallel-group study of adult patients with OSA (n=459).[1,2]
‡Median percent change from baseline to week 12 was calculated using the last observation carried forward and was not adjusted for covariates used in these primary endpoints. Seven patients were missing from baseline values and were not included in the calculations.[1,2,3]
§The percentage of patients improved on the PGIC scale includes those who reported very much, much, and minimal improvement.[2]

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

axsome

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

INDICATIONS AND USAGE

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

Limitations of Use

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

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

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

General Administration Instructions

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

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

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

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

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

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

Psychiatric Symptoms

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

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

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

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

ADVERSE REACTIONS

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

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

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

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

Most Common Adverse Reactions

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

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

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

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

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

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

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

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

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

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

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

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

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

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

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

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

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

*In OSA only.

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

Adverse Reactions Resulting in Discontinuation of Treatment

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

Increases in Blood Pressure and Heart Rate

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

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

Drugs that Increase Blood Pressure and/or Heart Rate

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

Dopaminergic Drugs

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Data

Animal Data

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

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

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

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

LACTATION

Risk Summary

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

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

Clinical Considerations

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

Pediatric Use

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

Geriatric Use

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

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

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

Renal Impairment

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

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

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

Dependence

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

OVERDOSAGE

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Consult with a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION

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

Potential for Abuse and Dependence

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

Primary OSA Therapy Use

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

Blood Pressure and Heart Rate Increases

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

Psychiatric Symptoms

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

Lactation

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

For more information, visit www.SUNOSI.com

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Should you recommend e-cigs to help patients quit?

BY KERRIE RUSHTON

HAZEMMKAMAL/Getty Images

In 2014, after smoking cigarettes for 40 years, Kati Markowitz decided to switch to vaping. She had heard the newer electronic cigarettes might be less harmful. And, at the time, she said, she wasn't aware of other options to try to quit smoking.

For 7 years, she vaped every day.

Then Ms. Markowitz received news she'd hoped never to hear: She had lung cancer. A nodule detected in a CT scan had grown. She was scheduled for treatment – the removal of an entire lobe from her right lung. But first, she said, her surgeon told her she had to quit vaping, which reduces the risk for postoperative complications and enables a healthy recovery.

Ms. Markowitz had thought switching to vaping would be less harmful than smoking cigarettes. Now, she no longer believes that's true.

"Did I fool myself by hoping to get lucky and not have any bad repercussions? Yes, I did," Ms. Markowitz said, adding that she wonders if vaping contributed to her lung cancer or if she'll experience other negative health effects in the future.

Researchers are divided on if e-cigarettes are as effective in smoking cessation as other nicotine replacement therapies like gums and lozenges. They also say more research is needed on the long-term health impacts of vaping to ultimately determine if vapes are a safe replacement for cigarettes.

"There is scientific research to support vaping as a cessation tool, but we wouldn't use it as a first line of defense because we still need longitudinal studies to understand the long-term risk of e-cigarettes," said Monica Hanna, MPH, assistant director of the Nicotine and Tobacco Recovery Program at RWJBarnabas Health's Institute for Prevention and Recovery, Eatontown, N.J. "We also need research to understand exactly how we could use e-cigarettes as a cessation device."

Vaping to quit

The first prototypes of e-cigarettes were developed in the 1930s, although what are now known as vapes weren't sold by manufacturers until the 2000s in the United States, following an invention by a former health official in China. The vape was touted by both researchers and manufacturers over the years of development as a way to quit smoking cigarettes.

The Consumer Advocates for Smoke-Free Alternatives Association, a nonprofit group that supports vaping and accepts donations from the e-cigarette industry, has compiled more than 13,000 testimonials from people who say vaping helped them give up smoking.

Studies show mixed results that using vapes can help traditional smokers quit.

A November 2022 Cochrane review showed a "high certainty of evidence that people are more likely to stop smoking traditional cigarettes for at least 6 months using e-cigarettes, or 'vapes,' than using nicotine replacement therapies, such as patches and gums." The meta-analysis examined 78 studies with more than 22,000 participants. And a 2019 study with 886 participants, published in the New England Journal Medicine (2019 Feb 14. doi: 10.1056/NEJMoa1808779), found smokers who tried vaping to quit were twice as likely after a year to have stopped smoking cigarettes than those who used nicotine replacement therapy.

"In terms of the global research, it's pretty clear that vaping can help smokers quit," said Peter Shields, MD, a professor in the department of internal medicine at The Ohio State University College of Medicine, Columbus, who specializes in the treatment of lung cancer.

But a 2013 study published in the Lancet (doi: 10.1016/S0140-6736[13]61842-5), and another from the Lancet in 2019 (doi: 10.1016/S2213-2600[19]30269-3), found only a modest improvement in cessation outcomes when participants used e-cigarettes paired with patches, compared with patches alone.

"For a disruptive technology that was supposed to end combustible tobacco use, there seems very little large-scale disruption," said Thomas Eissenberg, PhD, co-director of Virginia Commonwealth University's Center for the Study of Tobacco Products, Richmond.

Michael Joseph Blaha, MD, MPH, director of clinical research at the Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, pointed to research that shows a portion of people who start vaping to quit smoking end up using both products – or become so-called "dual" users.

"No one should say that e-cigarettes are safe, but compared to cigarettes, the data is consistent: They are not as harmful, and when a smoker switches, it's better for them."

"I do think there is fairly high-quality evidence that vaping can lead to more cessation, but at the tradeoff of more long-term dual users and more overall nicotine addiction," Dr. Blaha said. "Vaping remains a third-line clinical tool after nicotine replacement therapy and FDA-approved cessation medications."

The U.S. Food and Drug Administration (FDA) has not approved any e-cigarette or vaping device for smoking cessation, like it has for patches and gums, which means manufacturers cannot market their products as helping tobacco smokers quit.

"There is potential for vaping as a cessation device, but the evidence so far is too small to say for sure that vaping is a more effective tool than others for combustible tobacco cessation," Ms. Hanna, the tobacco cessation specialist, said.

Reducing harm?

Vapes have also been touted as a boon to individual and public health since cigarette smoking is the leading cause of preventable disease and disability in the United States, responsible for more than 480,000 deaths per year in the U.S., according to the U.S. Centers for Disease Control and Prevention (CDC).

Quitting smoking lowers the risk of developing various cancers, heart disease, stroke, and other serious diseases. The aim of nicotine replacement therapy is to help smokers quit by gradually providing the body with smaller doses of nicotine over time, without exposing the body to toxic chemicals found in cigarettes.

"No one should say that e-cigarettes are safe, but compared to cigarettes, the data is consistent: They are not as harmful, and when a smoker switches, it's better for them," Dr. Shields said. "Like with other nicotine replacement therapies, if there is a risk that someone stops vaping and returns to smoking, I would rather have them as long-term vapers since it is generally considered to be less harmful than combustible tobacco."

The FDA has allowed a handful of companies to market their electronic nicotine delivery systems as safer than traditional cigarettes by gaining approval through the Premarket Tobacco Product Applications (PMTA) process. In 2021, the agency announced its first PMTA authorization of an electronic cigarette to R.J. Reynolds for three of its tobacco-flavored vaping products. Regulators approved more products from three additional companies in 2022.

But the FDA has also denied others, including two products in 2023 from R.J. Reynolds, stating that, "the applications lacked sufficient evidence to demonstrate that permitting the marketing of the products would be appropriate for the protection of the public health."

Questions remain among some researchers on the effects of vaping if used long term. Data on the health effects of vapes are just beginning to emerge and are mainly from studies of animals or cells. Measuring health effects among vape users will entail decades more of study, since

Americans only gained access to the products in the 2000s.

Dr. Eissenberg said vaping likely does not cause the same diseases as cigarette smoking, but that does not mean they are not harmful. Ingredients found in e-cigarettes, such as heated propylene glycol, vegetable glycerin, and flavors, have only been used as food ingredients. The potential diseases caused by vapes are still unknown, because inhaling these heated ingredients is new. He also said he had "no issue" with an adult smoker vaping to help them quit smoking – as long they do so for a short period.

"I am very concerned that long-term use in adults could lead to considerable disease and death," Dr. Eissenberg said. "Simply put, the human lung evolved for one purpose: gas exchange of oxygen in, carbon dioxide out. Anything else that enters the lung is a challenge to the organ."

But Kenneth Warner, PhD, dean emeritus at the University of Michigan School of Public Health, Ann Arbor, said breaking the addiction to traditional cigarettes could reduce high rates of lung cancer in lower-income communities where rates of smoking are comparatively high.

About three times as many Americans smoked (12.6%) than vaped (4.7%) in 2021, but those who live in households with lower incomes are more likely to smoke. According to the CDC, use of tobacco is higher among adults who were uninsured (27.3%) or who had Medicaid coverage (28.6%) than among those with private insurance (16.4%). People with annual family incomes of less than $12,500 also are more likely to be diagnosed with lung cancer than those with family incomes of $50,000 or more. Public health researchers have attributed those disparities in part to higher rates of smoking in lower-income households.

Dr. Warner said many lower-income and other Americans may never quit smoking cigarettes because they believe making the switch to e-cigarettes will not benefit their health. A 2022 study, published in the American Journal of Preventive Medicine (2022. doi: 10.1016/j.amepre.2022.03.019), found that the percent of Americans who thought vaping was more harmful than smoking quadrupled between 2018 and 2020, from 6.8% to 28.3%. A third of respondents thought vaping was as harmful as smoking.

"We've convinced a large percentage of the American public that vaping is as harmful as smoking when it could be helping people quit smoking," Dr. Warner said. "People are dying right now."

Ms. Markowitz did quit smoking by taking up vaping. But now she questions if her lung cancer prognosis would have been delayed, or even avoided, if she'd tried a traditional method like a lozenge or gum instead. She vaped once an hour for most of her 7 years of using the devices.

"For people who are trying to stop smoking, I would recommend something like the patch instead," Ms. Markowitz said.

The Consumer Advocates for Smoke-Free Alternatives receives funding from the vaping industry.

Dr. Blaha, Dr. Eissenberg, Ms. Hanna, Dr. Shields, and Dr. Warner reported no funding from the tobacco or e-cigarette industry. Dr. Blaha and Dr. Warner receive tobacco-related funding from the FDA. Dr. Warner is a member of the FDA's Tobacco Products Scientific Advisory Committee. ■

CORONAVIRUS

Nasal COVID treatment shows early promise against multiple variants

BY DAMIAN MCNAMARA, MA
MDedge News

An antiviral therapy in early development has the potential to prevent COVID-19 infections when given as a nasal spray as little as 4 hours before exposure. It also appears to work as a treatment if used within 4 hours after infection inside the nose, new research reveals.

Known as TriSb92 (brand name Covidin, from drugmaker Pandemblock Oy in Finland), the viral inhibitor also appears effective against all coronavirus variants of concern, neutralizing even the Omicron variants BA.5, XBB, and BQ.1.1 in laboratory and mice studies.

Unlike a COVID vaccine that boosts a person's immune system as protection, the antiviral nasal spray works more directly by blocking the virus, acting as a "biological mask in the nasal cavity," according to the biotechnology company set up to develop the treatment.

The product targets a stable site on the spike protein of the virus that is not known to mutate. This same site is shared among many variants of the COVID virus, so it could be effective against future variants as well, researchers noted.

"In animal models, by directly inactivating the virus, TriSb92 offers immediate and robust protection" against coronavirus infection and severe COVID, said Anna R. Mäkelä, PhD, lead author of the study and a senior scientist in the department of virology at the University of Helsinki.

The study was published online March 24 in Nature Communications (2023. doi: 10.1038/s41467-023-37290-6).

A potential first line of defense

Even in cases where the antiviral does not prevent coronavirus infection, the treatment could slow infection. This could happen by limiting how much virus could replicate early in the skin inside the nose and nasopharynx (the upper part of the throat), said Dr. Mäkelä, who is also CEO of Pandemblock Oy, the company set up to develop the product.

"TriSb92 could effectively tip the balance in favor of the [the person] and thereby help to reduce the risk of severe COVID-19 disease," she said. The antiviral also could offer an alternative to people who cannot or do not respond to a vaccine.

"Many elderly people as well as individuals who are immunodeficient for various reasons do not respond to vaccines and are in the need of other protective measures," said Kalle Saksela, MD, PhD, senior author of the study and a virologist at the University of Helsinki.

The product targets a stable site on the spike protein of the virus that is not known to mutate. This same site is shared among many variants of the COVID virus, so it could be effective against future variants.

Multiple doses needed?

TriSb92 is "one of multiple nasal spray approaches but unlikely to be as durable as effective nasal vaccines," said Eric Topol, MD, a professor of molecular medicine and executive vice president of Scripps Research in La Jolla, Calif. Dr. Topol is also editor-in-chief of Medscape, WebMD's sister site for medical professionals.

"The sprays generally require multiple doses per day, whereas a single dose of a nasal vaccine may protect for months," he said.

"Both have the allure of being variant-proof," Dr. Topol added.

Thinking small

Many laboratories are shifting from treatments using monoclonal antibodies to treatments using smaller antibody fragments called "nanobodies" because they are more cost-effective and are able to last longer in storage, Dr. Mäkelä and colleagues noted.

Several of these nanobodies have shown promise against viruses in cell culture or animal models, including as an intranasal preventive treatment for SARS-CoV-2.

One of these smaller antibodies is being developed from llamas for example; another comes

NASAL *continued on following page*

High-dose prophylactic anticoagulation benefits patients with COVID-19 pneumonia

BY HEIDI SPLETE
MDedge News

Patients with hypoxemic COVID-19 pneumonia are at increased risk of thrombosis and anticoagulation-related bleeding; therefore, data to identify the lowest effective anticoagulant dose are needed, wrote Vincent Labbé, MD, of Sorbonne University, Paris, and colleagues.

Previous studies of different anticoagulation strategies for noncritically ill and critically ill patients with COVID-19 pneumonia have shown contrasting results, but some institutions recommend a high-dose regimen in the wake of data showing macrovascular thrombosis in patients with COVID-19 who were treated with standard anticoagulation, the authors wrote. However, no previously published studies have compared the effectiveness of the three anticoagulation strategies: high-dose prophylactic anticoagulation (HD-PA), standard-dose prophylactic anticoagulation (SD-PA), and therapeutic anticoagulation (TA), they said.

In the open-label Anticoagulation COVID-19 (ANTICOVID) trial, published in JAMA Internal Medicine (2023 Mar 22. doi: 10.1001/jamainternmed.2023.0456), the researchers identified 334 consecutively hospitalized adults aged 18 years and older being treated for hypoxemic COVID-19 pneumonia in 23 centers in France between April 2021 and December 2021.

The patients were randomly assigned to SD-PA (116 patients), HD-PA (111 patients), and TA (112 patients) using low-molecular-weight heparin for 14 days, or until either hospital discharge or weaning from supplemental oxygen for 48 consecutive hours, whichever outcome occurred first. The HD-PA patients received two times the SD-PA dose. The mean age of the patients was 58.3 years, and approximately two-thirds were men.

The primary outcomes were all-cause mortality and time to clinical improvement (defined as the time from randomization to a 2-point improvement on a 7-category respiratory function scale).

The secondary outcome was a combination of safety and efficacy at day 28 that included a composite of thrombosis (ischemic stroke, noncerebrovascular arterial thrombosis, deep venous thrombosis, pulmonary artery thrombosis, and central venous catheter–related deep venous thrombosis), major bleeding, or all-cause death.

For the primary outcome, results were similar among the groups; HD-PA had no significant benefit over SD-PA or TA. All-cause death rates for SD-PA, HD-PA, and TA patients were 14%, 12%, and 13%, respectively. The time to clinical improvement for the three groups was approximately 8 days, 9 days, and 8 days, respectively. Results for the primary outcome were consistent across all prespecified subgroups.

However, HD-PA was associated with a significant fourfold reduced risk of de novo thrombosis compared with SD-PA (5.5% vs. 20.2%) with no observed increase in major bleeding. TA was not associated with any significant improvement in primary or secondary outcomes compared with HD-PA or SD-PA. The current study findings of no improvement in survival or disease resolution in patients with a higher anticoagulant dose reflects data from previous studies, the researchers wrote in their discussion. "Our study results together with those of previous RCTs support the premise that the role of microvascular thrombosis in worsening organ dysfunction may be narrower than estimated," they said.

HD-PA was associated with a significant fourfold reduced risk of de novo thrombosis compared with SD-PA (5.5% vs. 20.2%) with no observed increase in major bleeding.

The findings were limited by several factors including the open-label design and the relatively small sample size, the lack of data on microvascular (vs. macrovascular) thrombosis at baseline, and the predominance of the Delta variant of COVID-19 among the study participants, which may have contributed to a lower mortality rate.

However, given the significant reduction in de novo thrombosis, the results support the routine use of HD-PA in patients with severe hypoxemic COVID-19 pneumonia, they concluded.

Over the course of the COVID-19 pandemic, "Patients hospitalized with COVID-19 manifested the highest risk for thromboembolic complications, especially patients in the intensive care setting," and early reports suggested that standard prophylactic doses of anticoagulant therapy might be insufficient to prevent thrombotic events, Richard C. Becker, MD, of the University of Cincinnati, and Thomas L. Ortel, MD, of Duke University, Durham, N.C., wrote in an accompanying editorial (JAMA Intern Med. 2023 Mar 22. doi: 10.1001/jamainternmed.2023.0625).

"This is the first study that specifically compared a standard, prophylactic dose of low-molecular-weight heparin to a 'high-dose' prophylactic regimen and to a full therapeutic dose regimen," Dr. Ortel said in an interview.

"Given the concerns about an increased thrombotic risk with prophylactic dose anticoagulation, and the potential bleeding risk associated with a full therapeutic dose of anticoagulation, this approach enabled the investigators to explore the efficacy and safety of an intermediate dose between these two extremes," he said.

In the current study, "It was notable that the primary driver of the improved outcomes with the 'high-dose' prophylactic regimen reflected the fourfold reduction in macrovascular thrombosis, a finding that was not observed in other studies investigating anticoagulant therapy in hospitalized patients with severe COVID-19," Dr. Ortel told this news organization. "Much initial concern about progression of disease in patients hospitalized with severe COVID-19 focused on the role of microvascular thrombosis, which appears to be less important in this process, or, alternatively, less responsive to anticoagulant therapy."

The clinical takeaway from the study, Dr. Ortel said, is the decreased risk for venous thromboembolism with a high-dose prophylactic anticoagulation strategy compared with a standard-dose prophylactic regimen for patients hospitalized with hypoxemic COVID-19 pneumonia, "leading to an improved net clinical outcome."

"Additional research is needed to determine whether a higher dose of prophylactic anticoagulation would be beneficial for patients hospitalized with COVID-19 pneumonia who are not in an intensive care unit setting," Dr. Ortel said. Studies are also needed to determine whether therapeutic interventions are equally beneficial in patients with variants other than Delta.

The study was supported by LEO Pharma. Dr. Labbé disclosed grants from LEO Pharma. Dr. Becker and Dr. Oriel reported no relevant disclosures. ■

NASAL *continued from previous page*

from experiments with yeast to develop synthetic nanobodies; and in a third case, researchers isolated nanobodies from llamas and from mice and showed they could neutralize the SARS-CoV-2 virus.

These nanobodies and TriSb92 target a specific part of the coronavirus spike protein called the receptor-binding domain (RBD). The RBD is where the coronavirus attaches to cells in the body. These agents essentially trick the virus by changing the structure of the outside of cells, so they look like a virus has already fused to them. This way, the virus moves on.

Key findings

The researchers compared mice treated with TriSb92 before and after exposure to SARS-CoV-2. When given in advance, none of the treated mice had SARS-CoV-2 RNA in their lungs, while untreated mice in the comparison group had "abundant" levels.

Other evidence of viral infection showed similar differences between treated and untreated mice in the protective lining of cells called the epithelium inside the nose, nasal mucosa, and airways.

Similarly, when given 2 or 4 hours after SARS-CoV-2 had already infected the epithelium, TriSb92 was linked to a complete lack of the virus's RNA in the lungs.

It was more effective against the virus, though, when given before infection rather than after, "perhaps due to the initial establishment of the infection," the researchers noted.

The company led by Dr. Mäkelä is now working to secure funding for clinical trials of TriSb92 in humans. ■

COPD

Dupilumab moves forward as possible treatment

BY HEIDI SPLETE
MDedge News

Dupilumab, a fully human monoclonal antibody, significantly improved quality of life and respiratory symptoms compared with placebo in a phase 3 trial of more than 900 adults with uncontrolled chronic obstructive pulmonary disease (COPD).

In the study, known as the BOREAS trial, dupilumab met its primary and secondary endpoints, with a significant reduction compared with placebo in exacerbations for adults with COPD that was uncontrolled despite use of the maximal standard-of-care inhaled therapy (triple therapy), according to a press release from manufacturers Regeneron and Sanofi.

Dupilumab, which inhibits the signaling of the interleukin-4 (IL-4) and interleukin-13 (IL-13) pathways, is currently approved in multiple countries as a treatment for certain patients with conditions including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, or prurigo nodularis in different age groups.

The drug is not an immunosuppressant, and would be the first biologic approved for COPD, according to the manufacturers.

In the BOREAS trial, 468 adults with COPD who were current or former smokers aged 40-80 years were randomized to dupilumab and 471 to placebo; both groups continued to receive maximal standard of care.

Over 52 weeks, patients in the dupilumab group experienced a 30% reduction in moderate to severe COPD exacerbations compared with placebo ($P = .0005$).

In addition, patients treated with dupilumab met the key secondary endpoints of significant improvement in lung function from baseline to 12 weeks compared with placebo (160 mL vs. 77 mL, $P < .0001$); this difference persisted at 52 weeks ($P = .0003$).

Dupilumab also met endpoints for improvement in patient-reported health-related quality of life based on the St. George's Respiratory Questionnaire and a reduction in the severity of respiratory symptoms of COPD based on the Evaluation Respiratory Symptoms: COPD Scale, according to the companies' statement.

The results represent a previously unreported magnitude of improvement for COPD patients treated with a biologic, principal investigator George D. Yancopoulos, MD, said in the statement.

"These results also validate the role type 2 inflammation plays in driving COPD in these patients, advancing the scientific community's understanding of the underlying biology of this disease," Dr. Yancopoulos added.

The safety results in the BOREAS trial were generally consistent with the known safety profile of Dupixent in its approved indications. Overall adverse event rates were similar for dupilumab and placebo patients (77% and 76%, respectively) and the overall safety profiles were consistent with the currently approved dupilumab indications, according to the manufacturers.

The adverse events that were more common in dupilumab patients compared with placebo patients were headache (8.1% vs. 6.8%), diarrhea (5.3% vs. 3.6%), and back pain (5.1% vs. 3.4%).

Adverse events leading to deaths were similar between the groups (1.7% in placebo patients and 1.5% in dupilumab patients).

Complete safety and efficacy results from the BOREAS trial are scheduled to be presented in a future scientific forum, and a second phase 3 trial of dupilumab for COPD, known as NOTUS, is ongoing, with data expected in 2024, according to the manufacturers.

The BOREAS trial was sponsored by Sanofi and Regeneron Pharmaceuticals. ■

INTERSTITIAL LUNG DISEASE

Tofacitinib may have protective effect against ILD in RA

BY LUCY HICKS

Patients with rheumatoid arthritis treated with tofacitinib (Xeljanz) were 69% less likely to develop interstitial lung disease (ILD), compared with those treated with adalimumab (Humira), according to a new retrospective study.

About 10% of patients with RA develop ILD, but data on how different biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) may affect the risk of developing ILD are lacking, the authors wrote. Identifying treatments that may have protective effects could be useful when prescribing treatments for patients with RA who are at higher risk for ILD, first author Matthew C. Baker, MD, clinical chief in the division of immunology and rheumatology at Stanford (Calif.) University, said in an interview.

In the analysis, published in JAMA Network Open (2023 Mar 20. doi: 10.1001/jamanetworkopen.2023.3640), researchers used the Optum Clinformatics Data Mart to identify claims data for patients with RA who were taking b/tsDMARDs from December 2003 to December 2019. Patients were excluded if they had a preexisting diagnosis of ILD or if they had less than 1 year of continuous enrollment in the data set.

The researchers identified 28,559 patients with RA who were treated with adalimumab (13,326), abatacept (Orencia; 5,676), rituximab (Rituxan; 5,444), tocilizumab (Actemra; 2,548), and tofacitinib (1,565). More than three-fourths of patients were female (78%), and their average age was 55.6 years old. During the study period, 276 developed ILD. An adjusted model showed a 69% lower incidence of ILD in patients treated with tofacitinib, compared with those treated with adalimumab (adjusted hazard ratio [aHR], 0.31; 95% confidence interval [CI], 0.12-0.78; $P = .009$). An additional sensitivity analysis showed a similar reduction in ILD risk in those taking tofacitinib, compared with adalimumab (aHR, 0.32; 95% CI, 0.13-0.82; $P < .001$). There was no significant difference in risk of developing ILD in the abatacept, rituximab, or tocilizumab groups, compared with adalimumab.

> *"Patients who generally looked similar with RA, but were given different treatments, had different risks of developing ILD."*

"Patients who generally looked similar with RA, but were given different treatments, had different risks of developing ILD," Dr. Baker said. "Based on what we found, most of the biologic therapies had similar rates of developing ILD, but the JAK [Janus kinase] inhibitor tofacitinib had a reduced risk." Additional research is necessary to see if tofacitinib shows the same benefit in prospective studies, he said.

"Even though this wasn't a clinical trial, it suggested that one of the medications that we use to treat RA could potentially prevent the development of ILD," Elizabeth Volkmann, MD, codirector of the Connective Tissue Disease-Related Interstitial Lung Disease Program at the University of California, Los Angeles, told this news organization. She was not involved with the study.

With retrospective studies, it is difficult to account for all confounding factors, even with adjusted models, she said. For example, the authors did not have data on patients' history of smoking, a known risk factor for ILD that could have affected which treatment was selected, they acknowledged. The tofacitinib group was also smaller than other treatment groups, which "may have contributed to a small number of events," the authors wrote. "However, the follow-up time was similar across all groups, and we used Cox proportional hazard models to investigate the association between time-to-event and use of treatment while controlling for the other baseline characteristics."

Both Dr. Baker and Dr. Volkmann agreed that future research could also investigate whether tofacitinib prevents the progression of ILD in patients with RA who already have the lung condition. "That's never been looked at before," Dr. Volkmann said.

Dr. Baker and a coauthor received support for this work from grants from the National Institutes of Health. Dr. Baker and Dr. Volkmann report no relevant financial relationships. ■

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.

#1 PRESCRIBED RESPIRATORY BIOLOGIC
for eosinophilic asthma*[1]

FOR PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA, YOU CAN REDUCE[2]:

~~EOS~~INOPHILS

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.

Results May Vary.

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

*Based on IQVIA data from July 2021 to June 2022.[1]

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

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

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

See Study Designs on next page.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

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

MOVE FORWARD WITH

Fasenra®
(benralizumab) Subcutaneous Injection 30 mg

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

INDICATION

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

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

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

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

STUDY DESIGNS

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

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

ZONDA (Trial 3)[7]

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

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

References: 1. Data on File, US-68618, AZPLP. **2.** FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2021. **3.** Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med.* 2016;111:21-29. **4.** Data on File, REF-28001, AZPLP. **5.** Bleecker ER, FitzGerald JM, Chanez P, et al; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting $ß_2$-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115-2127. **6.** FitzGerald JM, Bleecker ER, Nair P, et al; CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2128-2141. **7.** Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med.* 2017;376(25):2448-2458.

AstraZeneca

Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

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

Limitations of use:

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

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

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

General Administration Instructions

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

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

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

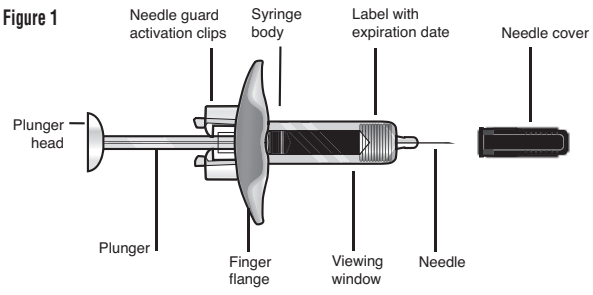
Autoinjector (FASENRA PEN™)

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

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

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

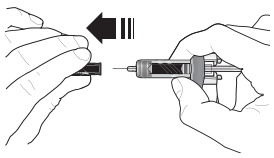
Figure 1



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

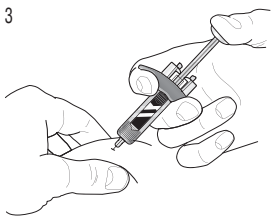
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



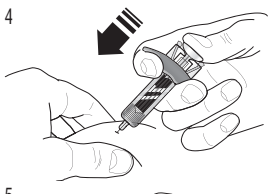
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without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

3



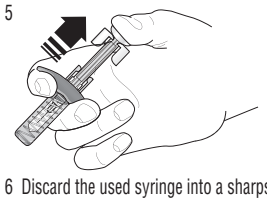
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



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

5



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

6 Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

28-Week Trial

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

Injection site reactions

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

Immunogenicity

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

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

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

Postmarketing Experience

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

Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

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

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Pregnancy Exposure Registry

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

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NETWORKS

Preventing sepsis readmission; new lung donor score; tele-rehab; and more ...

CRITICAL CARE NETWORK
Sepsis/Shock Section

We need more efforts to prevent sepsis readmissions

Sepsis remains the commonest diagnosis for hospital stays in the United States and the top hospital readmission diagnosis, with aggregate costs of $23.7 billion in 2013 (https://datatools.ahrq.gov/hcup-fast-stats; Kim H, et al. *Front Public Health*. 2022;10:882715; Torio C, Moore B. 2016. HCUP Statistical Brief #204).

Since 2013, the Hospital Readmissions Reduction Program (HRRP) adopted pneumonia as a readmission measure, and in 2016, this measure included sepsis patients with pneumonia and aspiration pneumonia. For 2023, the Centers for Medicare and Medicaid Services (CMS) suppressed pneumonia as a readmission measure due to COVID-19's significant impact (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program). Though sepsis is not a direct readmission measure, it could be one in the future. Studies found higher long-term mortality for patients with sepsis readmitted for recurrent sepsis (Pandolfi F, et al. *Crit Care*. 2022;26[1]:371; McNamara JF, et al. *Int J Infect Dis*. 2022;114:34).

A systematic review showed independent risk factors predictive of sepsis readmission: older age, male gender, African American and Asian ethnicities, higher baseline comorbidities, and discharge to a facility. In contrast, sepsis-specific risk factors were extended-spectrum beta-lactamase gram-negative bacterial infections, increased hospital length of stay during initial admission, and increased illness severity (Shankar-Hari M, et al. *Intensive Care Med*. 2020;46[4]:619; Amrollahi F, et al. *J Am Med Inform Assoc*. 2022;29[7]:1263; Gadre SK, et al. *Chest*. 2019;155[3]:483).

McNamara and colleagues found that patients with gram-negative bloodstream infections had higher readmission rates for sepsis during a 4-year follow-up and had a lower 5-year survival rates (*Int J Infect Dis*. 2022;114:34). Hospitals can prevent readmissions by strengthening antimicrobial stewardship programs to ensure appropriate and adequate treatment of initial infections. Other predictive risk factors for readmission are lower socioeconomic status (Shankar-Hari M, et al. *Intensive Care Med*. 2020;46[4]:619), lack of health insurance, and delays seeking medical care due to lack of transportation (Amrollahi F, et al. *J Am Med Inform Assoc*. 2022;29[7]:1263).

Sepsis readmissions can be mitigated by predictive analytics, better access to health care, establishing post-discharge clinic follow-ups, transportation arrangements, and telemedicine. More research is needed to evaluate sepsis readmission prevention.

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DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK
Lung Transplant Section

In March 2023, the Composite Allocation Score (CAS) will replace the Lung Allocation Score (LAS) for matching donor lungs to transplant candidates in the United States. The

Previously, candidates were subjected to strict geographical distributions within a 250-nautical-mile radius, which frequently resulted in those with lower LAS obtaining a transplant.

LAS was implemented in 2005 to improve lung organ utilization. Its score was determined by two main factors: (1) risk of 1-year waitlist mortality and (2) likelihood of 1-year post-transplant survival, with the first factor having twice the weight. However, LAS did not account for candidate biology attributes, such as pediatric age, blood type, allosensitization, or height. Long-term survival outcomes under LAS may be reduced, given the greater emphasis on waitlist mortality. Candidates were also subjected to strict geographical distributions within a 250-nautical-mile radius, which frequently resulted in those with lower LAS obtaining a transplant. CAS differs from the LAS in that it assigns an allocation score in a continuous distribution based on the following factors: medical urgency, expected survival benefit following transplant, pediatric age, blood type, HLA antibody sensitization, candidate height, and geographical proximity to the donor organ. Each factor has a specific weight, and because donor factors contribute to CAS, a candidate's score changes with each donor-recipient match run. Continuous distribution removes hard geographical boundaries and aims for more equitable organ allocation. To understand how allocation might change with CAS, Valapour and colleagues created various CAS scenarios using data from individuals on the national transplant waiting list (*Am J Transplant*. 2022;22[12]:2971).

They found that waitlist deaths decreased by 36%-47%. This effect was greatest in scenarios where there was less weight on placement efficiency (ie, geography) and more weight on post-transplant outcomes. Transplant system equity also improved in their simulation models. It will be exciting to see how candidate and recipient outcomes are affected once CAS is implemented.

Gloria Li, MD
Member-at-Large
Keith Wille, MD, MSPH
Member-at-Large

Reference

1. United Network for Organ Sharing. www.unos.org.

DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK
Pulmonary Physiology and Rehabilitation Section

Emerging role of tele-rehab: Efficacy and challenges

Pulmonary rehabilitation (PR) is an essential component of the management of chronic pulmonary disease. Interest in alternate PR delivery methods has grown in recent years. The official workshop report of the American Thoracic Society (Holland AE, et al. *Ann Am Thorac Soc*. 2021;18[5]:e12) identified 13 essential components of PR in response to new program models. They encompass patient assessment, program content, method of delivery, and quality assurance, and serve as a guide for successful implementation of emerging programs.

A recent study reported significant improvement in COPD Assessment Test (CAT) scores after PR in both in-person (n=383) and virtual programs (n=171). Similar improvements were found in health outcomes, attendance, and drop-out rate (Huynh VC, et al. *Chest*. 2023;163[3]:529). Another concurrent 3-year prospective study enrolled COPD patients in standard PR (n=89) or community based tele-PR (n=177) at seven tele-sites and one standard site (Alwakeel AJ, et al. *Ann Am Thorac Soc*. 2022;19[1]:39).

Dr. Zeba

This study established the accessibility, feasibility, and safety of a community based tele-PR program and noted no differences between groups in 6-minute walk test or CAT score improvement. On follow-up, only tele-PR participants had persistent improvements of CAT scores beyond 1 month after completion.

Ongoing challenges with tele-PR include standardization of programs and of initial clinical evaluations that determine eligibility for them. Patients on home oxygen and those with exercise desaturation are often excluded, but they have the most potential for improvement. Studies are needed to determine the characteristics of patients who would benefit most from non-traditional models of PR.

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SLEEP MEDICINE NETWORK
Respiratory-related Sleep Disorders Section

Home sleep apnea test: Peripheral arterial tonometry

OSA is associated with serious health consequences and increased health care utilization (Kapur V, et al. *Sleep*. 1999:22[6]:749).

Polysomnography (PSG) is the gold standard for diagnosis, but is expensive, cumbersome, and inconsistently accessible. Home sleep apnea test (HSAT) devices provide a cost effective, convenient method to diagnose OSA and are non-inferior to PSG when considering treatment outcomes in uncomplicated adults with suggestive symptoms (Kapur VK, et al. *J Clin Sleep Med*. 2017;13[3]:479; Skomro RP, et al. *Chest*. 2010;138[2]:257).

Utilization of HSAT devices has increased in recent years, partly due to the COVID-19 pandemic and limitations in insurance reimbursement for PSG as the initial diagnostic test. But while there are benefits to home testing with respect to convenience and increased access, we must take the clinical context into account.

Peripheral arterial tonometry (PAT) is a commonly used HSAT technology, which measures peripheral arterial vascular tone using plethysmography at the fingertip. It has a sensitivity of 80% and specificity of 83% for detecting OSA in patients without significant comorbidities and high pretest probability of OSA compared to PSG (Ward KL, et al. *J Clin Sleep Med*. 2015;11[4]:433). But PAT has also been criticized for lacking diagnostic accuracy, particularly when including patients with mild OSA in analysis (Ichikawa M, et al. *J Sleep Res*. 2022;31[6]:e13682).

It's important to use HSAT alongside awareness of its limitations and it should not replace good clinical judgment when making treatment decisions.

HSAT devices using PAT technology have been studied in patients with atrial fibrillation (Tauman R, et al. *Nat Sci Sleep*. 2020;12:1115), adolescents (Choi JH, et al. *J Clin Sleep Med*. 2018;14[10]:1741), and pregnant women (O'Brien LM, et al. J *Clin Sleep Med*. 2012;8[3]:287), and to assess OSA treatment adequacy with varying sensitivity and specificity. Study in special populations may allow for increased access to testing with the benefit of increased recognition of a generally underdiagnosed disorder. But it's important to use HSAT alongside awareness of its limitations and it should not replace good clinical judgment when making treatment decisions.

Dimple Tejwani, MD
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THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK

Lung Cancer Section

Sybil – Prophecies for lung cancer risk prediction?

The mortality benefit associated with lung cancer screening (LCS) using low dose CT (LDCT) relies, in large part, on adherence rates to annual screening of ≥90%. However, the first 1 million "real world" patients screened in the US had very low (22%) annual adherence (Silvestri, et al. *Chest*. 2023;S0012-3692[23]00175-7). Refining how we estimate future lung cancer risk is an important opportunity for personalized medicine to bolster adherence to follow-up after initial LDCT.

Researchers at MIT developed Sybil, a deep learning algorithm using radiomics on LDCT for LCS to accurately predict 6-year lung cancer risk (Mikhael, et al. J *Clin Oncol*. 2023;JCO2201345). The model was developed, trained, and tested in a total of 14,185 National Lung Screening Trial (NLST) participants including all cancer diagnoses. Within these data, Sybil's accuracy in predicting 1-year lung cancer risk had AUC 0.92 (95% CI, 0.88-0.95) and at 6 years, AUC 0.75 (95% CI, 0.72-0.78).

The model was validated in two large independent LCS datasets, one in the US and one in Taiwan, where an LDCT can be obtained regardless of a personal smoking history. The cancer prevalence in these datasets was 3.4% and 0.9%, respectively. Reassuringly, Sybil's performance was similar to the NLST data and was maintained in relevant subgroups such as sex, age and smoking history. Furthermore, Sybil reduced the false positive rate in the NLST to 8% at baseline scan, compared with 14% for Lung-RADS 1.0. Sybil's algorithm, unlike others, has been made publicly available and hopefully will spur further validation and prospective study.

Robert Smyth, MD
Member-at-Large

Using ABIM's Longitudinal Knowledge Assessment (LKA®) for your advantage

BY LYNN T. TANOUE, MD, MBA
Chair, ABIM Pulmonary Disease Board

The American Board of Internal Medicine's (ABIM) Longitudinal Knowledge Assessment (LKA®) has entered its second year of availability, and was launched in January 2023 for the disciplines of pulmonary disease and critical care medicine, as well as infectious disease. Tens of thousands of physicians nationwide are taking advantage of this option for a flexible assessment that also incorporates more learning opportunities. If you are due for an ABIM assessment in 2023 in pulmonary disease or critical care medicine, the deadline to enroll in LKA is June 30, 2023.


Dr. Tanoue

Many diplomates—including myself—are taking advantage of the flexibility offered by the LKA to maintain certification in one or more specialties. Others are using it to regain certifications that they allowed to lapse. Both scenarios offer a lower-stakes and less time-intensive route to maintaining or recertifying that also promotes relevant and timely learning in a given discipline. Remember that you can still choose to take the traditional 10-year Maintenance of Certification (MOC) exam in any discipline if you feel that works better for you than the LKA.

Detailed information about the LKA and how it works, as well as a walkthrough video and FAQs, are available on ABIM's website. Following are some suggestions based on the experience of physicians who are currently enrolled in the LKA.

Take it one day at a time

With 30 questions released each quarter, the LKA is designed to be manageable and work with your schedule. You could take one question a day or every few days over the course of the quarter or you can choose to do all 30 in one sitting—whatever works for you. Each correct answer also earns you 0.2 MOC points, meaning that over time, you could potentially achieve all of your required MOC points through the LKA alone.

Don't forget your time bank

Every question has a 4-minute time limit, but if you need more time to think through a question or look up a resource, you can draw from a 30-minute extra time bank that renews each year. On average, physicians answer most questions in less than 2 minutes.

Use resources

The LKA is essentially "open book," meaning you can use any resource to help with a question except for another physician. Some physicians cite online sites or hard copy medical references as reliable resources, and CHEST offers additional resources that can be helpful, as well.

Set up your work area for success

Many physicians report using two screens or two devices while taking the LKA—one with the LKA platform open to answer questions and one for looking up resources. Questions involving viewing of media will prompt you when a larger screen may be helpful.

Consider the cost savings

The LKA is included in your annual MOC fee for each certificate you maintain at no additional cost. If you use the LKA to meet your MOC assessment requirement, you don't need to take the traditional 10-year MOC exam or pay an additional exam fee.

Gauge areas of strength and weakness

Most questions on the LKA will give you rationale and feedback after you've answered, allowing you to brush up on knowledge gaps. In addition, you'll receive interim quarterly score reports starting after your fifth quarter of participation showing your current score relative to the passing standard, including areas where you might need to focus more study.

Regain lapsed certification

The LKA is a simple and lower-stakes way to regain certification in a specialty that has lapsed, though it should be noted that you must complete your 5-year LKA cycle and achieve a passing score for the certificate to become active again. In the meantime, you can use the LKA to refresh your knowledge of current information in that specialty.

Ask about disability accommodations

ABIM offers some accommodations for the LKA in compliance with Title III of the Americans with Disabilities Act (ADA) for individuals with documented disabilities who demonstrate a need for accommodation. Physicians requesting special testing accommodations under the ADA can submit a request on ABIM's website.

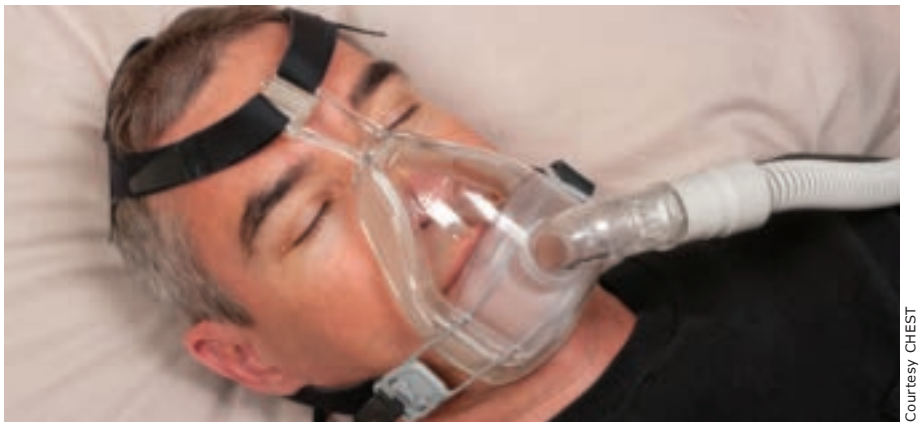
If you're due for an assessment in 2023, and you haven't looked into the LKA yet, now is the time: the second quarter closes on June 30, 2023, and you will not be able to enroll after that date. Sign in to your ABIM Physician Portal to see if you are eligible and visit ABIM.org/LKA to learn more. ■

Review highlights from CHEST's new clinical practice guideline

The American College of Chest Physicians® (CHEST) recently released a new clinical guideline, "Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report." Published in the journal *CHEST*®, the guideline contains 15 evidence-based recommendations, a good practice statement, and an ungraded consensus-based statement.

Endorsed by the American Association for Respiratory Care, the American Thoracic Society, the American Academy of Sleep Medicine, and the Canadian Thoracic Society, the guideline recommendations cover topics including mouthpiece ventilation, transition to home mechanical ventilation, salivary secretion management, and airway clearance therapies.

"Respiratory muscle weakness is a serious concern in patients with neuromuscular diseases. It can lead to inadequate ventilation, nighttime hypoventilation, and the inability to mobilize secretions, which is frequently the cause of death in this population," said lead author on the guideline, Akram Khan, MD, FCCP, Associate Professor, Pulmonary, Allergy, and Critical Care Medicine, Oregon Health & Science University. "We anticipate this guideline will standardize and improve the care provided to patients with neuromuscular diseases and subsequent weakness."


Courtesy CHEST

The guideline includes the following highlighted recommendations:

- For patients with neuromuscular diseases (NMD) and chronic respiratory failure, we recommend using noninvasive ventilation (NIV) for treatment. (Strong recommendation)
- For patients with NMD requiring NIV, we suggest individualizing NIV treatment to achieve ventilation goals. (Conditional recommendation)

HIGHLIGHTS *continued on following page*

PULMONARY PERSPECTIVES®

Relearning old lessons from a new disease: Prolonged noninvasive respiratory support for hypoxemic respiratory failure can harm patients

BY BENJAMIN T. WILSON, MD, AND ABHIMANYU CHANDEL, MD

The threshold for abandoning supportive measures and initiating invasive mechanical ventilation (IMV) in patients with respiratory failure is unclear. Noninvasive respiratory support (RS) devices, such as high-flow nasal cannula (HFNC) and noninvasive positive-pressure ventilation (NIV), are tools used to support patients in distress prior to failure and the need for IMV. However, prolonged RS in patients who ultimately require IMV can be harmful.

As the COVID-19 pandemic evolved, ICUs around the world were overrun by patients with varying degrees of respiratory failure. With this novel pathogen came novel approaches to management. Here we will review data available prior to the pandemic and relate them to emerging evidence on prolonged RS in patients with COVID-19. We believe it is time to acknowledge that prolonged RS in patients who ultimately require IMV is likely deleterious. Increased awareness and care to avoid this situation (often meaning earlier intubation) should be implemented in clinical practice.

Excessive tidal volume delivered during IMV can lead to lung injury. Though this principle is widely accepted, the recognition that the same physiology holds in a spontaneously breathing patient receiving RS has been slow to take hold. In the presence of a high respiratory drive injury from overdistension and large transpulmonary pressure, swings can occur with or without IMV. An excellent review summarizing the existing evidence of this risk was published years before the COVID-19 pandemic (Brochard L, et al. *AJRCCM*. 2017;195[4]:438).

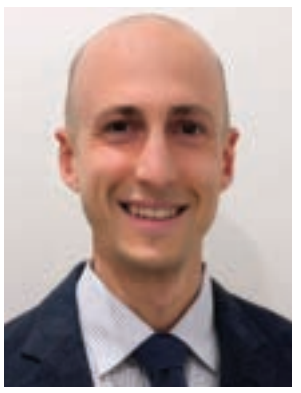
A number of pre-COVID-19 publications focused on examining this topic in clinical practice deserve specific mention. A study of respiratory mechanics in patients on NIV found it was nearly impossible to meet traditional targets for lung protective tidal volumes. Those patients who progressed to IMV had higher expired tidal volumes (Carteaux G, et al. *Crit Care Med*. 2016;44[2]:282). A large systematic review and metanalysis including more than 11,000 immunocompromised patients found delayed intubation led to increased mortality (Dumas G, et al. *AJRCCM*. 2021;204[2]:187). This study did not specifically implicate RS days and patient self-induced lung injury as factors driving the excess mortality; another smaller propensity-matched retrospective analysis of patients in the ICU supported with HFNC noted a 65% reduction in mortality among patients intubated after less than vs greater than 48 hours on HFNC who ultimately required IMV (Kang B, et al. *Intensive Care Med*. 2015;41[4]:623).

Despite this and other existing evidence regarding the hazards of prolonged RS prior to IMV, COVID-19's burden on the health care system dramatically changed the way hypoxemic respiratory failure is managed in the ICU. Anecdotally, during the height of the pandemic, it was commonplace to encounter patients with severe COVID-19 supported with very high RS settings for days or often weeks. Occasionally, RS may have stabilized breathing mechanics. However, it was often our experience that among those patients supported with RS for extended periods prior to IMV lung compliance was poor, lung recovery did not occur, and prognosis was dismal. Various factors, including early reports of high mortality among patients with COVID-19 supported with IMV, resulted in reliance on RS as a means for delaying or avoiding IMV. Interestingly, a propensity-matched study of more than 2,700 patients found that prolonged RS was associated with significantly higher in-hospital mortality but despite this finding, the practice increased over the course of the pandemic (Riera J, et al. *Eur Respir J*. 2023;61[3]:2201426). Further, a prospective study comparing outcomes between patients intubated within 48 hours for COVID-19-related respiratory failure to those intubated later found a greater risk of in-hospital mortality and worse long-term outpatient lung function testing (in survivors) in the latter group.

It has previously been postulated that longer duration of IMV prior to the initiation of extracorporeal membrane oxygenation (ECMO) support in patients with hypoxemic respiratory failure may contribute to worse overall ECMO-related outcomes. This supposition is based on the principle that ECMO protects the lung by reducing ventilatory drive, tidal volume, and transpulmonary pressure swings. Several studies have documented an increase in mortality in patients supported with ECMO for COVID-19-related respiratory failure over the course of the pandemic. These investigators have noted that time to cannulation, but not IMV days (possibly reflecting duration of RS), correlates with worse ECMO outcomes (Ahmad Q, et al. *ASAIO J*. 2022;68[2]:171; Barbaro R, et al. *Lancet*. 2021;398[10307]:1230). We wonder if this reflects greater attention to low tidal volume ventilation during IMV but lack of awareness of or the inability to prevent injurious ventilation during prolonged RS. We view this as an important area for future research that may aid in patient selection in the ongoing effort to improve COVID-19-related ECMO outcomes.

The COVID-19 pandemic remains a significant burden on the health care system. Changes in care necessitated by the crisis produced innovations with the potential to rapidly improve outcomes. Notably though, it also has resulted in negative changes in response to a new pathogen that are hard to reconcile with physiologic principles. Evidence before and since the emergence of COVID-19 suggests prolonged RS prior to IMV is potentially harmful. It is critical for clinicians to recognize this principle and take steps to mitigate this problem in patients where a positive response to RS is not demonstrated in a timely manner. ■

Dr. Wilson



Dr. Chandel

Drs. Wilson and Chandel are with the Department of Pulmonary and Critical Care, Walter Reed National Military Medical Center, Washington, DC.

HIGHLIGHTS *continued from previous page*

- For patients with NMD at risk for respiratory failure, we suggest pulmonary function testing at a minimum of every 6 months as appropriate to the course of the specific NMD. (Conditional recommendation)
- For patients with NMD and sialorrhea, we suggest a therapeutic trial of an anticholinergic medication as first-line therapy with continued use only if there are perceived benefits compared with side effects. (Conditional recommendation)

Each recommendation is classified as strong, referred to as "recommended," or conditional, referred to as "suggested." The panel offers graded recommendations when there is sufficient evidence and ungraded consensus-based statements in areas that were thought to warrant guidance, despite an insufficient grade of evidence.

The entire list of recommendations and population, intervention, comparator, and outcome questions included in the guideline can be accessed through the *CHEST* journal website at journal.chestnet.org. ■

SLEEP STRATEGIES

Counting electric sheep: Dreaming of AI in sleep medicine

BY MIRANDA TAN, DO, FCCP, AND SUMIT BHARGAVA, MD, FCCP

"Artificial intelligence (AI) in healthcare refers to the use of machine learning (ML), deep learning, natural language processing, and computer vision to process and analyze large amounts of health care data."

The preceding line is a direct quote from ChatGPT when prompted with the question "What is AI in health care?" (OpenAI, 2022). AI has rapidly infiltrated our lives. From using facial recognition software to unlock our cellphones to scrolling through targeted media suggested by streaming services, our daily existence is interwoven with algorithms. With the recent introduction of GPT-3 (the model that powers ChatGPT) in late 2022 and its even more capable successor, GPT-4, in March 2023, AI will continue to dominate our everyday environment in even more complex and meaningful ways.

For sleep medicine, the initial applications of AI in this field have been innovative and promising. To date, AI has been leveraged to explore sleep staging, respiratory event scoring, characterization of insomnia, prediction of circadian timing from gene expression, endotyping, and phenotyping of obstructive sleep apnea (OSA) (Bandyopadhyay A, et al. *Sleep Breath*. 2023;27[1]:39). Pépin and colleagues (*JAMA Netw Open*. 2020;3[1]:e1919657) combined ML with mandibular movement to diagnose OSA with a reasonable agreement to polysomnography as a novel home-based alternative for diagnosis. AI has also been used to predict adherence to positive airway pressure (PAP) therapy in OSA (Scioscia G, et al. *Inform Health Soc Care*. 2022;47[3]:274) and as a digital intervention tool accessed via a smartphone app for people with insomnia (Philip P, et al, *J Med Internet Res*. 2020;22[12]:e24268). The data-rich field of sleep medicine is primed for further advancements through AI, albeit with a few hurdles and regulations to overcome before becoming mainstream.

Future promise

Sleep medicine is uniquely positioned to develop robust AI algorithms because of its vast data trove. Using AI, scientists can efficiently analyze the raw data from polysomnography, consumer sleep technology (CST), and nightly remote monitoring (from PAP devices) to substantially improve comprehension and management of sleep disorders.

AI can redefine OSA through analysis of the big data available, rather than solely relying on the apnea-hypopnea index. In addition, novel variables such as facial structure; snoring index; temperature trends; and sleep environment, position, and timing using a camera-based contactless technology may be incorporated to enhance the diagnostic accuracy for OSA or better describe sleep quality. AI algorithms can also be embedded into the electronic health record (EHR) to facilitate screening for sleep disorders using patient characteristics, thus accelerating the recognition and evaluation of possible sleep disorders.

New ways of collecting data may deliver deeper insights into sleep health, as well. CST such as wearables, nearables, and phone applications are improving with each iteration, resulting in more data about sleep for millions of people over thousands of nights.

AI can help achieve precision medicine by integrating multimodal data to establish endotypes and phenotypes of various sleep disorders. Delineating endotypes and phenotypes allows for personalized treatment recommendations, which may improve patient adherence and health outcomes.

Treatment personalization can also be achieved through AI by predicting compliance to various therapies and responses, as well as by discovering alternative forms of delivery to accomplish desired health outcomes. For example, to predict PAP compliance, we can record a patient encounter and use natural language processing to analyze their opinion of their treatment,

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2023 documentation guidelines updates

BY HUMAYUN ANJUM, MD, FCCP

This article's goal is to draw attention to and give a general summary of the most significant modification to the documentation guidelines in 25 years, which went into effect on January 1, 2023. This is by no means an entire resource, so we urge our readers to study the official American Medical Association (AMA) materials and speak with a billing/coding professional at their clinic, facility, or hospital for additional information.

AMA, the Centers for Medicare and Medicaid Services (CMS), and CPT were all in agreement with the proposed modifications when the Proposed Rule for the 2023 CMS Guidelines for Fee Schedule modifications was first released in July 2022. The Proposed Rule was left unchanged when the Final Rule was released later that year. Given that these modifications have an effect on the distribution and assignment of E/M levels, it is prudent to understand and implement them. The goal of this thorough redesign is to record the excellent work that clinicians perform on a daily basis and to reduce the danger of medical litigation.

The fields most affected by these changes are critical care, hospital medicine, emergency medicine, surgery, obstetric hospital medicine, and pediatrics, whereas anesthesia, radiology, and neonatology have been less affected.

Medical Decision Making (MDM), which previously determined the level of E/M visits, has been altered as of 2023. It should be emphasized that the rules for critical care documentation have not changed. In addition, it is crucial to carefully record everything and support MDM with an "appropriate" history, review of systems, past medical/family/social history, and physical examination.

So, the focus in 2023 should be on MDM. There are three components of MDM, and it is scored by the highest two of three components:

1. Number and complexity of problems addressed (previously, it was the number of diagnosis of management options)
All acute, subacute, and chronic conditions affecting the patient's care and management on that specific day should be listed in the chart for this, together with information about the severity and/or acuity of each diagnosis (for example worsening, acute, stable, or improving). Additionally, any differential diagnoses and rule-out diagnoses pertaining to the patient should be mentioned. Finally, it's important to note whether systemic symptoms are present.

2. Amount and/or complexity of data to be reviewed
As an MDM credit is provided for each distinct test, this should identify all the diagnostic tests that were ordered or evaluated. Additionally, an independent interpretation of the diagnostics should be reported if relevant and if conducted. This includes a review of all previous external notes (from a different facility, discharge summaries or other inpatient records, nursing home notes, a review of the pharmacy database, EMS notes, and specialist notes), information from independent historians, and consultation with other clinicians or qualified health

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extracting relevant keywords and combining such processing with other available data, such as environmental factors, sleep schedule, medical history, and other information extracted from the EHR. As another example, AI can determine the optimal time for cancer therapy by predicting a patient's circadian timing (Hesse J, et al. *Cancers (Basel)*. 2020;12[11]:3103). Circadian timing of drug delivery may be relevant in other specialties including cardiovascular disease, endocrine disorders, and psychiatric conditions due to its associations with sleep. Integration of the various "-omics" (eg, proteomics, genomics, and transcriptomics) with physiologic, behavioral, and environmental data can offer opportunities for drug discovery and possible prediction of sleep disorders and sleep-related morbidity. Although generative pretrained transformers are currently used to predict text (ie, ChatGPT), it is theoretically possible to also apply this technique to identify patients at risk for future sleep disorders from an earlier age.

Challenges to an AI renaissance

Despite making strides in numerous specialties such as radiology, ophthalmology, pathology, oncology, and dermatology, AI has not yet gained mainstream usage. Why isn't AI as ubiquitous and heavily entrenched in health care as it is in other industries? According to the National Academy of Medicine's *AI in Healthcare: The Hope, The Hype, The Promise, The Peril*, there are several realities to address before we fully embrace the AI revolution (Matheny M, et al. 2019).

First, AI algorithms should be trained on quality data that are representative of the population. Interoperability between health care systems and standardization across platforms is required to access large volumes of quality data. The current framework for data gathering is limited due to regulations, patient privacy concerns, and organizational preferences. The challenges to data acquisition and standardization of information will continue to snarl progress unless there are legislative remedies.

Furthermore, datasets should be diverse enough to avoid introducing bias into the AI algorithm. If the dataset is limited and health inequities (eg, societal bias and social determinants of health) are excluded from the training set, then the outcome will perpetuate further explicit and implicit biases.

The Food and Drug Administration (FDA) reviews and authorizes AI/ML-enabled devices. Its current regulatory structure treats AI as a static process and does not allow for exercise of its intrinsic ability to continuously learn from additional data, thereby preventing it from becoming more accurate and evolving with the population over time. A more flexible approach is needed.

Lastly, recent advanced AI algorithms including deep learning and neural network methodology function like a "black box." The models are not explainable or transparent. Without clear comprehension of its methods, acceptance in clinical practice will be guarded and further risk of inherent biases may ensue.

A path forward

But these challenges, like any, can be overcome. Research in the area of differential privacy and the adoption of recent data-sharing standards (eg, HL7 FHIR) can facilitate access to training data (Saripalle R, et al. *J Biomed Inform*. 2019;94:103188). Regulators are also open to incorporating feedback from the AI research community and industry in favor of innovation in this frenetic domain. The FDA developed the *AI/ML Software as a Medical Device Action Plan* in response to stakeholder feedback for oversight (FDA, 2021). Specifically, the "Good Machine Learning Practice" will be developed to describe AI/ML best practices (eg, data management, training, interpretability, evaluation, and documentation) to guide product development and standardization.

Sleep medicine has significantly progressed over the last several decades. Rather than maintain the status quo, AI can help fill the existing knowledge gaps, augment clinical practice, and streamline operations by analyzing and processing data at a volume and efficiency beyond human capacity. Fallibility is inevitable in machines and humans; however, like humans, machines can improve with continued training and exposure.

We asked ChatGPT about the future of AI in sleep medicine. It states that AI could have a "significant impact" on sleep disorders diagnosis, treatment, prevention, and sleep tracking and monitoring. Only time will tell if its claims are accurate.

Dr. Tan

Dr. Bhargava

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providers (QHPs) about the management or test interpretations.

3. Risk of complications and/or morbidity or mortality
This category includes all diagnoses or treatments that are significantly impacted by social determinants of health; prescription drug management that was taken into account, started, or adjusted during that particular encounter; parenteral drug administration; discussions and decisions about the patient's goals of care; and decisions regarding the need for hospitalization. (admit to inpatient or observation status, transfer to higher level of care, against medical advice, refusal of hospitalization, hospice discharge).

In summary, following are the top 10 MDM points that need to considered by the clinician while documenting:

1. Capture the acuity, severity, and intensity of the services provided during the encounter.
2. Capture all the diagnoses addressed and patient-specific differential diagnoses/rule out diagnoses.
3. Capture any prior external notes reviewed.
4. Capture when and why there was a need to talk to an independent historian.
5. Independently interpret any diagnostics (EKG, radiograph, ultrasound, CT, MRI).
6. Capture all discussions with other clinicians or QHPs.
7. Capture hospitalization/admission/transfer to higher level of care.
8. Document the need for prescription drug management.
9. Document the social determinants of health impact that would limit the diagnosis/treatment plan.
10. Capture any procedures planned or done as well as any plans for surgery.

In the upcoming issues of this year, we will try to focus individually on some of these areas and provide general templates for our readers to ensure that each of us is able to implement these effectively into our daily practice. We hope that this review has helped to clarify the new documentation guidelines. ■

Reference

1. 2023 CPT® Evaluation and Management (E/M) Code and Guideline Changes (https://www.ama-assn.org/system/files/2023-e-m-descriptors-guidelines.pdf. Effective January 1, 2023).

This month in the journal *CHEST*®

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

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By Varun Sharma, MBChB, et al.

Cardiovascular Complications Are the Primary Drivers of Mortality in Hospitalized Patients With SARS-CoV-2 Community-Acquired Pneumonia
By Ahmed Shebl Ali, MD, et al.

Real-World Evidence of Neutralizing Monoclonal Antibodies for Preventing Hospitalization and Mortality in COVID-19 Outpatients
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Moral Distress in Canadian Intensivists
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Nebulized vs IV Tranexamic Acid for Hemoptysis
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Value-Based Care for Chest Physicians
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Genetic factors also contribute to asthma risk, but highly variable heritability suggests that the nongenetic exposures play an important role. "However, whether healthy nongenetic exposure could decrease the risk of asthma and mitigate the adverse effect of genetic risk remains largely unknown," the authors state. They hypothesized that healthier sleep could decrease future asthma risk and mitigate the hazards of genetic effects.

Using data from the UK Biobank, they investigated the independent and combined effects of sleep pattern and PRSs on asthma incidence.

In the UK Biobank cohort (455,405 adults aged 38-73 years, who were enrolled from 2006 to 2010), 17,836 were diagnosed with asthma over 10 years of follow-up. PRSs were constructed for each participant on the basis of their having any of 17 single-nucleotide polymorphisms that are significantly associated with asthma. Participants were stratified into three groups: those at high genetic risk, those at intermediate genetic risk, and those at low genetic risk. Around 1 in 3 participants were classified as being at high genetic risk (150,429), and another third (151,970) were classified as being at intermediate risk. The remainder were classified as being at low risk. Some 7,105 people at high genetic risk and 5,748 at intermediate genetic risk were diagnosed with asthma during the monitoring period.

Comprehensive sleep scores, which ranged from 0 to 5, were constructed on the basis of self-reported sleep traits. Higher scores represented healthier sleep patterns. A healthy sleep pattern was defined as early chronotype; getting from 7 to 9 hours of sleep every night; never or rare insomnia; no snoring; and no frequent daytime sleepiness. On the basis of their responses, 73,223 people met the criteria for a healthy sleep pattern; 284,267, an intermediate sleep pattern; and 97,915, a poor sleep pattern.

"Compared with non-cases, asthma cases were more likely to have lower education levels, unhealthy sleep traits and patterns, obesity, higher PRS, more smoking, more alcohol consumption, hypertension, diabetes, depression, gastroesophageal reflux. and more air pollution exposure," the authors report. All five healthy sleep traits were independently associated with lower risk for asthma. Never/rare insomnia and sleep duration of 7-9 hours a night were seemingly the most influential; they were associated with risk reductions of 25% and 20%, respectively.

Analysis showed that, compared with the low-risk group, the hazard ratios and 95% confidence intervals (CI) for the highest PRS group and the poor sleep pattern group were 1.47 (95% CI, 1.41-1.52) and 1.55 (95% CI, 1.45-1.65), respectively.


Dr. Maselli

Risk was twofold higher in the presence of a combination of poor sleep and high genetic susceptibility (hazard ratio [HR], 2.22; 95% CI, 1.97-2.49; $P < .001$). Conversely, a healthy sleep pattern was associated with a lower risk of asthma in the low (HR, 0.56; 95% CI, 0.50-0.64), intermediate (HR, 0.59; 95% CI, 0.53-0.67), and high genetic susceptibility groups (HR, 0.63; 95% CI, 0.57-0.70). A population-attributable risk analysis indicated that improving these sleep traits would prevent 19% of asthma cases. Also, a subset analysis suggested that a healthy sleep pattern might reduce the risk of asthma among those at high genetic risk by 37%.

The study findings suggest that analysis of sleep patterns is warranted for all asthma patients, said coauthor Qing Wang, PhD, Cheeloo College of Medicine, Shandong University, Jinan, China, in an interview. "In our results, the effects of sleep and genetics were independent. Therefore, what we learned about the effects of sleep on asthma could be applied to all the patients, including those with a high or low genetic predisposition. In addition, we believe that intervening among those with high genetic predisposition could be more beneficial since they are more likely to have asthma. However, because this study is observational, a large clinical trial is absolutely needed to provide causal evidence, especially before guidelines modifications can be considered."

Complex and multifactorial

"Addressing relevant asthma comorbid conditions continues to be an integral part of asthma care," commented Diego J. Maselli, MD, FCCP, associate professor of medicine and interim chief, division of pulmonary diseases and critical care, UT Health, San Antonio, and an editorial advisory board member for *CHEST Physician*, in an interview. "There is mounting evidence that sleep patterns and obstructive sleep apnea may influence asthma control. This association is complex and multifactorial. It is important to remember that obstructive sleep apnea may coexist with other conditions, such as obesity and gastroesophageal reflux disease, that in turn can also worsen asthma control and influence clinical outcomes.

"Yet, even after controlling for these factors, sleep disturbances have been associated with poor asthma outcomes. It is reasonable, particularly in patients with uncontrolled and/or severe asthma, to screen for sleep disturbances. There are multiple questionnaires and clinical tools that can be employed to screen for coexisting sleep apnea and other conditions. Although genetic testing has shown some promise in identifying individuals at risk, these assays are not widely available and are not ready yet for routine clinical practice. Therefore, sleep studies should be reserved for patients who have symptoms and test positive for screening questionnaires and other tools.

"The study by Xiang and colleagues adds to the field of study, but further evidence is required to change practice guidelines at this time. Fortunately, sleep studies are readily available now with more widespread use of home testing, so patients can be easily tested. The majority third-party payers have identified that diagnosing these disorders is cost-effective and are able to reimburse sleep studies," Dr. Maselli concluded.

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