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In 2018, wildfire smoke led to 24 days of poor air quality in Seattle, including 9 days rated as "unhealthy" on the U.S. Air Quality Index.

Wildfire smoke linked to COPD, asthma exacerbations, but long-term effects still under study

BY DOUG BRUNK
MDedge News

The 2019 wildfire season is underway in many locales across the United States, exposing millions of individuals to smoky conditions that will have health consequences ranging from stinging eyes to scratchy throats to a trip to the ED for asthma or chronic obstructive pulmonary disease (COPD) exacerbation. Questions about long-term health impacts are on the minds of many, including physicians and their patients who live with cardiorespiratory conditions.

John R. Balmes, MD, a pulmonologist at the University of California, San Francisco, and an expert on the respiratory and cardiovascular effects of air pollutants, suggested that the best available published literature points to "pretty strong evidence for acute effects of wildfire smoke on respiratory health, meaning people with preexisting asthma and COPD are at risk for exacerbations, and probably for respiratory tract infections as well." He said, "It's a little less clear, but there's good biological plausibility for increased risk of respiratory tract infections because when your alveolar macrophages are

Wildfire smoke // *continued on page 7*

FDA advisory panel recommends approval of peanut desensitization therapy

BY MICHELE G. SULLIVAN
MDedge News

A pill designed to desensitize peanut-allergic children and teenagers may be on the way. The Food and Drug Administration's Allergenic Products Advisory Committee has voted to recommend approval of the AR101 peanut protein capsules (Palforzia) for use in oral immunotherapy in those aged 4-17 years old with a confirmed peanut allergy. Conditions for approval include stipulations that a black-box warning and medication use guide are included in the packaging, the panel said. The FDA usually follows the recommendations of its advisory panels. The peanut pill is on the way.

The committee members voted 7-2 that the drug was effective and 8-1 that it was safe.

John Kelso, MD, the sole dissenter on safety, voiced concerns about the dearth of long-term follow-up in Aimmune Therapeutic's body of research and the finding that children who received the treatment during the dose-escalation and

Peanut // *continued on page 4*

INSIDE HIGHLIGHT

NEWS FROM CHEST
Critical Care Commentary
Should PEEP be titrated based on esophageal pressures?
Page 55

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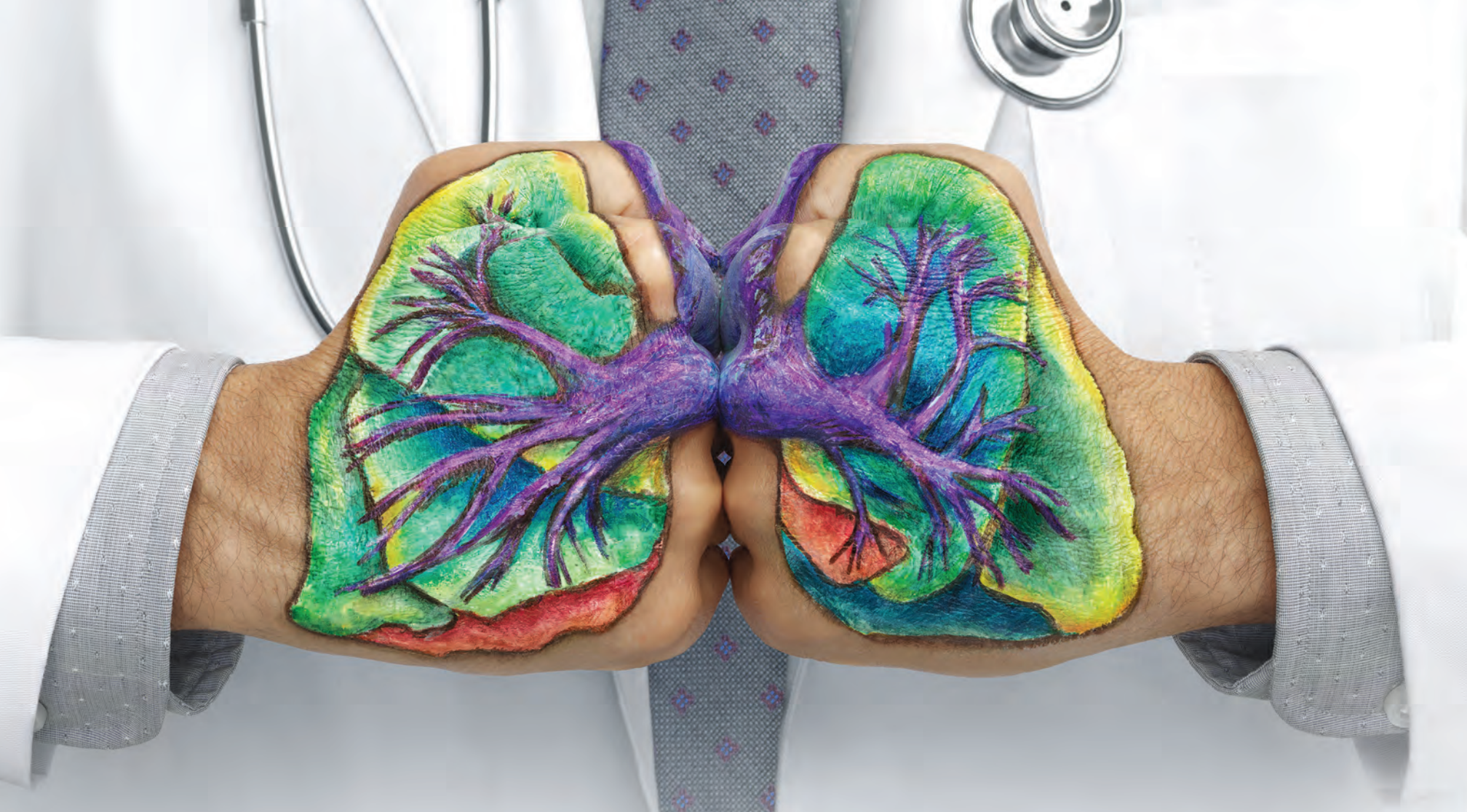

Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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Help preserve more lung function. Reduce lung function decline.[1–3]

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Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[4]

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In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF[1–4]*

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The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[1†]

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Genentech offers a breadth of patient support and assistance services to help your patients with IPF[‡]

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More than 42,000 patients have taken pirfenidone worldwide[4§]

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

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

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

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

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

Learn more about Esbriet and how to access medication at EsbrietHCP.com

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[1] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide ($\%DL_{co}$) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[2] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[3] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1,2] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,3,4] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[1,3]**

†Serious adverse reactions, including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[1]

‡Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

High cost of peanut desensitization therapy remains a concern // *continued from page 1*

maintenance periods had twice the number of allergic reactions requiring epinephrine, compared with those who received placebo. There are no long-term safety data to rely on yet, he added.

"Efficacy has not been demonstrated, except on the day the peanut challenge is administered," said Dr. Kelso, an allergist at the Scripps Clinic, San Diego, adding that only long-term follow-up data would fully convince him that the drug's benefits outweigh the risks.

In the discussion, however, other committee members pointed out that new drugs are often approved without long-term efficacy and safety data. Those data are extrapolated from clinical trials, and only real-world experience will confirm the data, the investigators noted.

Company representatives did not explicitly address the potential cost of the therapy, but a recent review by the Institute for Clinical and Economic Review estimated the cost to be $4,200 a year. Palforzia would

have to be taken every day, for an unknown amount of time, to maintain peanut tolerance.

"Using prices from analysts for AR101 ($4,200 a year), we estimated that only 41% of eligible patients could be treated in a given year without exceeding ICER's budget impact threshold," the institute concluded in a publicly released analysis.

Palforzia comes in individual packs of capsules filled with peanut protein, not flour. The capsules come in doses of 0.5, 1, 10, 20, 100, and 300 mg. A single-dose sachet contains 300 mg. Treatment begins with 0.5-6 mg over 1 day and escalates every 2 weeks until 300 mg is reached or there is a reaction requiring epinephrine. Passing at least a 300-mg dose was the requirement for exiting the escalation phase and moving on to the daily, year-long maintenance phase.

The four efficacy studies presented showed that 96% of patients tolerated 300 mg; 84% tolerated 600 mg; and 63% 1,000 mg – about 10 times the reactive dose observed in the placebo controls.

The capsule, however, is not a panacea. The company advises that families continue with the peanut avoidance diet. "It's important to remember that reactive episodes can occur with dosing, and accidental exposures can occur at unpredictable times, away from home, and despite the best efforts at avoidance," Dr. Adelman said. "This is not a drug for everyone, but it is an effective desensitization tool and would clearly be the first therapy to treat a food allergy, providing statistically significant and clinically important improvement. Outcomes align with patients' goals."

Safety was assessed in 709 treated patients who received the medication and 292 who received placebo. Treatment-related adverse events were most common in initial dosing: 89% of the treatment group and 58% of the placebo group experienced at least one adverse event during that time. Adverse events were mostly mild to moderate and decreased in severity over the study period.

Respiratory events were more common in those in the active group, especially in children with asthma. These events included cough, wheezing, dyspnea, dysphonia, throat irritation and tightness, and exercise-induced asthma. There was, however, no "concerning change" in asthma control.

Systemic allergic reactions and anaphylaxis were more common in the active-dose group. Systemic reactions during dose escalation occurred in 9.4% of active patients and 3.8% those taking placebo. During the maintenance phase, they occurred in 8.7% and 1.7% of patients, respectively. Three patients in the active group had a serious systemic reaction – two during up-dosing and one during maintenance. During initial dose escalation and up-dosing combined, 6.1% of patients in the active group and 3.1% in the placebo group had a systemic reaction requiring epinephrine. This was most often administered outside of the clinic.

There were 12 cases of eosinophilic esophagitis, all of which resolved after medication withdrawal from the study medication. The patch is designed to desensitize allergic children aged 4-11 years through a skin-patch method known as epicutaneous immunotherapy. Results from two controlled clinical trials were included in the submission.

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ABIM: Self-paced MOC pathway currently under development

BY ALICIA GALLEGOS

MDedge News

Physician groups are praising a new option by the American Board of Internal Medicine (ABIM) that will offer doctors a self-paced pathway for maintenance of certification (MOC) in place of the traditional long-form assessment route.

The new longitudinal assessment option, announced in late August, would enable physicians to acquire and demonstrate ongoing knowledge through shorter evaluations of specific content. The option, currently under development, also would provide doctors with immediate feedback about their answers and share links to educational material to address knowledge gaps, according to an announcement. While details are still being flushed out, a summary of the longitudinal assessment concept by the American Board of Medical Specialties explains that the approach draws on the principles of adult learning and modern technology "to promote learning, retention, and transfer of information."

Developing a longitudinal assessment option is part of ABIM's ongoing evolution, Marianne M. Green, MD, chair for ABIM's board of directors and ABIM President Richard J. Baron, MD, wrote in a joint letter to internists posted on ABIM's blog.

"We recognize that some physicians may prefer a more continuous process that easily integrates into their lives and allows them to engage seamlessly at their preferred pace, while being able to access the resources they use in practice," the doctors wrote.

Douglas DeLong, MD, chair of the American College of Physician's (ACP) board of regents said the option is a positive, first step that will support lifelong learning. He noted the new option is in line with recommendations by the American Board of Medical Specialties' Continuing Board Certification: Vision for the Future Commission, which included ACP concerns.

"It's pretty clear that some of the principles of adult learning – frequent information with quick feedback, repetition of material, and identifying gaps in knowledge – is really how people most effectively learn," Dr. DeLong said in an interview. "Just cramming for an examination every decade hasn't ever really been shown to affect long-term retention of knowledge or even patient care outcomes."

Alan Lichtin, MD, chair of the MOC working group for the American Society of Hematology (ASH), said the self-paced pathway is a much-needed option, particularly the immediate feedback on test questions.

Dr. Baron

"For years, ASH has been advocating that ABIM move from the traditional sit-down testing to an alternative form of 'formative' assessment that has been adapted by other specialty boards," Dr. Lichtin said in an interview. Anesthesiology and pediatrics have novel testing methods that fit into physicians' schedules without being so disruptive and anxiety provoking. There is instantaneous feedback about whether the answers are correct or not. It is not useful to study hard for a time-intensive, comprehensive test only to get a summary of what was missed a long time after the test. By that point, the exam material is no longer fresh in one's mind and therefore the feedback is no longer useful."

The new pathway is still under development, and ABIM has not said when the option might be launched. In the meantime, the current MOC program and its traditional exam will remain in effect. The board is requesting feedback and comments from physicians about the option. Dr. Baron wrote that more information about the change will be forthcoming in the months ahead.

The ABIM announcement comes on the heels of an ongoing legal challenge levied at the board by a group of internists over its MOC process.

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Wildfire smoke particles can enter deep into the lungs // *continued from page 1*

overloaded with carbon particles that are toxic to those cells, they don't function as well as a first line of defense against bacterial infection, for example."

The new normal of wildfires

Warmer, drier summers in recent years in the western United States and many other regions, attributed by climate experts to global climate change, have produced catastrophic wildfires (PNAS.2016 Oct 18;113[42]11770-5; Science. 2006 Aug 18;313:940-3). Forest fires in 2018 caused hazardous smoke conditions in Portland, Seattle, Vancouver, and Anchorage and many smaller communities. Such events are expected to be repeated often in the coming years (Int J Environ Res Public Health. 2019 Jul 6;16[13]).

"Smoke is composed primarily of carbon dioxide, water vapor, carbon monoxide, particulate matter, hydrocarbons and other organic chemicals, nitrogen oxides, trace minerals and several thousand other compounds," according to the U.S. Environmental Protection Agency (Wildfire smoke: A guide for public health officials 2019. Washington, D.C.: EPA, 2019). The EPA report noted, "Particles with diameters less than 10 mcm (particulate matter, or PM_{10}) can be inhaled into the lungs and affect the lungs, heart, and blood vessels. The smallest particles, those less than 2.5 mcm in diameter ($PM_{2.5}$), are the greatest risk to public health because they can reach deep into the lungs and may even make it into the bloodstream."

Research on health impact

Wayne Cascio, MD, and his colleagues initiated an epidemiology study to investigate the effects of exposure on cardiorespiratory outcomes in the population affected by fire (Environ Health Perspect. 2011 Oct;119[10]:1415-20). By combining satellite data with syndromic surveillance drawn from hospital records in 41 counties contained in the North Carolina Disease Event Tracking and Epidemiologic Collection Tool, he and his colleagues found that exposure to the peat wildfire smoke led to increases in the cumulative risk ratio for asthma (relative risk, 1.65), chronic obstructive pulmonary disease (RR, 1.73), and pneumonia and acute bronchitis (RR, 1.59). ED visits related to cardiopulmonary symptoms and heart failure also were significantly increased (RR, 1.23 and 1.37, respectively). "That was really the first study to strongly identify a cardiac endpoint related to wildfire smoke exposure," said Dr. Cascio, who directs the EPA's National Health and Environmental Effects Research Laboratory. Those early findings have been replicated in subsequent research about the acute health effects of exposure to wildfire smoke, which contains $PM_{2.5}$ and other toxic substances from structures, electronic devices, and automobiles destroyed in the path of flames, including heavy metals and asbestos. Most of the work has focused on smoke-related cardiovascular and respiratory ED visits and hospitalizations.

A study of the 2008 California wildfire season's impact on ED visits accounted for ozone levels in addition to $PM_{2.5}$ in the smoke. $PM_{2.5}$ inhalation during the wildfires was associated with increased risk of an ED visit for asthma (RR, 1.112; 95% confidence interval, 1.087-1.138) for a 10 mcg/m^3 increase in $PM_{2.5}$ and COPD (RR, 1.05; 95% CI, 1.019-1.0825), as well as for combined respiratory visits (RR, 1.035; 95% CI, 1.023-1.046) (Environ Int. 2109 Aug;129:291-8).

Researchers who evaluated the health impacts of wildfires in California during the 2015 fire season found an increase in all-cause cardiovascular and respiratory ED visits, especially among those aged 65 years and older during smoke days. Rates of all-cause cardiovascular ED visits were elevated across levels of smoke density, with the greatest increase on dense smoke days and among those aged 65 years or older (RR,1.15; 95% CI, 1.09-1.22). All-cause cerebrovascular visits were associated with dense smoke days, especially among those aged 65 years and older (RR, 1.22; 95% CI, 1.00-1.49). Respiratory conditions also were increased on dense smoke days (RR, 1.18; 95% CI, 1.08-1.28) (J Am Heart Assoc. 2018 Apr 11;7:e007492. doi: 10.1161/JAHA.117.007492).

Courtesy Peter Buschmann/US Forest Service

Unknown long-term effects

When it comes to the long-term effects of wildfire smoke on human health outcomes, much less is known. "We know that there are immediate respiratory health effects from wildfire smoke," said Colleen E. Reid, PhD, of the department of geography at the University of Colorado Boulder. "What's less known is everything else."

Air pollution has been shown to adversely affect health, but whether exposure to wildfire smoke confers a similar risk is less clear. "Until just a few years ago we haven't been able to study wildfire exposure measures on a large scale," said EPA scientist Ana G. Rappold, PhD, a statistician in the environmental public health division of the National Health and Environmental Effects Research Laboratory. "It's also hard to predict wildfires, so it's hard to plan for an epidemiologic study if you don't know where they're going to occur."

Dr. Rappold and colleagues examined cardiopulmonary hospitalizations among adults aged 65 years and older in 692 U.S. counties within 200 km of 123 large wildfires during 2008-2010 (Environ Health Perspect. 2019;127[3]:37006. doi: 10.1289/EHP3860). They observed that an increased risk of $PM_{2.5}$-related cardiopulmonary hospitalizations was similar on smoke and non-smoke days across multiple lags and exposure metrics, while risk for asthma-related hospitalizations was higher during smoke days. "One hypothesis is that this was an older study population, so naturally if you're inhaling smoke, the first organ that's impacted in an older population is the lungs," Dr. Rappold said. "If you go to the hospital for asthma, wheezing, or bronchitis, you are taken out of the risk pool for cardiovascular and other diseases. That could explain why in other studies we don't see a clear cardiovascular signal as we have for air pollution studies in general. Another aspect to this study is that the exposure metric was $PM_{2.5}$, but smoke contains many other components, particularly gases, which are respiratory irritants. It could be that this triggers a higher risk for respiratory [effects] than regular episodes of high $PM_{2.5}$ exposure, just because of the additional gases that people are exposed to."

Another complicating factor is the paucity of data about solutions to long-term exposure to wildfire smoke. "If you're impacted by high-exposure levels for 60 days, that is not something we have experienced before," Dr. Rappold noted. "What are the solutions for that community? What works? Can we show that by implementing community-level resilience plans with HEPA [high-efficiency particulate air] filters or other interventions, do the overall outcomes improve? Doctors are the first ones to talk with their patients about their symptoms and about how to take care of their conditions. They can clearly make a difference in emphasizing reducing exposures in a way that fits their patients individually, either reducing the amount of time spent outside, the duration of exposure, and the level of exposure."

Advice for vulnerable patients

While research in this field advances, the unforgiving wildfire season looms, ensuring more destruction of property and threats to cardiorespiratory health. "There are a lot of questions that research will have an opportunity to address as we go forward, including the utility and the benefit of N95 masks, the utility of HEPA filters used in the house, and even with HVAC [heating, ventilation, and air conditioning] systems," Dr. Cascio said.

The way he sees it, the time is ripe for clinicians and officials in public and private practice settings to refine how they distribute information to people living in areas affected by wildfire smoke. "So, why couldn't the hospital send out a text message or an email to all of the patients with COPD, coronary disease, and heart failure when an area is impacted by smoke, saying, 'Check your air quality and take action if air quality is poor?' Physicians don't have time to do this kind of education in the office for all of their patients. I know that from experience. But if one were to only focus on those at highest risk, and encourage them to follow our guidelines, which might include doing HEPA filter treatment in the home, we probably would reduce the number of clinical events in a cost-effective way."

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INNOVATIVE MEDICINE **Best Practices**

Treatment of Unresectable Stage III Non-small Cell Lung Cancer

Introduction

With a recent renaissance in cancer diagnostics and treatment, there is renewed promise for many who previously held little hope. Lung cancer represents the second most frequently diagnosed cancer, a close second to breast cancer, at 12.9% of expected new cancer cases in 2019.[1] However, the 23.5% death rate predicted for lung cancer outranks breast, prostate, colorectal, and skin melanomas combined.[1] Five-year lung cancer survival rates have increased from 11% in 1975 to more than 20% in 2016.[1] This relatively low rate of survival can probably be explained by the fact that the majority of patients are diagnosed with locally advanced disease (Stage III, disease metastatic to mediastinal or supraclavicular nodes) or advanced disease (Stage IV, disease metastatic to other organs).[2-4] Recent advancements in treatment are proving effective in improving patient outcomes[5,6]; combined with adherence to screening recommendations and immediate referral to appropriate specialists, earlier diagnosis and staging can help lead to improved outcomes.[7-9]

Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of lung cancer diagnoses, including histological identification of adenocarcinoma, squamous cell, large cell, and undifferentiated carcinomas.[10-12] Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or Stage III disease.[12] A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy.[5,13] About 40% of patients with NSCLC are diagnosed with Stage IV disease, and the treatment goal in these patients is to manage symptoms, improve quality of life, and extend survival.[13,14] Treatment options include systemic chemotherapy, targeted mutation therapies, radiation, immunotherapy, and on occasion surgery.[7] It is vital that we increase early diagnosis, accurate staging, and referral to the appropriate specialists in lung cancer to ensure that treatment is optimized and more lives are potentially saved.[7]

Screening and Diagnosis

Unlike with breast, prostate, and colorectal cancers, systematic screening for lung cancer is not a well-established population-based practice, and its role is not fully grasped by primary caregivers.[15] Risk factors such as history of tobacco use and exposure to second-hand smoke are common knowledge, but other environmental exposures (diesel smoke, pollution, and other cancer-causing agents) are difficult to quantify.[16,17] Populations with lifestyles with higher exposure to these factors are generally more reticent to intervention and skeptical of the benefits of treatment, while others may be concerned that radiation-based screening techniques contribute to the risk.[15] In addition to patient perceptions that defer intervention, presenting symptoms of cough and dyspnea are frequently confounded with other respiratory conditions, creating a delay in early detection and staging.[9] Even further delays have been seen when patients present with more generalized symptoms like fatigue or bone or joint pain.[9]

Based on the National Lung Screening Trial (NLST),[18] the American College of Chest Physicians (ACCP) has published recommendations that low-dose computerized tomography (LDCT) scans be performed annually on patients meeting the following criteria: (1) 30 pack-year current smoker or former smoker between the ages of 55 and 74 years, (2) former smokers who have quit within the past 15 years, and (3) no comorbidities that potentially preclude curative treatment benefit.[15] The National Comprehensive Cancer Network® (NCCN®) also encourages patients to seek yearly screening if they are 50 years or older, have a 20 or more pack-year smoking history, and have other known risk factors besides second-hand smoke exposure, such as radon exposure.[19] Screening with LDCT, in select patients at high risk for lung cancer, decreased the relative risk of death from lung cancer by 20% when compared with chest radiography.[18] As such, efforts are being made to educate general practitioners and the public about this tremendous benefit.[15,19,20]

The goal of screening is to identify a lung cancer in the earliest possible stage, which, as **Table 1** demonstrates, directly improves survivability.[19] However, imaging alone does not provide accurate staging, and once lung cancer is suspected, time is of the essence in ensuring no further progression. Various target time recommendations have been published advocating for improved wait times across the care spectrum, ranging from 30 to 52 days of median wait time from diagnosis to first treatment.[23,24] Yet one Canadian study showed that despite the recommended time of 2 weeks between symptom onset and diagnosis, the actual median time to diagnosis was 4.5 months.[9] It has been estimated that every 4 weeks between scans represents the potential for a 13% progression.[25] Kasymjanova et al describe 2 studies and a meta-analysis demonstrating that increased wait times impart a negative effect on recurrence and survival.[23] In their own study, it was noted that reduced wait times particularly benefited Stage III NSCLC survival.[23]

Because pulmonologists may be the first specialist a patient sees, they are relied upon to diagnose, stage, and coordinate care for many patients with lung cancer.[26] Because Stage III NSCLC is a curative intent setting,[13,27] it is of particular importance to coordinate more complicated surgical, radiation, and chemotherapy care for these patients as soon as the diagnosis and stage have been ascertained.[7] While initial chest computed tomography or positron emission tomography (PET) scans often determine tumor size(s) and location(s), and presence of hilar or mediastinal nodes and extrathoracic lesions (excluding the brain), these studies cannot be the sole factors used in staging, and they falsely overstage 19% of the time and understage 13% of the time.[28] The ACCP guidelines recommend magnetic resonance imaging (MRI) of the brain for patients with clinical Stage III or IV disease with or without symptoms of intracranial disease,[29] whereas NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend staging brain MRI in patients with clinical Stage IB (optional), IIA/B, IIIA/B/C and IV.[30]

Diagnostic procedures to obtain accurate histological diagnosis and staging and adequate tissue samples for molecular testing must be considered, ideally with input from a multidisciplinary team (MDT) composed of pulmonologists, thoracic surgeons, and radiology specialists who are board certified and have expertise in thoracic oncology whenever any stage of NSCLC is suspected.[30] PET imaging can be used to identify the optimal biopsy site that produces the highest yield, is minimally invasive, and is most likely to confer the highest staging.[30] Whenever possible, procedures should be combined (bronchoscopy and endobronchial ultrasound with needle aspiration of lymph nodes) to improve time to diagnosis and clinical staging.[30] Invasive mediastinal staging is recommended before surgical resection.[30] The organization of lung cancer care requires development of a multidisciplinary program committed but not limited to the expeditious coordination of the patient's care among various disciplines to avoid unnecessary tests and procedures, delay in care, costly care, and patient frustration and anxiety.[31] Multidisciplinary care has been shown to decrease time to diagnosis and improve referral for appropriate treatment.[32] In particular, patients with Stage III NSCLC are more

TABLE 1. Summary of NSCLC Staging & Prognosis[3,21,22]

Stage	TNM Classification[21] (Tumor, Node, Metastases)	Nodal Zones & Stations[3,22]		Treatment/Goal[22]	5-Year Survival[21]
IA_1	T1a or T1a(mi), N0, M0			Surgery or radiation	92%
IA_2	T1b, N0, M0			Surgery ± radiation, OR Radiation	83%
IA_3	T1c, N0, M0				77%
IB	T2a, N0, M0			Surgery ± Chemotherapy± Radiation	68%
IIA	T2b, N0, M0				60%
IIB	T1a-c, N1, M0 <or> T2a-b, N1, M0 <or> T3, N0, M0	N1 generally resectable N2 heterogenous resectability	N1 = Hilar Zone if ipsilateral • Station 10 (Hilar nodes) Peripheral Zone if ipsilateral • Station 11 (Interlobar nodes) • Station 12 (Lobar Nodes) • Station 13 (Segmental Nodes) • Station 14 (Subsegmental Nodes		53%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or> T3-4, N1, M0 <or> T4, N1, M0			Surgery ± Chemotherapy ± Radiation	36%
IIIB	T3, N2, M0 <or> T4, N2, M0		N2 = Lower Zone if ipsilateral • Station 8 (Paraesophageal nodes) • Station 9 (Pulmonary ligament nodes) Subcarinal Zone if ipsilateral • Station 7 (Subcarinal nodes) Aortopulmonary Zone • Station 5 (subaortic & aortopulmonary nodes) • Station 6 (para-aortic nodes) Superior Mediastinal Zone • Station 2 (Upper paratracheal nodes) • Station 3 (Prevascular & retrotracheal nodes) • Station 4 (Lower paratracheal nodes)		26%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or>	N2 = heterogenous resectability N3 generally non-resectable		Radiation ± Chemotherapy ± Immunotherapy	36-41%†
IIIB	T1a-c, N3, M0 <or> T2a-b, N3, M0 <or> T3, N2, M0 <or> T4, N2, M0		N3 = Supraclavicular Zone • Station 1 (Low cervical, supraclavicular, sternal notch nodes • contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, superclavicular nodes	Radiation ± Chemotherapy ± Immunotherapy	24-26%†
IIIC	T3-4, N3, M0				12-13%†
IVA	Any T, Any N, M1a-b			Palliative Care with Systemic Therapy	0%
IVB	Any T, Any N, M1c				0%

Abbreviations: M1a, separate tumor contralateral lobe or primary tumor with pleural/pericardial nodules or malignant effusions; M1b, single extrathoracic mass; M1c, multiple extrathoracic masses; mi, minimally invasive adenocarcinoma.
T1a ≤ 1cm; T1b >1cm, ≤ 2cm; T1c >2cm, ≤ 3cm; T2a >3cm, ≤ 3cm; T2b >4cm, ≤ 5cm; T3 >5cm, ≤ 7cm; T4 >7cm.
†Reflects changes in 5-year survival of all stage III NSCLC when staging included pathology information.

likely to receive appropriate treatment when referred to oncology specialists.[7] Still, data suggest that up to 20% of patients diagnosed with Stage III NSCLC are never evaluated by an oncologist.[33]

The tumor, node, metastasis (TNM) system for staging has been used since 1944.[8] Now governed by the International Association for the Study of Lung Cancer (IASLC), the eighth edition took effect in 2017.[21] Several changes from the seventh edition, including new TNM definitions and addition of categories, have caused shifts in staging, with a greater emphasis on tumor size and invasion of surrounding tissues.[3] As a result, Stage III now includes subtype C (T3-T4, N3, M0), which is still treated in a curative intent setting.[21] Additionally, nodal zones were further broken down into more specific stations that clearly define anatomic landmarks within each zone, as this too proved to be associated with prognosis.[3] Differentiating Stage IIIC from Stage IVA has provided more patients the opportunity to be treated in a curative intent setting, as further data collection and new research are expanding within each subtype and allowing for individualized treatment approaches.[3,21]

Clinically, the distinction between resectable and unresectable Stage III disease is of significance because unresectable Stage III does not afford a treatment path as well-established as resectable disease (surgery).[34] Unresectable generally includes Stage IIIA tumors (T1-T2 tumors with multiple positive ipsilateral mediastinal notes), often described as bulky or extensive; Stage IIIB (T1-T2 tumors with positive contralateral mediastinal or supraclavicular nodes or T3-T4 tumors with positive ipsilateral mediastinal nodes); and Stage IIIC (T3-T4 tumors with positive contralateral mediastinal or supraclavicular nodes).[11]

Treatment of Stage III NSCLC

Patients clinically determined to have resectable Stage III NSCLC are candidates for a variety of treatment options, none of which have proven to be superior.[11] The 2019 NCCN Guidelines® suggest the following course for resectable Stage III NSCLC: (1) Preoperative chemotherapy (CT) and radiation (CTR), or preoperative CT followed by postoperative RT (split-panel decision); and (2) surgery, using minimally invasive techniques where possible.[30] The panel acknowledges that controversy remains regarding the sequencing of surgery, chemotherapy, and radiation techniques.

The majority of patients with Stage III NSCLC have unresectable disease.[35] Platinum-based CT has been preferred over other chemotherapeutic modalities for over 3 decades.[36] Evidence supports its use as part of definitive CRT along with a minimum of 60 Gy in escalated doses; concurrent treatment is currently preferred over sequential in all histological findings.[30] Accelerated RT alone imparts some benefit to those who refuse CT.[11]

Severe immune-mediated adverse reactions are associated with all immune checkpoint inhibitors, including pneumonitis, causing discontinuation.[37] A recent retrospective single-center study suggests that patients who are on corticosteroids for cancer-unrelated indications have similar outcomes on immunotherapy as patients who are receiving 0 to < 10 mg of prednisone.[37] However, additional mechanistic studies as well as prospective clinical trials are needed to identify whether the use of corticosteroids affects specific aspects of the immune system necessary for immunotherapy activity. Optimal treatment duration for immune checkpoint inhibitors requires further study, and their use in patients with autoimmune disorders and a past organ transplantation should be avoided.[38]

Conclusion

Locally advanced and metastatic NSCLC patients have benefitted from intensive research into immunologic approaches to treatment. Accurate diagnosis and staging are critical, particularly in the differentiation between Stage III, which is treated with curative intent, and Stage IV, which is metastatic. CRT is the current standard of care for unresectable Stage III disease and has shown improvement in overall survival, while the introduction of immunotherapy following CRT treatment can be discussed as a treatment option. To reap the benefits of these advances in treatment, patients with suspected or confirmed lung cancer should be managed by an MDT that includes a pulmonologist, thoracic surgeon, and medical and radiation oncologists, and referral for appropriate treatment of Stage III and IV NSCLC is crucial to improving patient outcomes.

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Pulegone levels in mint-flavored e-liquids, smokeless tobacco products exceed FDA limits

BY LUCAS FRANKI
MDedge News

A group of mint- and menthol-flavored e-liquids and smokeless tobacco products contained significantly more pulegone – a known carcinogen that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms – than the Food and Drug Administration considers acceptable, according to new findings.

Pulegone, an oil extract from mint plants such as peppermint, spearmint, and pennyroyal, was banned as a food additive by the agency in 2018, and the tobacco industry has taken steps to minimize pulegone levels in cigarettes because of the toxicity concerns.

Studies from the Centers for Disease Control and Prevention, however, have indicated that mint- and menthol-flavored e-cigarette liquids and smokeless tobacco products marketed in the United States contain substantial amounts of the substance, Sairam V. Jabba, DVM, PhD, and Sven-Eric Jordt, PhD, said in a research letter published in JAMA Internal Medicine.

Dr. Jabba and Dr. Jordt, both with the department of anesthesiology at Duke University, Durham, N.C., calculated the margin of exposure in five e-liquids (V2 Menthol, V2 Peppermint, Premium Menthol, South Beach Smoke Menthol, and South Beach Smoke Peppermint) and one smokeless tobacco product (Skoal Xtra Mint snuff) by dividing the no–observed adverse event level (13.39 mg/kg of bodyweight per day) by the mean human exposure to e-liquids or smokeless tobacco. The FDA considers margin-of-exposure values of 10,000 or less to require mitigation strategies.

The six products included in the analysis had pulegone concentration levels ranging from 25.7 to 119.0 mcg/g (a menthol cigarette has a pulegone concentration of 0.037-0.290 mcg/g). Based on those levels, light daily use (5 mL e-liquid, 10 g smokeless tobacco, half a pack of cigarettes) exposed e-cigarette users to 44-198 times more pulegone, compared with menthol cigarettes, and exposed smokeless tobacco users to 168-1,319 times as much pulegone. The margin of exposure ranged from 1,298 to 6,012, all below the threshhold the FDA deems acceptable.

For heavy daily use (20 mL e-liquid, 30 g smokeless tobacco, two packs of cigarettes), e-cigarette users were exposed to 282-1,608 times more pulegone, compared with menthol cigarettes; smokeless tobacco users were exposed to 126-990 times more pulegone. The margin of exposure ranged from 325 to 1,503.

The study findings "appear to establish health risks associated with pulegone intake and concerns that the FDA should address before suggesting mint- and menthol-flavored e-cigarettes and smokeless tobacco products as alternatives for people who use combustible tobacco products," Dr. Jabba and Dr. Jordt concluded.

The study was funded by a grant from the National Institute of Environmental Health Sciences. Dr. Jordt reported receiving grants from the NIEHS and the National Institute on Drug Abuse, personal fees from Hydra Biosciences and Sanofi, and nonfinancial support from GlaxoSmithKline. Dr. Jabba reported no disclosures.

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Tocilizumab preserves lung function in systemic sclerosis

BY SARA FREEMAN
MDedge News

MADRID – Tocilizumab (Actemra) preserved lung function in patients with early systemic sclerosis (SSc), according to a secondary endpoint analysis of the phase 3, double-blind, randomized, controlled focuSSced trial.

After 48 weeks, a significantly lower proportion of patients treated with tocilizumab than placebo experienced any decline in lung function from baseline (50.5% versus 70.3% (P = .015), as defined by the percentage increase in predicted forced vital capacity (%pFVC). When only patients with interstitial lung disease (ILD) were considered, the respective percentages were 51.7% and 75.5% (P = .003).

In SSc-ILD patients, a clinically meaningful decline of 10% or more of the %pFVC in lung function was seen in 24.5% given placebo but in just 8.6% of those treated with tocilizumab.

"ILD is a major complication of scleroderma; it has high morbidity and mortality ... and it's largely irreversible," Dinesh Khanna, MD, said at the European Congress of Rheumatology.

"In this day and age, when we treat ILD, we wait for a patient to develop clinical ILD," added Dr. Khanna, director of the scleroderma program at the University of Michigan, Ann Arbor. Clinical ILD can be defined by symptoms, abnormal pulmonary function tests, and marked abnormalities on high-resolution computed tomography (HRCT) scans. He indicated that, if improving ILD was not possible, then the next best thing would be to stabilize the disease and ensure there was no worsening in lung function.

Robert Lodge/MDedge News

Dr. Dinesh Khanna spoke at the European Congress of Rheumatology, on the use of tocilizumab. Watch the interview at https://tinyurl.com/.y3ydsecu.

As yet, there are no disease-modifying treatments available to treat SSc but there are "ample data that interleukin-6 plays a very important role in the pathogenesis of scleroderma," Dr. Khanna observed. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor.

Data from the phase 2 faSScinate trial showed initial promise for the drug in SSc where a numerical, but not statistically significant, improvement in skin thickening was seen, and the results had hinted at a possible benefit on lung function (Lancet. 2016 Jun 25;387:2630-40).

However, in the phase 3 focuSSced trial, there was no statistically significant difference in the change from baseline to week 48 modified Rodnan skin score (mRSS) between tocilizumab and placebo, which was the primary endpoint. The least-square mean change in mRSS was –6.14 for tocilizumab and –4.41 for placebo (P = .0983).

A total of 205 patients with SSc were studied and randomized, 1:1 in a double-blind fashion, to receive either a once-weekly, subcutaneous dose of 162 mg tocilizumab or a weekly subcutaneous placebo injection for 48 weeks.

For inclusion in the study, patients had to have SSc that met American College of Rheumatology and European League Against Rheumatism (EULAR) criteria and be diagnosed less than 60 months previously. Patients had to have an mRSS of 10-35 units and active disease with one or more of the following: C-reactive protein of 6 mg/L or higher; erythrocyte sedimentation rate of 28 mm/h or higher; and platelet count of330 x 10^9 L.

Roche/Genentech sponsored the study. Dr. Khanna acts as a consultant to Roche/Genentech and eight other pharmaceutical companies. He owns stock in Eicos Sciences.

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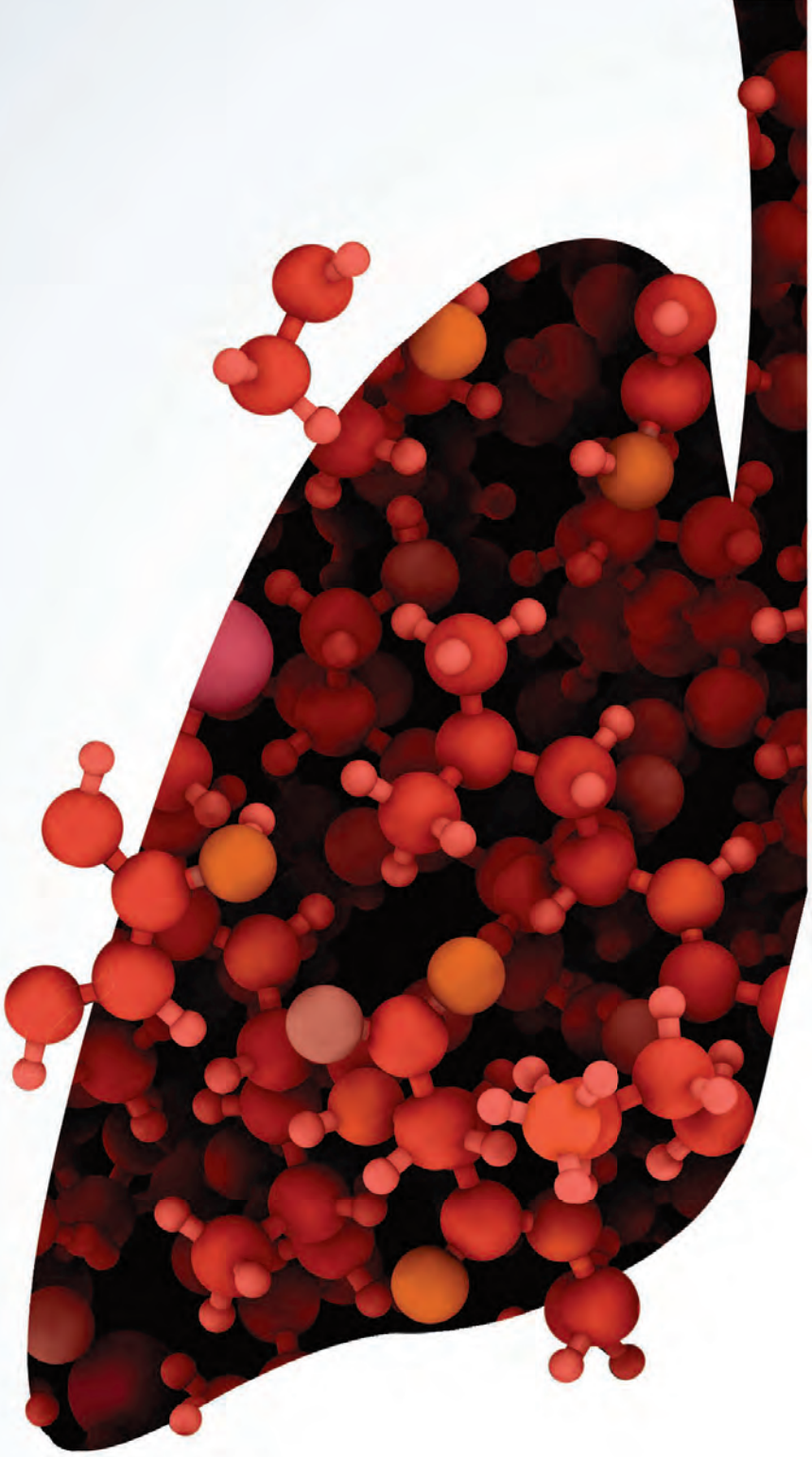
SOURCE: Khanna D et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):202-3, Abstract OP0245. doi: 10.1136/annrheumdis-2019-eular.2120



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Benefits of peanut desensitization may not last

BY HEIDI SPLETE
MDedge News

About a third of peanut-allergic patients given oral immunotherapy (OIT) passed a peanut challenge when the therapy was reduced, based on data from a phase 2 randomized trial of individuals with confirmed peanut allergies.

Previous studies have shown that desensitization to peanuts can be successful, but sustained response to oral immunotherapy after treatment reduction or discontinuation has not been well studied, wrote R. Sharon Chinthrajah, MD, of Stanford (Calif.) University, and colleagues.

"We found that OIT with peanut was able to desensitise people with peanut allergy to 4,000 mg of peanut protein, but that discontinuation of peanut, or even a reduction to 300 mg daily, increased the likelihood of regaining clinical reactivity to peanut," they wrote. "With peanut allergy therapies in varying stages of clinical development, and some nearing [Food and Drug Administration] approval, vital questions remain regarding the durability of treatment effects and the appropriate maintenance doses."

In the Peanut Oral Immunotherapy Study: Safety Efficacy and Discovery (POISED), published in The Lancet, the researchers randomized 120 participants to three groups:

- 60 patients built up to a maintenance dose of 4,000 mg of peanut protein for 104 weeks followed by total discontinuation (peanut-0).
- 35 patients built up to a maintenance dose of 4,000 mg of peanut protein for 104 weeks followed by a 300-mg maintenance dose of peanut protein in the form of peanut flour (peanut-300).
- 25 patients had an oat flour placebo.

All participants were trained on how and when to use epinephrine autoinjector devices to treat allergic symptoms such as respiratory problems (cough, shortness of breath, or change in voice), widespread hives or erythema, repetitive vomiting, persistent abdominal pain, angioedema of the face, or feeling faint.

The primary outcome was passing a double-blind, placebo-controlled, food challenge (DBPCFC) to 4,000 mg of peanut protein, which was measured at baseline and at weeks 104, 117, 130, 143, and 156.

Overall, 35% of the peanut-0 group passed the challenge at 104 and 117 weeks, compared with 4% of the placebo group. At week 156 after discontinuing OIT, 13% of the peanut-0 group met the DBPCFC challenge, compared with 4% of the placebo group. However, 37% of participants randomized to a reduced peanut protein dose of 300 mg passed the challenge at 156 weeks, suggesting that more data are needed on optimal maintenance dosing strategies.

Baseline demographics were similar across all groups. The median age at study enrollment was 11 years and the median allergy duration was 9 years. The most common adverse events were mild gastrointestinal and respiratory problems. Adverse events decreased over time in all three groups.

"Higher levels of peanut-specific IgE to total IgE ratio, peanut sIgE, Ara h 1, Ara h 2, and Ara h 1 IgE to peanut-specific IgE ratio at baseline in participants were associated with increased frequencies of adverse events during active peanut OIT," the researchers noted.

The study findings were limited by several factors including the ability of participants to tolerate 4,000 mg of peanut protein after achieving a maintenance dose but conducting serial testing only for those who passed the challenge. In addition, the results may be limited to peanut and not generalizable to other food allergies, the researchers said.

However, the results suggest that OIT remains a promising treatment for peanut allergies, and the association of biomarkers with clinical outcomes "might help the practitioner in identifying good candidates for OIT and those individuals who warrant increased vigilance against allergic reactions during OIT," they said.

The National Institutes of Health supported the study. The researchers had no financial conflicts to disclose.

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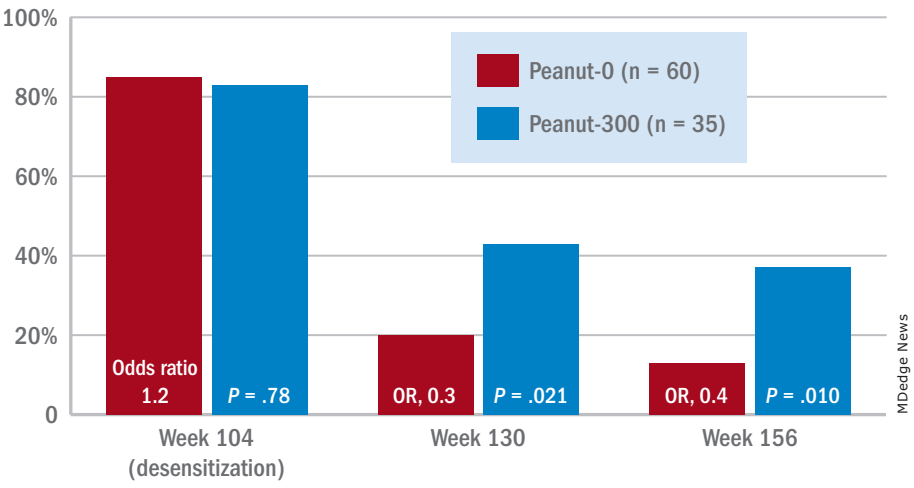
SOURCE: Chinthrajah RS et al. Lancet. 2019 Sep 12. doi: 10.1016/S0140-6736(19)31793-3.

OIT patients who passed food challenge to peanut



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Note: Based on data from a phase 2 randomized trial of peanut oral immunotherapy (OIT).
Source: Lancet. 2019 Sep 12. doi: 10.1016/S0140-6736(19)31793-3

Allergy immunotherapy may modify asthma severity

BY MARK S. LESNEY
MDedge News

The use of a grass-based allergy immunotherapy (AIT) lowered the risk of progression from milder to more severe asthma, according to the results of a large, real-world, industry-sponsored, observational study.

The researchers analyzed a cohort of 1,739,440 patients aged 12 years and older using 2005-2014 data from a statutory health insurance database in Germany. From this population, 39,167 individuals aged 14 years or older were classified as having incident asthma during the observation period and were included in the study.

The severity of asthma was classified according to the treatment steps recommended by the Global Initiative for Asthma (GINA).

Among these, 4,111 patients (10.5%) received AIT. AIT use was associated with a significantly decreased likelihood of asthma progression from GINA step 1 to step 3 (hazard ratio, 0.87; 95% confidence interval, 0.80-0.95) and GINA step 3 to step 4 (HR, 0.66; 95% CI, 0.60-0.74).

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Medications for GINA step 2 (3.5%) and GINA step 5 (0.03%) were rarely prescribed, so the researchers could not analyze the transition between GINA steps 1 and 2, step 2 and 3, and step 4 and 5.

A total of 8,726 patients had at least one transition between GINA steps 1, 3, or 4, and 1,085 had two transitions, though not all 39,167 patients were under risk of severity progression into all GINA steps, according to the authors.

The findings are consistent with earlier studies that indicate grass-based immunotherapy can effectively treat asthma symptoms and potentially asthma progression (J Allergy Clin Immuno. 2012;129[3];717-25; J Allergy Clin Immunol. 2018;141[2]:529-38).

"This study indicates that AIT may modify the course of asthma. Our study supports the assumption that treatment with AIT may prevent the progression from mild to more severe asthma," the authors concluded.

The study was financially supported by ALK-Abelló; several of the authors were also employees of or received funding from the company.

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SOURCE: Schmitt J et al. Allergy. 2019. doi: 10.1111/all.14020.

Vaping habit may lead to nicotine addiction in teens

BY RICHARD FRANKI
MDedge News

Adolescents' past 30-day use of e-cigarettes more than doubled from 2017 to 2019, and in 2019 almost 12% of high school seniors reported that they were vaping every day, according to data from the Monitoring the Future surveys.

Daily use – defined as vaping on 20 or more of the previous 30 days – was reported by 6.9% of 10th-grade and 1.9% of 8th-grade respondents in the 2019 survey, which was the first time use in these age groups was assessed. "The substantial levels of daily vaping suggest the development of nicotine addiction," Richard Miech, PhD, and associates said Sept. 18 in the New England Journal of Medicine.

From 2017 to 2019, e-cigarette use over the previous 30 days increased from 11.0% to 25.4% among 12th graders, from 8.2% to 20.2% in 10th graders, and from 3.5% to 9.0% of 8th graders.

By 2019, over 40% of 12th-grade students reported ever using e-cigarettes, along with more than 36% of 10th graders and almost 21% of 8th graders. Corresponding figures for past 12-month use were 35.1%, 31.1%, and 16.1%, they reported.

The analysis was funded by a grant from the National Institute on Drug Abuse to Dr. Miech.

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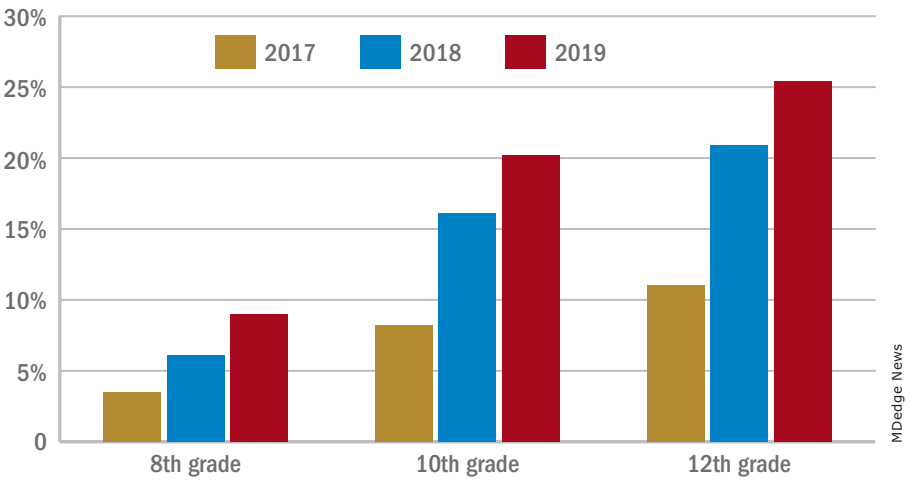
SOURCE: Miech R et al. N Engl J Med. 2019 Sep 18. doi: 10.1056/NEJMc1910739.

Prevalence of vaping among adolescents in the past 30 days



Note: Based on data from the Monitoring the Future surveys.
Source: N Engl J Med. 2019 Sep 18. doi: 10.1056/NEJMc1910739

Serum testosterone and estradiol levels associated with current asthma in women

BY THERESE BORDEN
MDedge News

Elevated serum levels of circulating sex hormones were found to be associated with lower odds of asthma in women, possibly explaining in part the different prevalence of asthma in men and women, according to the findings of a large cross-sectional population based study.

Yueh-Ying Han, PhD, of the Children's Hospital of Pittsburgh and colleagues investigated the role of free testosterone and estradiol levels and current asthma among adults. The impact of obesity on that association was also examined. The investigators analyzed data from 7,615 adults (3,953 men and 3,662 women) who participated in the 2013-2014 and 2015-2016 U.S. National Health and Nutrition Examination Survey. The data included health interviews, examination components, and laboratory tests on each patient. Serum samples were analyzed by the division of laboratory sciences of the Centers for Disease Control and Prevention. Logistic regression was used for the multivariable analysis of sex hormone levels (as quartiles) and current asthma, and the analysis was done separately on men and women. Pregnant women were excluded, in addition to individuals with incomplete data. The exclusions tended to be Hispanic ethnicity, former smokers, lower income, and lack private insurance. The overall prevalence of current asthma in the sample was 9% (6% in men and 13% in women).

Three models were generated based on serum levels in women and in men.

For model 1 (unadjusted for estradiol), women whose serum testosterone levels were in the second and fourth quartiles had 30%-45% significantly lower odds of having current asthma than those whose serum testosterone level was in the lowest quartile. Among men, those whose serum testosterone levels were in the second and fourth quartiles had 12%-13% lower odds for current asthma.

For model 2 (unadjusted for free testosterone), women whose serum estradiol levels were in the third quartile had 34% significantly lower odds of having current asthma than those whose estradiol levels were in the lowest quartile. The findings were similar for men, that is, those whose serum estradiol levels were in the third quartile had 30% lower odds for having asthma, compared with those with in the lowest quartile.

The investigators wrote, "Androgens such as testosterone may reduce innate and adaptive immune responses, while estrogen and progesterone may enhance T-helper cell type 2 allergic airway inflammation."

For model 3 (a multivariable model including serum levels of both estradiol and free testosterone), women whose serum testosterone levels were in the second and fourth quartiles had 30% and 44% lower odds of current asthma than those whose serum testosterone levels were in the lowest quartile. But in this multivariable model, the association between serum estradiol and current asthma was not significant. Among men (models 1-3), the magnitude of the estimated effect of serum testosterone and serum estradiol on current asthma was similar to that observed in female participants, but neither serum testosterone nor serum estradiol was significantly associated with current asthma.

The investigators then analyzed the impact of obesity on the relationship between serum hormone levels and obesity. Obesity was defined as body mass index equal to or greater than 30 kg/m^2. A total of 1,370 men and 1,653 women were included in this analysis. In multivariable analyses of the obese participants, adjustment without (model 1) and with (model 3) serum estradiol, serum free-testosterone levels in the highest (fourth) quartile were significantly associated with reduced odds of asthma in obese women. In multivariable analyses without (model 2) and with (model 3) testosterone, serum estradiol levels above the first quartile were significantly associated with reduced odds of current asthma in obese women.

In contrast to the results in obese women, neither serum free testosterone nor serum estradiol was significantly associated with current asthma in obese men or nonobese women.

Dr. Han and coauthors suggested a possible mechanism of the role of sex hormones in asthma. "Androgens such as testosterone may reduce innate and adaptive immune responses, while estrogen and progesterone may enhance T-helper cell type 2 allergic airway inflammation."

They concluded: "We found that elevated serum levels of both free testosterone and estradiol were significantly associated with reduced odds of asthma in obese women, and that elevated levels of serum estradiol were significantly associated with reduced odds of asthma in nonobese men. Our findings further suggest that sex steroid hormones play a role in known sex differences in asthma among adults."

One coauthor has received research materials from Merck and GlaxoSmithKline (inhaled steroids), as well as Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in National Institutes for Health–funded studies, unrelated to the current work. The other authors reported no conflicts of interest.

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SOURCE: Han Y-Y et al. J Respir Crit Care Med. 2019 Sep 16. doi: 10.1164/rccm.201905-0996OC.

NOW APPROVED to treat excessive daytime sleepiness (EDS) in adult patients with narcolepsy or obstructive sleep apnea (OSA)

There's a new way to help patients caught in...

THE EXCESSIVE DAYTIME SLEEPINESS ZONE

INDICATIONS AND USAGE

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.

INTRODUCING ONCE-DAILY SUNOSI—a NEW, dual-acting daytime treatment for EDS indicated for adult patients with narcolepsy or OSA. SUNOSI is not a stimulant. At week 12, SUNOSI 150 mg improved wakefulness through **9 HOURS**.[1]

Visit SUNOSIhcp.com or contact a Jazz representative to learn more

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

Psychiatric Symptoms

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

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

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

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

MOST COMMON ADVERSE REACTIONS

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

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

Reference: 1. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2019.

Jazz Pharmaceuticals

SUNOSI™ (solriamfetol) CIV
75, 150 mg tablets

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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Dapagliflozin moves from antidiabetic to HF drug

BY MITCHEL L. ZOLER
MDedge News

Dr. John McMurray

Dr. Deepak L. Bhatt

Mitchel L. Zoler/MDedge News

PARIS – Treatment with the SGLT2 inhibitor dapagliflozin produced a statistically significant 27% drop in cardiovascular death or heart failure events in patients with existing heart failure with reduced ejection fraction and no diabetes, results that in a stroke changed the status of dapagliflozin from fundamentally a drug that treats diabetes to a drug that treats heart failure.

"Dapagliflozin offers a new approach to the treatment of heart failure with reduced ejection fraction" (HFrEF), John McMurray, MD, said at the annual congress of the European Society of Cardiology.

The results he reported from the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) trial showed statistically significant benefits when adding dapagliflozin to guideline-directed therapy for a list of outcomes that include a 17% drop in all-cause death compared with placebo, an 18% fall in cardiovascular death, and a 25% relative reduction in total heart failure hospitalizations plus cardiovascular deaths during a median follow-up of just over 18 months. The primary endpoint of the reduction in cardiovascular death, first heart failure hospitalization, or an urgent heart failure visit fell by 25% in the enrolled patients with diabetes (45% of the study population, all with type 2 diabetes), and by 27% in the remaining patients who had no diabetes, showing that the presence of diabetes had no impact on the heart failure benefit from dapagliflozin. The absolute reduction in the primary endpoint was about 5%, with a number needed to treat of 21 to prevent one primary endpoint during 18 months of treatment.

Dr. Mann

Dr. McMurray's report of the primary endpoint and the finding that the drug was as effective in patients without diabetes as in those with diabetes were met with loud applause by the packed congress audience.

The efficacy results also showed that 58% of patients on dapagliflozin had a clinically meaningful (5-point or greater) increase in their quality of life score on the Kansas City Cardiomyopathy Questionnaire after 8 months on treatment compared with a 51% rate in the placebo patients, a statistically significant difference.

The safety results showed no new signals for a drug that already has regulatory approval but was being used in a novel population. The rate of major hypoglycemia was virtually nonexistent, 0.2%, and identical in both treatment arms. All adverse events occurred at roughly equal rates in the dapagliflozin and placebo groups, with a 5% rate of adverse events leading to study discontinuation in both arms, and a serious adverse event rate of 38% in the dapaglifolzin patients and 42% in the placebo patients. The rate of worsening renal function was less than 2% in both arms and not statistically different.

"This is as close to a home run as you see in heart failure treatment," commented Douglas L. Mann, MD, professor of medicine at Washington University, St. Louis, and a heart failure clinician and researcher.

DAPA-HF "is a landmark trial. It took a diabetes drug and used it in patients without diabetes, a concept that would have been considered outlandish 5 years ago. Scientifically it's huge," commented Deepak L. Bhatt, MD, professor of medicine at Harvard Medical School in Boston.

The DAPA-HF results were another step in the remarkable journey toward heart failure intervention taken by the SGLT2 (sodium glucose cotransport 2) inhibitor class of drugs that includes dapagliflozin as well as canagliflozin (Invokana) and empagliflozin (Jardiance), a path that began 4 years ago with the report of empagliflozin's unexpected efficacy for reducing cardiovascular death and heart failure hospitalizations in a large cardiovascular-safety study, EMPA-REG OUTCOME (N Engl J Med. 2015 Nov 26;373[22]:2117-28). Subsequent reports showed similar effects benefiting heart failure and survival for canagliflozin and dapagliflozin, and now with DAPA-HF the evidence extended the benefit to heart failure patients regardless of whether they have diabetes. Additional studies now in progress are exploring the same question for empagliflozin and canagliflozin.

The results from DAPA-HF are likely a class effect for all these SGLT2 inhibitors, suggested Dr. McMurray in a video interview, a view shared by several other experts. He cautioned clinicians against using dapagliflozin to treat patients with heart failure with reduced ejection fraction but without diabetes until this indication receives regulatory approval, and even then using dapagliflozin or other SGLT2 inhibitors this way may take some getting used to on the part of cardiologists and other clinicians.

"The results put dapagliflozin in the same league as [standard HFrEF drugs], but using it will require a shift in thinking. "I'm sure most cardiologists are not familiar with the SGLT2 inhibitors; we'll have to educate them," conceded Dr. McMurray, professor of medical cardiology at the University of Glasgow. However, other aspects of dapagliflozin and this drug class in general may make the SGLT2 inhibitors particularly attractive and spur their use once labeling changes.

The adverse-event profile seen in DAPA-HF looked very "clean," said Dr. Mann, especially compared with the other medical classes recommended in guidelines for patients with HFrEF: the angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid-receptor antagonists such as spironolactone, and the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan (Entresto). "I think dapagliflozin will have a huge uptake [for treating HFrEF], because it will be easy for primary care physicians to prescribe. It will be easier to use than traditional heart failure medications." Once approved for heart failure use, Dr. Mann predicted a standard dosing regimen for HFrEF patients of an ACE inhibitor, ARB or ARNI, a beta-blocker, a mineralocorticoid-receptor antagonist, and an SGLT2 inhibitor. He suggested that this large and cumbersome collection of medications could conceivably be simplified into a polypill.

DAPA-HF was sponsored by AstraZeneca, the company that markets dapagliflozin (Farxiga). AstraZeneca paid Glasgow University to cover Dr. McMurray's salary during the time he spent working as principal investigator of DAPA-HF. Dr. McMurray had no other relevant disclosures. Dr. Mann has been a consultant to Bristol-Myers Squibb, LivaNova, Novartis, and Tenaya Therapeutics. Dr. Bhatt has received research funding from AstraZeneca, and he has served as a consultant to or received research funding from several other companies.

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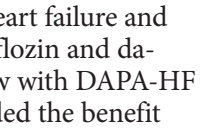
VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: Interesting study with important findings that appear to be a game changer in the treatment of HFrEF.



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Women may be treated with lower doses of HF drugs

BY RANDY DOTINGA
MDedge News

Men and women react differently to common drugs used to treat heart failure with reduced ejection fraction (HFrEF), according to findings from a new European study, and women may be able to safely cut their doses in half and get the same level of relief as that provided by larger doses.

"This study ... brings into question what the true optimal medical therapy is for women versus men," the study authors, led by Bernadet T. Santema, MD, of the University Medical Center Groningen (the Netherlands), wrote in an article published in the Lancet.

Dr. Santema and colleagues noted that current guidelines for the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) and beta-blockers for men and women with heart failure do not differentiate between the genders, despite findings showing that, "with the same dose, the maximum plasma concentrations of ACE inhibitors, ARBs, and beta-blockers were up to 2.5 times higher in women than in men."

In addition, the researchers wrote, women are much more likely than men to suffer side effects from medications, and the effects tend to be more severe.


Dr. Santema

HFrEF accounts for an estimated 50% of the 5.7 million patients with heart failure in the United States (Nat Rev Dis Primers. 2017 Aug 24. doi: 10.1038/nrdp.2017.58; Card Fail Rev. 2017;3[1]:7-11).

For the new study, researchers launched an ad hoc analysis of the findings of a prospective study of HFrEF patients in 11 European countries (1,308 men and 402 women) who took drugs in the three classes. Patients were receiving suboptimal medication doses at the start of the study, and physicians were encouraged to increase their medication. The median follow-up for the primary endpoint was 21 months.

"In men, the lowest hazards of death or hospitalization for heart failure occurred at 100% of the recommended dose of ACE inhibitors or ARBs and beta-blockers, but women showed about 30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels," the researchers wrote. "These sex differences were still present after adjusting for clinical covariates, including age and body surface area."

The researchers analyzed an Asian registry (3,539 men, 961 women) as a comparison and found the identical numbers.

"Our study provides evidence supporting the hypothesis that women with HFrEF might have the best outcomes with lower doses of ACE inhibitors or ARBs and beta-blockers than do men, and lower doses than recommended in international guidelines for heart failure," they wrote. However, they added that it was not likely that sex-specific studies analyzing doses would be performed.

In an accompanying editorial, Heather P. Whitley, PharmD, and Warren D. Smith, PharmD, noted that clinical research has often failed to take gender differences into account. They wrote that the study – the first of its kind – was well executed and raises important questions, but the analysis did not take into account the prevalence of adverse effects or the serum concentrations of the various medications. Although those limitations weaken the findings, the study still offers evidence that gender-based, drug-dose guidelines deserve consideration, wrote Dr. Whitley, of Auburn (Ala.) University, and Dr. Smith, of Baptist Health System, Montgomery, Ala. (Lancet. 2019 Aug 22. doi: 10.1016/S0140-6736[19]31812-4).

The study was funded by the European Commission. Several study authors reported various disclosures. Dr. Whitley and Dr. Smith reported no conflicts of interest.

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SOURCE: Santema BT et al. Lancet. 2019 Aug 22. doi: 10.1016/S0140-6736(19)31792-1.

Visceral adiposity tied to higher risk of masked hypertension

BY M. ALEXANDER OTTO
MDedge News

NEW ORLEANS – Visceral adiposity, but not body mass index or total body fat, significantly correlated with elevated 24-hour ambulatory systolic blood pressure, greater systolic variability, and masked hypertension in a study from the University of Pennsylvania, Philadelphia.

Subjects in the highest quartile of visceral fat had a 6.3-fold greater odds of masked hypertension – normal in the office, but high at home – compared with those in the lowest quartile (95% confidence interval, 1.2-33.1).

The study findings suggest that central obesity, in particular, should trigger 24-hour ambulatory blood pressure monitoring (ABPM). "Every obese person should get a 24-hour" ABPM, but "we really need to be pushing [it] in people who have central adiposity. These are the patients ... we really need to focus on" because of the risk of masked hypertension, a "ticking time bomb" that greatly increases the risk of cardiovascular events, said lead investigator Jordana B. Cohen, MD, an assistant professor of medicine at the university.

The study also helps explain why body mass index hasn't been consistently linked to masked hypertension in previous studies; some studies likely included subjects with high BMIs but not central obesity.

Waist circumference, a marker of visceral adiposity, also correlated with elevated 24-hour systolic pressure and greater variability, but a trend for masked hypertension was not statistically significant, Dr. Cohen reported at the joint scientific sessions of the American Heart Association (AHA) Council on Hypertension, AHA Council on Kidney in Cardiovascular Disease, and American Society of Hypertension.


Dr. Cohen

It's long been known that visceral fat – fat around the abdominal organs – is metabolically active and associated with greater cardiovascular risk, but it's relationship to blood pressure hadn't been well described, so Dr. Cohen and her team decided to take a look.

They ran whole-body dual-energy x-ray absorptiometry scans on 96 hypertensive adults on a stable dose of one antihypertensive drug for at least 2 months and correlated the findings with ABPM. Subjects were an average of 58 years old, almost 60% were women, almost half were black, and 54% were obese, with BMIs of at least 30 kg/m^2.

After adjustment for age, sex, race, and antihypertensive class, the team found a significant, linear correlation between visceral fat and mean 24-hour systolic blood pressure. Patients with a visceral adiposity of about 0.1 kg/m^2, for instance, had a mean pressure of around 130 mm Hg, compared with patients with more than 0.6 kg/m^2, who had a mean of almost 150 mm Hg. Findings were similar for waist circumference over a range of 70-150 cm.

The correlations were weak (r = 0.3), but Dr. Cohen said they might improve with ongoing enrollment. Both measures also correlated with systolic variability.

Overall, the highest quartiles of waist circumference and visceral adiposity correlated with the highest mean systolic pressures and greatest variability, compared with the lowest quartiles. Visceral adiposity was the only measure significantly linked with masked hypertension. Trends in those directions for increasing BMI and total body fat mass were not statistically significant.

Mean BMI in the study was 31.7 kg/m^2, and mean waist circumference was 104 cm. Mean 24-hour systolic blood pressure was 135 mm Hg and mean 24-hour systolic variability was 13 mm Hg. Almost 30% of the subjects had masked hypertension. Drug classes included beta-blockers, calcium channel blockers, diuretics, ACE inhibitors, and angiotensin receptor blockers.

Dr. Cohen plans to investigate drug response versus visceral adiposity once the recruitment goal of 150 subjects is reached.

There was no external funding, and the investigators reported that they didn't have any relevant disclosures.

aotto@mdedge.com

SOURCE: Cohen JB et al. Joint Hypertension 2019, Abstract P2052.

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The FIRST AND ONLY once-daily nebulized LAMA, for a full 24 hours of lung function improvement[1]

Proven 24-hour control[1]
Consistent improvement in trough FEV_1 vs placebo over 24 hours on days 84/85[1,2]

The primary endpoint was change from baseline in trough (predose) FEV_1 at day 85 vs placebo: YUPELRI demonstrated a statistically significant difference vs placebo in study 1 (146 mL, *P*<.0001 [YUPELRI, n=189; placebo, n=191]) and study 2 (147 mL, *P*<.0001 [YUPELRI, n=181; placebo, n=187]).[1,2]

In study 1, LS mean changes from baseline in FEV_1 ranged from 55.8 mL to 240.4 mL in the YUPELRI group, and from -113.6 mL to 59.6 mL in the placebo group. In study 2, LS mean changes from baseline in FEV_1 ranged from 19.8 mL to 148.5 mL in the YUPELRI group, and from -176.4 mL to -13.0 mL in the placebo group.

In studies 1 and 2, a prespecified exploratory analysis using serial spirometry was performed on a substudy population (YUPELRI, n=89; placebo, n=83) over 24 hours on days 84/85. In a pooled analysis, YUPELRI demonstrated consistent improvement in trough FEV_1 vs placebo over the 24-hour period.

Demonstrated safety profile[1]
Refer to the Important Safety Information below for additional information

Once-daily dosing[1]
Administered with any standard jet nebulizer with a mouthpiece

Up to 100% of patients with Medicare Part B are expected to be covered*
Permanent J-CODE J7677

*This is not a guarantee of coverage. Site of care will determine coverage. Check with your patient's insurance provider for coverage rules and restrictions. In certain limited instances, YUPELRI may be covered through a patient's Medicare Part D pharmacy benefit.

Indication

YUPELRI® inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Important Safety Information

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD, or for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

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

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Patients should be instructed to immediately consult their healthcare provider if they develop any signs and symptoms of acute narrow-angle glaucoma, including eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema.

Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur.

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If a reaction occurs, YUPELRI should be stopped at once and alternative treatments considered.

The most common adverse reactions occurring in clinical trials at an incidence greater than or equal to 2% in the YUPELRI group, and higher than placebo, included cough, nasopharyngitis, upper respiratory infection, headache and back pain.

Coadministration of anticholinergic medicines or OATP1B1 and OATP1B3 inhibitors with YUPELRI is not recommended.

YUPELRI is not recommended in patients with any degree of hepatic impairment.

Please see Brief Summary of Full Prescribing Information on the adjacent pages.

Learn more at YUPELRIHCP.com

References: 1. YUPELRI [package insert]. Morgantown, WV: Mylan Specialty L.P.; May 2019. **2.** Data on file.

Mylan®
Theravance Biopharma

YUPELRI® (revefenacin) inhalation solution, for oral inhalation

Initial U.S. Approval: 2018

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

YUPELRI inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

WARNINGS AND PRECAUTIONS

Deterioration of Disease and Acute Episodes

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD. YUPELRI has not been studied in subjects with acutely deteriorating COPD. The initiation of YUPELRI in this setting is not appropriate.

YUPELRI is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

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

Paradoxical Bronchospasm

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

Worsening of Narrow-Angle Glaucoma

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

YUPELRI should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered.

ADVERSE REACTIONS

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

- Paradoxical bronchospasm *[see Warnings and Precautions]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions]*
- Worsening of urinary retention *[see Warnings and Precautions]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions]*

Clinical Trial Experience

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

The YUPELRI safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with YUPELRI 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

YUPELRI was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with YUPELRI at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy. Patients with unstable cardiac disease, narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

Table 1 shows the most common adverse reactions that occurred with a frequency of greater than or equal to 2% in the YUPELRI group and higher than placebo in the two 12 week placebo- controlled trials.

The proportion of subjects who discontinued treatment due to adverse reactions was 13% for the YUPELRI-treated subjects and 19% for placebo-treated subjects.

Table 1: Adverse Events with YUPELRI ≥2% Incidence and Higher than Placebo

	Placebo (N = 418)	YUPELRI 175 mcg (N = 395)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (4%)	17 (4%)
Infections and Infestations		
Nasopharyngitis	9 (2%)	15 (4%)
Upper respiratory tract infection	9 (2%)	11 (3%)
Nervous System Disorders		
Headache	11 (3%)	16 (4%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (1%)	9 (2%)

Other adverse reactions defined as events with an incidence of ≥1.0%, less than 2.0%, and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain, and bronchitis.

52-Week Trial

YUPELRI was studied in one 52-week, open-label, active-control (tiotropium 18 mcg once daily) trial in 1,055 patients with COPD. In this trial, 335 patients were treated with YUPELRI 175 mcg once daily and 356 patients with tiotropium. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled 12-week studies described, with the exception that concurrent LABA or LABA/ICS therapy was used in 50% of patients. The adverse reactions reported in the long-term safety trial for YUPELRI were consistent with those observed in the placebo-controlled studies of 12-weeks.

DRUG INTERACTIONS

Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of YUPELRI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions]*.

Transporter-Related Drug Interactions

OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) could lead to an increase in systemic exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended *[see Clinical Pharmacology.]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with YUPELRI in pregnant women. Women should be advised to contact their physician if they become pregnant while taking YUPELRI. In animal reproduction studies, subcutaneous administration of revefenacin to pregnant rats and rabbits during the period of organogenesis produced no evidence of fetal harm at respective exposures approximately 209 times the exposure at the maximum recommended human dose (MRHD) (on an area under the curve [AUC] basis) *(see Data).*

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

Data

Animal Data

In an embryo fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 209 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

In an embryo fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7 to 19, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 694 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Placental transfer of revefenacin and its active metabolite was observed in pregnant rabbits.

In a pre- and postnatal development (PPND) study in pregnant rats dosed during the periods of organogenesis and lactation from gestation day 6 to lactation day 20, revefenacin had no adverse developmental effects on pups at exposures up to 196 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Lactation

Risk Summary

There is no information regarding the presence of revefenacin in human milk, the effects on the breastfed infant, or the effects on milk production. However, revefenacin was present in the milk of lactating rats following dosing during pregnancy and lactation *(see Data).*

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUPELRI and any potential adverse effects on the breastfed infant from YUPELRI or from the underlying maternal condition.

Data

Animal Data

In a PPND study *[see Pregnancy],* revefenacin and its active metabolite were present in milk of lactating rats on lactation day 22. Milk-to-plasma concentration ratios were up to 10 for revefenacin and its active metabolite.

Pediatric Use

YUPELRI is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of YUPELRI in geriatric patients is necessary.

Clinical trials of YUPELRI included 441 subjects aged 65 years and older, and of those, 101 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

The systemic exposure of revefenacin is unchanged while that of its active metabolite is increased in subjects with moderate hepatic impairment. The safety of YUPELRI has not been evaluated in COPD patients with mild-to-severe hepatic impairment. YUPELRI is not recommended in patients with any degree of hepatic impairment. *[see Clinical Pharmacology].*

Renal Impairment

No dosage adjustment is required in patients with renal impairment. Monitor for systemic antimuscarinic side effects in COPD patients with severe renal impairment. *[see Clinical Pharmacology].*

OVERDOSAGE

An overdose of YUPELRI may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding. In COPD patients, orally inhaled administration of YUPELRI at a once-daily dose of up to 700 mcg (4 times the maximum recommended daily dose) for 7 days was well tolerated.

Treatment of overdosage consists of discontinuation of YUPELRI along with institution of appropriate symptomatic and/or supportive therapy.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies in Sprague-Dawley rats and CD1 mice were conducted to assess the carcinogenic potential of revefenacin. No evidence of tumorigenicity was observed in male and female rats at inhaled doses up to 338 mcg/kg/day (approximately 35 times the MRHD based upon summed AUCs for revefenacin and its active metabolite). No evidence of tumorigenicity was observed in male and female mice at inhaled doses up to 326 mcg/kg/day (approximately 40 times the MRHD based on summed AUCs for revefenacin and its active metabolite).

Revefenacin and its active metabolite were negative for mutagenicity in the Ames test for bacterial gene mutation. Revefenacin was negative for genotoxicity in the *in vitro* mouse lymphoma assay and *in vivo* rat bone marrow micronucleus assay.

There were no effects on male or female fertility and reproductive performance in rats at subcutaneous revefenacin doses up to 500 mcg/kg/day (approximately 30 times the MRHD on an mg/m^2 basis for revefenacin).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use) with each new prescription and refill.

Not for Acute Symptoms

Inform patients that YUPELRI is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with YUPELRI without healthcare provider guidance since symptoms may recur after discontinuation.

Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue YUPELRI.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Instructions for Administering YUPELRI

It is important for patients to understand how to correctly administer YUPELRI using a standard jet nebulizer [see Instructions for Use]. Instruct patients that YUPELRI should only be administered via a standard jet nebulizer. Patients should be instructed not to inject or swallow the YUPELRI solution. Patients should be instructed not to mix other medications with YUPELRI.

Patients should not inhale more than one dose at any one time. The daily dosage of YUPELRI should not exceed one unit-dose vial. Inform patients to use the contents of one vial of YUPELRI orally inhaled daily at the same time every day. Patients should throw the plastic dispensing vials away immediately after use. Due to their small size, the vials pose a danger of choking to young children.

REV-2019-0194

Daily polypill lowered CV risk in underserved community

BY JAKE REMALY
MDedge News

A daily polypill regimen improved cardiovascular risk factors in a socioeconomically vulnerable minority population, in a randomized controlled trial.

Patients at a federally qualified community health center in Alabama who received treatment with a combination pill for 1 year had greater reductions in systolic blood pressure and LDL cholesterol than did patients who received usual care, according to results published online on Sept. 19 in the New England Journal of Medicine.

"The simplicity and low cost of the polypill regimen make this approach attractive" when barriers such as lack of income, underinsurance, and difficulty attending clinic visits are common, said first author Daniel Muñoz, MD, of Vanderbilt University in Nashville, Tenn., and coinvestigators. The investigators obtained the pills at a cost of $26 per month per participant.

Common risk factors with low treatment rates

People with low socioeconomic status and those who are nonwhite have high cardiovascular mortality, and the southeastern United States and rural areas have disproportionately high levels of cardiovascular disease burden, according to the investigators. The rates at which people with low socioeconomic status receive treatment for hypertension and hypercholesterolemia – leading cardiovascular disease risk factors – "are strikingly low," Dr. Muñoz and colleagues said.

"Although the precision approach has clear virtues, a broader approach may benefit patients who face barriers to accessing the full advantages of precision medicine."

To assess the effectiveness of a polypill-based strategy in an underserved population with low socioeconomic status, the researchers conducted the randomized trial.

They enrolled 303 adults without cardiovascular disease, and 148 of the patients were randomized to receive the polypill, which contained generic versions of atorvastatin (10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg). The remaining 155 patients received usual care. All participants scheduled 2-month and 12-month follow-up visits.

The participants had an average age of 56 years, 60% were women, and more than 95% were black. More than 70% had an annual household income of less than $15,000. Baseline characteristics of the treatment groups did not significantly differ.

At baseline, the average BP was 140/83 mm Hg, and the average LDL cholesterol level was 113 mg/dL.

In all, 91% of the participants completed the 12-month trial visit. Average systolic BP decreased by 9 mm Hg in the group that received the polypill, compared with 2 mm Hg in the group that received usual care. Average LDL cholesterol level decreased by 15 mg/dL in the poly -pill group, versus 4 mg/dL in the usual-care group.

Changes in other medications

Clinicians discontinued or reduced doses of other antihypertensive or lipid-lowering medications in 44% of the patients in the polypill group and none in the usual-care group. Clinicians escalated therapy in 2% of the participants in the polypill group and in 10% of the usual-care group.

Side effects in participants who received the polypill included a 1% incidence of myalgias and a 1% incidence of hypotension or light-headedness. Liver function test results were normal.

Five serious adverse events that occurred during the trial – two in the polypill group and three in the usual-care group – were judged to be unrelated to the trial by a data and safety monitoring board.

The authors noted that limitations of the trial include its open-label design and that it was conducted at a single center.

"It is important to emphasize that use of the polypill does not preclude individualized, add-on therapies for residual elevations in blood-pressure or cholesterol levels, as judged by a patient's physician," said Dr. Muñoz and colleagues. "We recognize that a 'one size fits all' approach to cardiovascular disease prevention runs counter to current trends in precision medicine, in which clinical, genomic, and lifestyle factors are used for the development of individualized treatment strategies. Although the precision approach has clear virtues, a broader approach may benefit patients who face barriers to accessing the full advantages of precision medicine."

The study was supported by grants from the American Heart Association Strategically Focused Prevention Research Network and the National Institutes of Health. One author disclosed personal fees from Novartis outside the study.

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SOURCE: Muñoz D et al. N Engl J Med. 2019 Sep 18;381(12):1114-23. doi: 10.1056/NEJMoa1815359.

Drug abuse–linked infective endocarditis spiking in U.S.

BY JENNIE SMITH
MDedge News

Hospitalizations for infective endocarditis associated with drug abuse doubled in the United States from 2002 to 2016, in a trend investigators call "alarming," and link to a concurrent rise in opioid abuse.

Patients tend to be younger, poorer white males, according to findings published online in the Journal of the American Heart Association.

For their research, Amer N. Kadri, MD, of the Cleveland Clinic and colleagues looked at records for nearly a million hospitalizations for infective endocarditis (IE) in the National Inpatient Sample registry. All U.S. regions saw increases in drug abuse–linked cases of IE as a share of IE hospitalizations. Incidence of drug abuse–associated IC rose from 48 cases/100,000 population in 2002 to 79/100,000 in 2016. The Midwest saw the highest rate of change, with an annual percent increase of 4.9%.

While most IE hospitalizations in the study cohort were of white men (including 68% for drug-linked cases), the drug abuse–related cases were younger (median age, 38 vs. 70 years for non-drug-related IE), and more likely male (55.5% vs. 50%). About 45% of the drug-related cases were in people receiving Medicaid, and 42% were in the lowest quartile of median household income.

sdominick/Getty Images

The drug abuse cases had fewer renal and cardiovascular comorbidities, compared with the nondrug cases, but were significantly more likely to present with HIV, hepatitis C, alcohol abuse, and liver disease. Inpatient mortality was lower among the drug-linked cases – 6% vs. 9% – but the drug cases saw significantly more cardiac or valve surgeries, longer hospital stays, and higher costs.

"Hospitalizations for IE have been increasing side by side with the opioid epidemic," the investigators wrote in their analysis. "The opioid crisis has reached epidemic levels, and now drug overdoses have been the leading cause of injury-related death in the U.S. Heroin deaths had remained relatively low from 1999 until 2010 whereas it then increased threefold from 2010-2015." The analysis showed a rise in drug abuse–associated IE "that corresponds to this general period." The findings argue, the investigators said, for better treatment for opioid addiction after hospitalization and greater efforts to make drug rehabilitation available after discharge. The researchers described as a limitation of their study the use of billing codes that changed late in the study period, increasing detection of drug abuse cases after 2015. They reported no outside funding or conflicts of interest.

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SOURCE: Kadri AN et al. J Am Heart Assoc. 2019;8:e012969..

High-flow nasal cannula: Higher limit cut down on bronchiolitis ICU transfers

BY M. ALEXANDER OTTO
MDedge News

SEATTLE – ICU transfers for acute bronchiolitis dropped 63% at Johns Hopkins All Children's Hospital in St. Petersburg, Fla., after the high-flow nasal cannula limit on the floor was raised from 6 L/min to 12 L/min, and treatment was started in the emergency department, according to a presentation at Pediatric Hospital Medicine.

A year before the change was made in April 2018, there were 17 transfers among 249 bronchiolitis patients treated on the floor, a transfer rate of 6.8%. In the year after the change, there were 8 among 319 patients, a transfer rate of 2.5%. Raising the limit to 12 L/min prevented an estimated 14 transfers, for a total savings of almost $250,000, said pediatric hospitalist and assistant professor Shaila Siraj, MD.

The change was made after Dr. Siraj and her colleagues noticed that, when children topped out at 6 L, they sometimes only needed a slightly higher flow rate in the ICU, maybe 8 L or 10 L, for a short while before they came back to the floor. Given the safety of high-flow nasal cannula (HFNC), the ICU transfer often seemed like a waste of time and resources.


Dr. Shaila Siraj


Dr. Anthony Sochet

"You have to ask what floor resources you have, what's your ability to escalate when you need to. Use data from your own institution to guide where you pick your cutoffs. Adequate staffing is really about respiratory [therapist]/nursing ratios, not the physicians," said Dr. Sochet.

"As hospitalists, we felt we could safely take care of these patients," Dr. Siraj said.

So she and her colleague pediatric critical care specialist Anthony Sochet, MD, also an assistant professor of pediatrics, reviewed over a year's worth of data at All Children's. They found that 12 L/min – roughly 1.5 L/kg/min – was the cutoff that best discriminated between patients who needed intubation and those who did not, "so that's what we chose," Dr. Sochet said.

For simplicity, they broke limits down by age: a maximum flow rate of 8 L/min for children up to 6 months old; 10 L for children aged 6-12 months; and up to 12 L/min for children age 12-24 months. The fraction of inspired oxygen remained the same at 50%. Children were started at maximum flows, then weaned down as they improved. Respiratory assessments were made at least every 4 hours.

The changes were part of a larger revision of the hospital's pathway for uncomplicated bronchiolitis in children up to 2 years old; it was a joint effort involving nurses, respiratory therapists, and pediatric hospitalists, and ED and ICU teams.

Early initiation in the ED was "probably one of the most important" changes; it kept children from wearing out as they struggled to breathe. Kids often start to improve right away, but when they don't after 30-60 minutes, it's an indication that they should probably be triaged to the ICU for possible intubation, Dr. Siraj said.

Dr. Sochet was careful to note that institutions have to assess their own situations before taking similar steps. "Not everyone has a tertiary care ICU staffed 24 and 7," he said.

"You have to ask what floor resources you have, what's your ability to escalate when you need to. Use data from your own institution to guide where you pick your cutoffs. Adequate staffing is really about respiratory [therapist]/nursing ratios, not the physicians," he said.

In addition, "in an otherwise healthy child that just has [HFNC] for bronchiolitis, there is absolutely no reason why you should be withholding feeds." Fed children will feel better and do better, he said.

The presenters had no disclosures.

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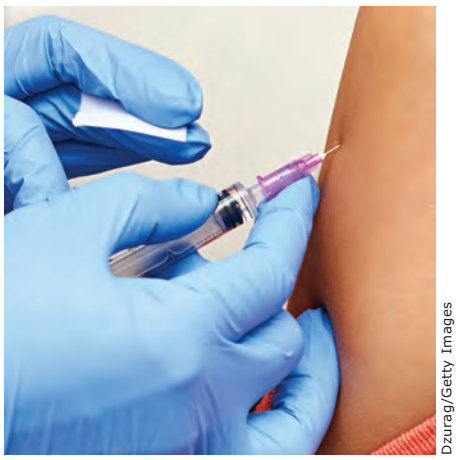
Susan Millard, MD, FCCP, comments: Quite a bit more research needs to be done regarding use of high-flow nasal cannula (HFNC) therapy for bronchiolitis patients. In addition, at the end of the article, the researcher comments on feeding patients on high-flow nasal cannula therapy. I want to see more research in this area. My perspective is that we receive consults on babies who are on the floor, unable to wean from HFNC, and the first thing we recommend is to stop feeding those babies orally. Is the airway being safely protected without micro-aspiration when on HFNC for acute respiratory failure?

Parent education ups pediatric flu vaccination rate

BY CHRISTOPHER PALMER
MDedge News

A brief educational handout about influenza and vaccination prior to seeing a health care provider increased pediatric vaccination rates by the season's end, according to a randomized clinical trial published in Pediatrics.

Vanessa P. Scott, MD, MS, of Columbia University, New York, and colleagues randomized 400 parent-child dyads into any of three



Dzurag/Getty Images

arms: receiving a handout based on national data, receiving a handout based on local data, or receiving usual care. This convenience sample was drawn from two pediatric clinics in New York between August 2016 and March 2017.

After adjustment for parents' education level, the trial found that parents who received either handout were significantly more likely than were those receiving usual care to vaccinate their children by the end of season (75% and 65%, respectively; adjusted odds ratio, 1.68; 95% confidence interval, 1.06-2.67), but the effects of any intervention versus those of usual care on vaccination on day of visit were not statistically significant (59% vs. 53%; aOR, 1.36; 95% CI, 0.89-2.09). The researchers had hoped that using a targeted approach based on local data would increase vaccine receipt, but that was not seen in the results.

They did find that, across all three arms in the trial, baseline parental intent to vaccinate (likely versus unlikely) was associated with vaccination rates: Both vaccination on clinic visit day (70% vs. 22%; aOR, 8.38; 95% CI, 4.85-14.34) and vaccination by end of season (87% vs. 29%; aOR, 18.26; 95% CI, 9.94-33.52) were affected.

Strengths of the study included the randomized, controlled design and assessment of baseline factors, such as intention to vaccinate, to reduce confounding effects. Limitations included use of a convenience sample, which could have introduced selection bias.

One author was an unremunerated coinvestigator of an unrelated trial that received an investigator-initiated grant from the Pfizer Medical Education Group. Two authors were funded by other grants, but no potential conflicts of interests to disclose were indicated by any of the authors in this study.

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SOURCE: Scott VP et al. Pediatrics. 2019. doi: 10.1542/peds.2018-2580.

Study shows how to predict CF bronchiectasis in children early in life

BY MICHELE G. SULLIVAN
MDedge News

Among preschool children with cystic fibrosis, airway disease as measured by the Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF) accurately predicts bronchiectasis in grade school, reported Nynke R. Bouma, BSc, and colleagues.

"Even though bronchiectasis is present in 60% to 80% of children with CF in school age, the extent and severity of bronchiectasis in preschool children are generally lower. ... however, diffuse airway abnormalities such as airway wall thickening and mucus plugging are observed in many preschool children. It is hypothesized that these preschool airway changes reflect diffuse airway disease that eventually will result in bronchiectasis in school age," they noted.

The PRAGMA-CF image scoring system can measure airway disease and can also be used to monitor disease progression, noted Ms. Bouma of Sophia Children's Hospital, Rotterdam, and colleagues. The study was published in Pediatric Pulmonology. PRAGMA-CF is a composite score of airway wall thickening, mucus plugging, and bronchiectasis as percent disease (%disease). "In preschool children, %disease measured by PRAGMA-CF on chest CT allows quantification of early clinically relevant morphological features of CF airway disease and it is associated with later school-age bronchiectasis," the team wrote. "These findings support the use of %disease as a clinically relevant outcome measure in early CF lung disease."

The team conducted a prospective cohort study of 61 children (mean age 4 years) with cystic fibrosis, following them for a mean of 5 years. A total of 122 CT scans were available from this group, in addition to spirometry data and cystic fibrosis quality of life scores.

From preschool age to school age, the %disease on PRAGMA-CF increased significantly, from a mean of 0.7% to 1.73%. Scores on another composite measuring tool (%MUPAT, a composite score of airway wall thickening and mucus plugging) went from 0.46 to 0.58 – not a significant difference. A multivariate analysis corrected for age in each school group and the type of scanner used to acquire the images. That analysis determined that each 1% increase in %disease at preschool age resulted in an increase of 1.18% of bronchiectasis at school age.

A cross-sectional analysis of the group at school age found significant associations between the %disease and percent of forced expiratory volume and the cystic fibrosis quality of life score.

At least one pulmonary exacerbation requiring intravenous antibiotics occurred in 19 of the patients. However, the investigators didn't find any significant interactions between the %disease in preschool and these exacerbations.

"These findings are in line with previous studies in school-aged children that showed that mucus plugging is associated with inflammation and airway wall thickening, and that these are thought to be risk factors for later bronchiectasis," they concluded. "We suggest that %disease and %MUPAT could be used as a clinically relevant outcome measure in clinical studies in preschool patients with cystic fibrosis, as these measures predict later bronchiectasis. Percent disease may be preferred as it captures all the principal features of CF airways disease including bronchiectasis."

Ms. Bouma had no financial disclosures.

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SOURCE: Bouma NR et al. Pediatr Pulmonol. 2019 Sep 9. doi: 10.1002/ppul.24498

Case study: CPAP kept infants with bronchiolitis out of ICU

BY M. ALEXANDER OTTO
MDedge News

SEATTLE – Rady Children's Hospital in San Diego has been doing continuous positive airway pressure (CPAP) for infants with bronchiolitis on the general pediatrics floors safely and with no problems for nearly 20 years, according to a presentation at Pediatric Hospital Medicine meeting.

It's newsworthy because "very, very few" hospitals do bronchiolitis CPAP outside of the ICU. "The perception is that there are complications, and you might miss kids that are really sick if you keep them on the floor." However, "we have been doing it safely for so long that no one thinks twice about it," said Christiane Lenzen, MD, a pediatric hospitalist at Rady and an assistant clinical professor of pediatrics at the University of California, San Diego.

It doesn't matter if children have congenital heart disease, chronic lung disease, or other problems, she said, "if they are stable enough for the floor, we will see if it's okay."

Rady's hand was forced on the issue because it has a large catchment area but limited ICU beds, so for practical reasons and within certain limits, CPAP moved to the floors. One of Dr. Lenzen's colleagues noted that, as long as there's nurse and respiratory leadership buy in, "it's actually quite easy to pull off in a very safe manner."


Dr. Lenzen

Rady has a significant advantage over community hospitals and other places considering the approach, because it has onsite pediatric ICU services for when things head south. Over the past 3 or so years, 52% of the children the pediatric hospital medicine service started on CPAP (168/324) had to be transferred to the ICU; 17% were ultimately intubated.

Many of those transfers were caused by comorbidities, not CPAP failure, but other times children needed greater respiratory support; in general, the floor CPAP limit is 6 cm H_2O and a fraction of inspired oxygen of 50%. Also, sometimes children needed to be sedated for CPAP, which isn't done on the floor.

With the 52% transfer rate, "I would worry about patients who are sick enough to need CPAP staying" in a hospital without quick access to ICU services, Dr. Lenzen said at the meeting sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

Even so, among 324 children who at least initially were treated with CPAP on the floor – out of 2,424 admitted to the pediatric hospital medicine service with bronchiolitis – there hasn't been a single pneumothorax, aspiration event, or CPAP equipment–related injury, she said.

CPAP on the floor has several benefits. ICU resources are conserved, patient handoffs and the work of transfers into and out of the ICU are avoided, families don't have to get used to a new treatment team, and infants aren't subjected to the jarring ICU environment.

For it to work, though, staff "really need to be on top of this," and "it needs to be very tightly controlled" with order sets and other measures, the presenters said. There's regular training at Rady for nurses, respiratory therapists, and hospitalists on CPAP equipment, airway management, monitoring, troubleshooting, and other essentials.

Almost all children on the pediatric floors have a trial of high-flow nasal cannula with an upper limit of 8 L/min. If the Respiratory Assessment Score hasn't improved in an hour, CPAP is considered. If a child is admitted with a score above 10 and they seem to be worsening, they go straight to CPAP.

Children alternate between nasal prongs and nasal masks to prevent pressure necrosis, and are kept nil per os while on CPAP. They are on continual pulse oximetry and cardiorespiratory monitoring. Vital signs and respiratory scores are checked frequently, more so for children who are struggling.

The patient-to-nurse ratio drops from the usual 4:1 to 3:1 when a child goes on CPAP, and to 2:1 if necessary. Traveling nurses aren't allowed to take CPAP cases.

The presenters didn't report any disclosures.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: It would take a unique and detailed hospital care map to safely manage acute CPAP on the floor. More research is imperative.

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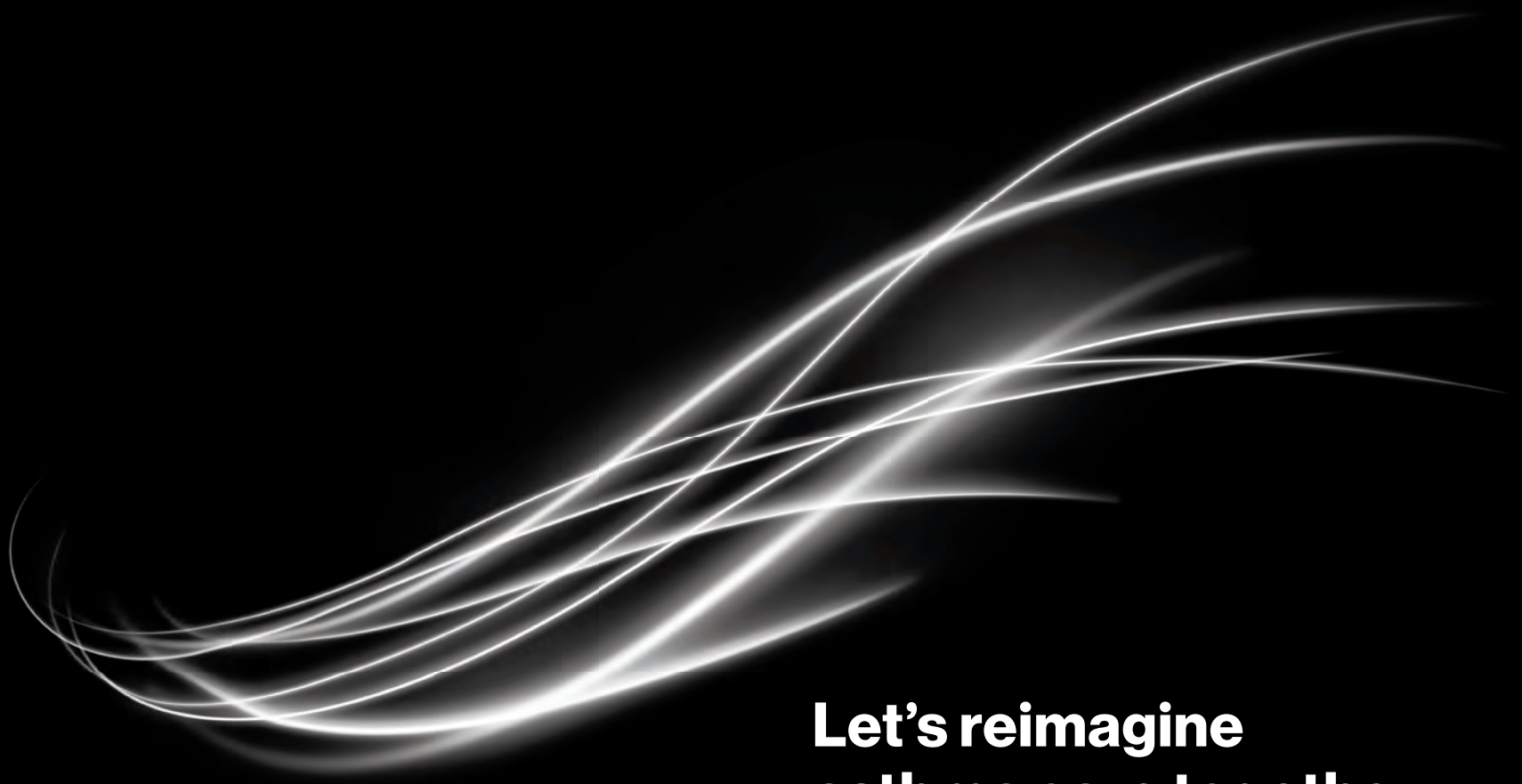

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Guideline: Blood CO_2 can be used to screen for OHS

BY JENNIE SMITH
MDedge News

A blood test for elevated carbon dioxide may be used in screening adults for obesity hypoventilation syndrome, according to new guidelines.

Obese adults with sleep disordered breathing and increased blood carbon dioxide levels during the day are likely to have obesity hypoventilation syndrome (OHS), a result of shallow or slow breathing that can lead to respiratory failure, heart failure, pulmonary hypertension, and death. Pulmonologists and sleep specialists may be the first to see and diagnose patients with OHS in the outpatient setting, while other cases are diagnosed in the hospital when patients present with hypercapnic respiratory failure.

Screening for OHS usually involves measuring arterial blood gases, which is not standard practice in outpatient clinics. Patients often remain undiagnosed and untreated until late in the course of the disease, according to the American Thoracic Society, which in August published a new diagnosis and management guideline aiming to boost early diagnosis and reduce variability in treatment (Am J Respir Crit Care Med. 2019;200:3,e6-e24).

The guideline authors, led by Babak Mokhlesi, MD, of the University of Chicago, recommend a simpler screening method – measuring serum bicarbonate only – to rule out OHS in obese patients with nighttime breathing problems.

Serum bicarbonate should be measured in obese patients with sleep-disordered breathing and a low likelihood of OHS, Dr. Mokhlesi and colleagues recommend in the guideline. If serum bicarbonate is below 27 mmol/L, it is not necessary to conduct further testing as the patient is unlikely to have OHS.

In patients whose serum bicarbonate is higher than 27 mmol/L, or who are strongly suspected of having OHS at presentation because of severe obesity or other symptoms, arterial blood gases should be measured and a sleep study conducted. The guideline authors said that there is insufficient evidence to recommend that pulse oximetry be used in the diagnostic pathway for OHS.

First-line treatment for stable, ambulatory patients with OHS should be positive airway pressure during sleep, rather than noninvasive ventilation, Dr. Mokhlesi and colleagues concluded. For patients with comorbid obstructive sleep apnea – as many as 70% of OHS patients also have OSA – the first-line treatment should be continuous positive airway pressure (CPAP) at night, the guideline states.

Patients hospitalized with respiratory failure and suspected of having OHS should be discharged with noninvasive ventilation until diagnostic procedures can be performed, along with PAP titration in a sleep lab.

In patients initially treated with CPAP who remain symptomatic or whose blood carbon dioxide does not improve, noninvasive ventilation can be tried, the guidelines say. Finally, patients diagnosed with OHS should be guided to weight-loss interventions with the aim of reducing body weight by 25%-30%. This can include referral for bariatric surgery in patients without contraindications.

Dr. Mokhlesi and colleagues acknowledged that all of the recommendations contained in the guideline are classed as "conditional," based on the quality of evidence assessed.

The American Thoracic Society funded the study. Dr. Mokhlesi and 7 coauthors disclosed financial conflicts of interest, while an additional 13 coauthors had none. Disclosures can be found on the AJRCCM website.

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SOURCE: Mokhlesi B et al. Am J Respir Crit Care Med. 2019;200:3,e6-24.

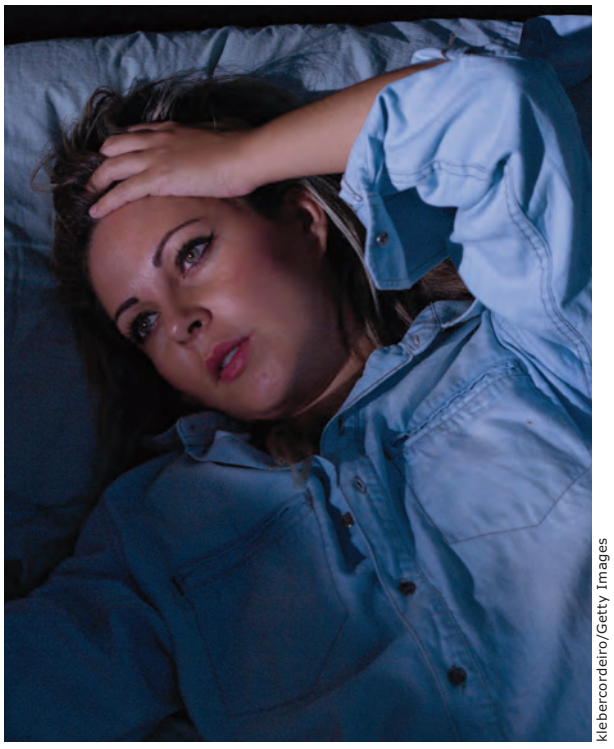
Childhood behavioral issues may signal adult insomnia risk

BY CHRISTOPHER PALMER
MDedge News

The odds of adulthood insomnia are significantly higher among those with childhood behavioral problems, according to research published in JAMA Network Open.

Yohannes Adama Melaku, MPH, PhD, of the Adelaide (Australia) Institute for Sleep Health at Flinders University and coauthors drew data from the 1970 UK Birth Cohort Study. This study followed an initial cohort of 16,571 babies who were born during a single week, with follow-up at ages 5, 10, 16, 26, 30, 38, 42, and 46 years. For the purposes of this study, the investigators looked at participants who, at 42 years of age, were alive and not lost to follow-up and who responded to an invitation to be interviewed; the sample sizes in the analysis were 8,050 participants aged 5 years, 9,090 participants aged 10 years, 9,653 participants aged 16 years, and 9,841 participants aged 42 years.

Behavior was measured at ages 5 years and 16 years using the Rutter Behavioral Scale (RBS) and at age 10 years using a visual analog scale, and insomnia symptoms were assessed through interviewing participants in adulthood about duration of sleep, difficulty initiating and maintaining sleep, and not feeling rested on waking. Participants were organized into normal behavior (less than or equal to 80th percentile on RBS), moderate behavioral problems (greater than the 80th percentile but less than or equal to the 95th percentile), and severe behavioral problems (above 95th percentile). The investigators then devised two models for their analysis: Model 1 adjusted for sex, parent's social class and educational level, marital status, educational status, and social class, and model 2 adjusted for physical activity level and body mass index trajectory (from 10 to 42 years), perceived health status, and number of noncommunicable diseases, although this latter model yielded fewer statistically significant results in some analyses.



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Odds for difficulty initiating or maintaining sleep as an adult was increased among participants with severe behavioral problems at age 5 years in model 1 (adjusted odds ratio, 1.50; 95% confidence interval, 1.14-1.96; $P = .004$), as well as for those with severe problems at 10 years (aOR, 1.30; 95% CI, 1.14-1.63; $P = .001$), and at 16 years (aOR, 2.17; 95% CI, 1.59-2.91; P less than .001). The aORs also were higher individually for difficulty initiating sleep and for difficulty maintaining sleep in all age groups.

The association with adulthood insomnia was stronger in participants with externalizing behavioral problems such as lying, bullying, having restlessness, and fighting than it was in those with internalizing behavioral problems such as worry, fearfulness, and solitariness.

"Although early sleep problems should be identified, we should additionally identify children with moderate to severe behavioral problems that persist throughout childhood as potential beneficiaries of early intervention with a sleep health focus," the authors wrote.

One of the study's limitations was a lack of standardized insomnia measures in the cohort study; however, the researchers suggested that the symptoms included reflect those of standardized measures and diagnostic criteria.

"This study is the first, to our knowledge, to suggest an unfavorable association of early-life behavioral problems with adulthood sleep health, underlining the importance of treating behavioral problems in children and addressing insomnia from a life-course perspective," they concluded.

No study sponsor was identified. The authors reported no relevant financial disclosures.

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SOURCE: Melaku YA et al. JAMA Netw Open. 2019 Sep 6. doi: 10.1001/jamanetworkopen.2019.10861.

Less CPAP time linked to exacerbation in COPD/OSA overlap syndrome

BY JAKE REMALY
MDedge News

Among patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), lung function and continuous positive airway pressure (CPAP) use are independent predictors of COPD exacerbations and all-cause mortality, according to a retrospective cohort study.

"These factors should be taken into account when considering the management and prognosis of these patients," the researchers said in the Clinical Respiratory Journal.

Prior studies have found that patients with COPD and OSA – that is, with overlap syndrome – "have a substantially greater risk of morbidity and mortality, compared to those with either COPD or OSA alone," said Philippe E. Jaoude, MD, and Ali A. El Solh, MD, both of the Veterans Affairs Western New York Healthcare System in Buffalo.

To identify factors associated with COPD exacerbation and all-cause mortality in patients with overlap syndrome, Dr. Jaoude and Dr. El Solh reviewed the electronic health records of patients with simultaneous COPD and OSA. They compared patients with overlap syndrome who had an acute exacerbation of COPD during a 42-month period with a control group of patients with overlap syndrome who did not have exacerbations during that time. Patients with exacerbations and controls were matched 1:1 by age and body mass index.

"Multivariate logistic regression analysis identified the independent risk factors associated with COPD exacerbations as active smoking, worse airflow limitation, and lower CPAP utilization."

Eligible patients were aged 42-90 years, had objectively confirmed COPD, and had documented OSA by in-laboratory polysomnography (that is, at least five obstructive apneas and hypopneas per hour). The investigators defined a COPD exacerbation as a sustained worsening of a patient's respiratory condition that warranted additional treatment.

Of 225 eligible patients, 92 had at least one COPD exacerbation between March 2014 and September 2017. Patients with COPD exacerbation and controls had a mean age of about 68 years. The group of patients with exacerbation had a higher percentage of active smokers (21% vs. 9%) and had poorer lung function (mean forced expiratory volume in 1 second percent predicted: 55.2% vs. 64.5%).

"Although the rate of CPAP adherence between the two groups was not significantly different, the average time of CPAP use was significantly higher in patients with no recorded exacerbation," the researchers reported.

In all, 146 patients (79.4%) survived, and 38 patients (20.6%) died during the study period. The crude mortality rate was significantly higher in the group with COPD exacerbations (14% vs. 7%).

"Multivariate logistic regression analysis identified the independent risk factors associated with COPD exacerbations as active smoking, worse airflow limitation, and lower CPAP utilization," they said. "As for all-cause mortality, a higher burden of comorbidities, worse airflow limitation, and lower time of CPAP use were independently associated with poor outcome." The researchers noted that they cannot rule out the possibility that patients who were adherent to CPAP were systematically different from those who were not. The authors declared no conflicts.

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SOURCE: Jaoude P et al. Clin Respir J. 2019 Aug 22. doi: 10.1111/crj.13079.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, FCCP, comments: In 1985, this comorbid association of COPD and OSA was named by David Flenley the "overlap syndrome" (Clin Chest Med. 1985;6:651-61). He posited that the COPD-OSA association had more deleterious effects than either disorder alone. Indeed, we learned over the years that the overlap syndrome presents with worse nocturnal hypoxemia and hypercapnia, more disturbed sleep, more frequent and more severe cardiac arrhythmias, daytime pulmonary hypertension, and higher mortality than either condition. Several (nonrandomized) studies showed that Positive Airway Pressure (PAP) therapy could mitigate the outcome differences noted previously between COPD and overlap syndrome. In the recent study published by Jaoude and El Solh (Clin Respir J. 2019), the authors found that lung function and PAP use were independent predictors of all-cause mortality and COPD exacerbations. While this was a retrospective analysis, the study reinforces the concept that the emerging phenoendotype of the overlap syndrome may delineate a patient category with much higher morbidity and mortality risks than the ones represented by the mere additive effects of these (and other) comorbidities. Perhaps not surprisingly, patients without COPD exacerbations had longer average time of PAP usage, while lower comorbid burden, better lung function, and longer use of PAP were correlates of better survival in this cohort. Appropriately, the authors indicate that the PAP usage category (long vs short use time) may be in fact a surrogate sign of totally different patient populations. As such, subjects more adherent to the proposed therapeutic plans may intrinsically have better motivation, superior follow-up care, longer PAP time, and improved overall outcomes, a dilemma unfortunately not easily solved in observational studies. Nevertheless, this analysis reinforces the previous signals from the literature on the potential benefits of PAP use in COPD-OSA overlap syndrome.

FDA approves Wakix for excessive daytime sleepiness

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved pitolisant (Wakix) for excessive daytime sleepiness among patients with narcolepsy, according to a release from the drug's developer.

Approval of this once-daily, selective histamine 3–receptor antagonist/inverse agonist was based on a pair of multicenter, randomized, double-blind, placebo-controlled studies that included a total of 261 patients. Patients in both studies experienced statistically significant improvements in excessive daytime sleepiness according to Epworth Sleepiness Scale scores.

Rates of adverse advents at or greater than 5% and more than double that of placebo included insomnia (6%), nausea (6%), and anxiety (5%). Patients with severe liver disease should not use pitolisant. Pitolisant has not been evaluated in patients under 18 years of age, and patients who are pregnant or planning to become pregnant are encouraged to enroll in a pregnancy exposure registry.

Jeffrey Dayno, MD, chief medical officer of the drug maker, Harmony Biosciences, stated, "Wakix is the only non-scheduled treatment option approved for adult patients with narcolepsy, and it offers an important benefit/risk profile to address the unmet medical need that exists in people living with narcolepsy."

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Vitamin C infusion falls short for sepsis and ARDS

BY HEIDI SPLETE
MDedge News

Vitamin C infusion did not improve outcomes related to organ failure, inflammation, or vascular injury for patients with sepsis and acute respiratory distress syndrome, based on data from 167 adults.

"Previous research found that vitamin C attenuates systemic inflammation, corrects sepsis-induced coagulopathy, and attenuates vascular injury," wrote Alpha A. Fowler III, MD, of Virginia Commonwealth University, Richmond, and colleagues.

"The inability of vitamin C to affect C-reactive protein and thrombomodulin levels in this trial possibly resulted from the advanced stages of sepsis that were present before the development of ARDS."

To examine the impact of vitamin C infusion on patients with sepsis and acute respiratory distress syndrome (ARDS), the researchers designed the CITRIS-ALI trial, a randomized, double-blind, placebo-controlled study conducted at 7 medical intensive care units in the United States.

In the study, published in JAMA, the researchers randomized 167 adults with sepsis and ARDS to receive high-dose intravenous vitamin C (50 mg/kg in 5% dextrose in water) or placebo (5% dextrose in water only) every 6 hours for 96 hours. The primary outcomes were measures of organ failure based on changes in the modified Sequential Organ Failure Assessment score (mSOFA), inflammation (based on changes in C-reactive protein), and vascular injury based on thrombomodulin.

Overall, no significant differences appeared between the vitamin C and placebo groups, respectively in the three primary outcome measures: change in average SOFA score (3-point change vs. a 3.5-point change) at 96 hours; change in C-reactive protein levels (change of 54.1 mcg/mL vs. 46.1 mcg/mL) at 168 hours; and change in thrombomodulin levels (14.5 ng/mL vs. 13.8 ng/mL) at 168 hours.

The average age of the patients was 55 years, and 54% were men.

The researchers also assessed 46 secondary outcomes. Most of these showed no significant differences between the groups, but 28-day all-cause mortality was significantly lower in the vitamin C group, compared with the placebo group (46.3% vs. 29.8%), the researchers said. Vitamin C also was significantly associated with increased ICU-free days to day 28 and hospital-free days to day 60, compared with placebo.

No significant differences were seen between the groups on 43 other secondary outcomes including ventilator-free days and vasopressor use. However, "these findings were based on analyses that did not account for multiple comparisons and therefore must be considered exploratory," they said.

"The inability of vitamin C to affect C-reactive protein and thrombomodulin levels in this trial possibly resulted from the advanced stages of sepsis that were present before the development of ARDS," the researchers noted.

The findings were limited by several factors including the variability in the timing of vitamin C administration and the use of a single high dose of vitamin C, they emphasized. However, the results suggest that further research may be needed to determine the potential of vitamin C for improving outcomes in patients with sepsis and ARDS, they said.

The study was supported by the National Heart, Lung, and Blood Institute, National Center for Advancing Translational Sciences, VCU Wright Center for Translational Science Award, VCU Investigational Drug Services, and McGuff Pharmaceuticals, who supplied the vitamin C free of charge. Dr. Fowler disclosed funding from Virginia Polytechnic Institute and State University, Richmond; the NHLBI; and study materials from McGuff Pharmaceuticals.

SOURCE: Fowler AA et al. JAMA. 2019 Oct 1;322:1261-70. doi:10.1001/jama.2019.11825.

Palliative care programs continue growth in U.S. hospitals

BY RICHARD FRANKI
MDedge News

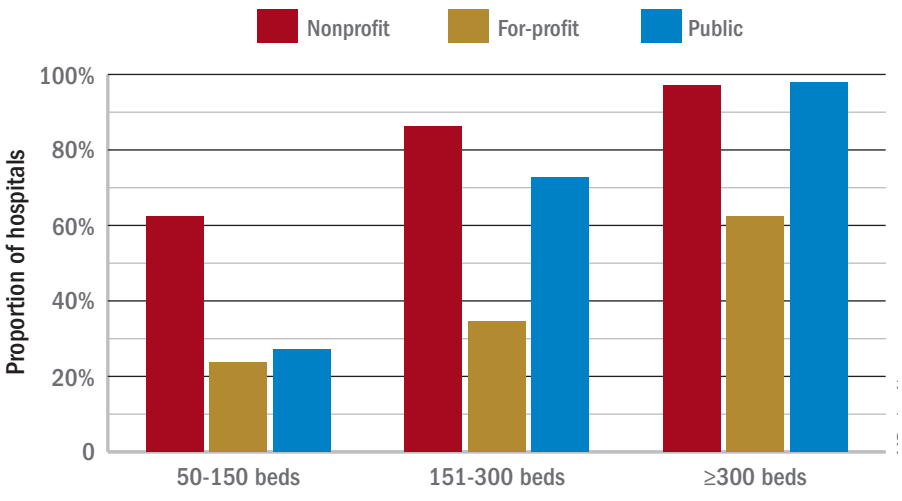
Growth continues among palliative care programs in the United States, although access often depends "more upon accidents of geography than it does upon the needs of patients," according to the Center to Advance Palliative Care and the National Palliative Care Research Center.

"As is true for many aspects of health care, geography is destiny. Where you live determines your access to the best quality of life and highest quality of care during a serious illness," said Diane E. Meier, MD, director of the Center to Advance Palliative Care, in a written statement.

In 2019, more than 72% of U.S. hospitals with 50 or more beds have a palliative care team, compared with 67% of hospitals in 2015 and 53% in 2008, the two organizations said in their 2019 report card on palliative care access. What hasn't changed since 2015, however, is the country's overall grade, which remains a B.

Delaware, New Hampshire, Rhode Island, and Vermont have a palliative care program in all of their hospitals with 50 or more beds and each earned a grade of A (palliative care rate of greater than 80%), along with 17 other states. The lowest-performing states – Alabama, Mississippi, New Mexico, Oklahoma, and Wyoming – all received Ds for having a rate below 40%, the CAPC said.

Hospitals with palliative care by size and tax status, 2019



Note: The report card included 1,723 hospitals with a palliative care program and ≥50 beds.
Source: Center to Advance Palliative Care, National Palliative Care Research Center

The urban/rural divide also is prominent in palliative care: "90% of hospitals with palliative care are in urban areas. Only 17% of rural hospitals with fifty or more beds report palliative care programs," the report said.

Hospital type is another source of disparity. Small, nonprofit hospitals are much more likely to offer access to palliative care than either for-profit or public facilities of the same size, but the gap closes as size increases, at least between nonprofit and public hospitals. For the largest institutions, the public hospitals pull into the lead, 98% versus 97%, over the nonprofits, with the for-profit facilities well behind at 63%.

"High quality palliative care has been shown to improve patient and family quality of life, improve patients' and families' health care experiences, and in certain diseases, prolong life. Palliative care has also been shown to improve hospital efficiency and reduce unnecessary spending," said R. Sean Morrison, MD, director of the National Palliative Care Research Center.

The report card is based on data from the American Hospital Association's Annual Survey Database, with additional data from the National Palliative Care Registry and Center to Advance Palliative Care's Mapping Community Palliative Care initiative. The final sample included 2,409 hospitals with 50 or more beds.

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CDC activates Emergency Operations Center for vaping-injury resources

BY KATIE LENNON
MDedge News

The Centers for Disease Control and Prevention has activated its Emergency Operations Center for the purpose of improving multiple agencies' responses to the current investigation into cases of lung injury associated with vaping. The CDC is fast-tracking Web resources such as up-to-date information concerning ongoing research and discovery as well as channels for reporting cases

The CDC is fast-tracking Web resources such as up-to-date information, recommendations, and reporting channels for public health officials, clinicians, hospitals, and critical care facilities.

and recommendations for clinical management aimed at public health officials, clinicians, hospitals, and critical care facilities.

This move allows the CDC "to provide increased operational support" to CDC staff to meet the evolving challenges of the outbreak of vaping -related injuries and deaths, says a statement from the CDC.

"CDC has made it a priority to find out what is causing this outbreak," noted CDC Director Robert Redfield, MD, in the statement.

The agency "continues to work closely with the U.S. Food and Drug Administration to collect information about recent e-cigarette product use, or vaping, among patients and to test the substances or chemicals within e-cigarette products used by case patients," according to the statement.

The CDC provided email addresses and site addresses for gathering information and communicating about e-cigarettes. Information about the collection of e-cigarettes for possible testing by FDA can be obtained by contacting FDAVapingSampleInquiries@fda.hhs.gov. To communicate with CDC about this public health response, clinicians and health officials can contact LungDiseaseOutbreak@cdc.gov.

More information on the current outbreak related to e-cigarettes is available at https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.

General information on electronic cigarette products, can be found at www.cdc.gov/e-cigarettes.

Individuals should consider refraining from e-cigarette use while the cases of lung injury are being investigated, the CDC said.

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Study challenges fluid resuscitation guidelines

BY TED BOSWORTH
MDedge News

Although guideline recommended, treating children in shock with a bolus of saline or albumin fluid imposes counterproductive effects on respiratory and neurologic function, ultimately increasing risk of death, according to a detailed analysis of available data, including a randomized trial.

Several sets of guidelines for resuscitation of patients in shock have advocated volume expansion with bolus intravenous fluid, but that recommendation was based on expected physiologic benefits, not a randomized trial. The only randomized trial associated this approach showed increased mortality, and a new analysis of these and other data appears to explain why.

According to the findings of a study lead by Michael Levin, MD, of the department of medicine at Imperial College London and colleagues, "volume resuscitation is associated with deterioration of respiratory function and neurological function in some patients." Their study was published in Lancet Respiratory Medicine. The authors stated that saline-induced hyperchloremic acidosis appears to have been "a major contributor" to the observed increase in adverse outcomes.

The key take-home message is that "normal saline and other unbuffered crystalloid solutions should be avoided in resuscitating seriously ill patients," according to the authors, who believe the findings might be relevant to adults as well as children.

The controversy about the role of volume expansion for management of shock was ignited by a 2011 trial called FEAST (N Engl J Med. 2011;364:2483-95). That trial, which randomized African children with severe febrile illness to a bolus of 20-40 mg of 5% albumin solution, a bolus of 0.9% saline solution, or no bolus, was halted early when 48-hour mortality data showed a lower death rate in the no-bolus group (7.3%) than either the albumin (10.6%) or saline (10.5%) bolus groups.

The FEAST result was unexpected and so contrary to accepted thinking that it prompted widespread debate, including whether findings in the resource-poor area of the world where the FEAST trial was conducted could be extrapolated to centers elsewhere in the world. As an argument for benefit: Fluid resuscitation is known to increase pulse pressure and urinary output. As an argument against benefit: Pulmonary edema is a known complication of bolus fluid replacement.

In an attempt to address and potentially resolve this controversy, data collected in the FEAST trial along with four other sets of data involving volume expansion in critically ill children were evaluated with a focus on changes in cardiovascular, neurological, and respiratory function. Analysis of blood biochemistry and blood oxygen transport were also conducted.

The cardiovascular, respiratory, and neurologic functions were scored on the basis of objective measurements, such as heart rate, respiratory rate, and blood pressure. These measures were evaluated prior to fluid administration and at 1 hour, 4 hours, 8 hours, 24 hours, and 48 hours after fluid administration. Odds ratio (OR) of an adverse outcome were evaluated in the context of each 10-unit change in these scores.

Relative to baseline, there was worsening respiratory and neurological function after fluid administration. Although cardiovascular function improved, hemoglobin concentrations were lower in those who received fluid than in those who did not. Fluid resuscitation was also associated with lower bicarbonate and increased base deficit and chloride at 24 hours.

Regression modeling with physiological variables suggests "that the increased mortality in FEAST can be explained by bolus-induced worsening in respiratory and neurological function, hemodilution, and hyperchloremic acidosis," according to the authors.

The authors disclosed no conflicts.

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SOURCE: Levin M et al. Lancet Respir Med. 2019;7:581-93.

High mortality rates trail tracheostomy patients

BY HEIDI SPLETE
MDedge News

Long-term outcomes after tracheostomy are generally poor and health care costs are high, especially for older patients, findings of a large retrospective study suggest.

Current outcome prediction tools to support decision making regarding tracheostomies are limited, wrote Anuj B. Mehta, MD, of National Jewish Health in Denver, and colleagues. "This study provides novel and in-depth insight into mortality and health care utilization following tracheostomy not previously described at the population-level."

In a study published in Critical Care Medicine, the researchers reviewed data from 8,343 nonsurgical patients seen in California hospitals from 2012 to 2013 who received a tracheostomy for acute respiratory failure.

Overall, the 1-year mortality rate for patients who had tracheostomies (the primary outcome) was 46.5%, with in-hospital mortality of 18.9% and 30-day mortality of 22.1%. Pneumonia was the most common diagnosis for patients with respiratory failure (79%) and some had an additional diagnosis, such as severe sepsis (56%).

Patients aged 65 years and older had significantly higher mortality than those under 65 (54.7% vs. 36.5%). The average age of the patients was 65 years; approximately 46% were women and 48% were white. The median survival for adults aged 65 years and older was 175 days, compared with median survival of more than a year for younger patients.

Secondary outcomes included discharge destination, hospital readmission, and health care utilization. A majority (86%) of patients were discharged to a long-term care facility, while 11% were sent home and approximately 3% were discharged to other destinations.

Nearly two-thirds (60%) of patients were readmitted to the hospital within a year of tracheostomy, and readmission was more common among older adults, compared with younger (66% vs. 55%).

In addition, just over one-third of all patients (36%) spent more than 50% of their days alive in the hospital in short-term acute care, and this rate was significantly higher for patients aged 65 years and older, compared with those under 65 (43% vs. 29%). On average, the total hospital cost for patients who survived the first year after tracheostomy was $215,369, with no significant difference in average cost among age groups.

The study findings were limited by several factors including the use of data from a single state, possible misclassification of billing codes, and inability to measure quality of life, the researchers noted.

However, "our findings of high mortality, low median survival for older patients, high readmission rates, potentially burdensome cost, and informative outcome trajectories provide significant insight into long-term outcomes following tracheostomy," they concluded.

Dr. Mehta and several colleagues reported receiving funding from the National Institutes of Health. The researchers disclosed no conflicts.

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SOURCE: Mehta AB et al. Crit Care Med. 2019 Aug 8. doi: 10.1097/CCM.0000000000003959.

Hospital-acquired *C. diff.* tied to 'high-risk' antibiotic classes

BY MARK S. LESNEY
MDedge News

The use of four antibiotic classes designated "high risk" was found to be an independent predictor of hospital-acquired *Clostridioides difficile* (CDI), based upon an analysis of microbiologic and pharmacy data from 171 hospitals in the United States.

The high-risk antibiotic classes were second-, third-, and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and lincosamides, according to a report by Ying P. Tabak, PhD, of Becton Dickinson in Franklin Lakes, N.J., and colleagues published in Infection Control & Hospital Epidemiology.

Of the 171 study sites, 66 (39%) were teaching hospitals and 105 (61%) were nonteaching hospitals. The high-risk antibiotics most frequently used were cephalosporins (47.9%), fluoroquinolones (31.6%), carbapenems (13.0%), and lincosamides (7.6%). The sites were distributed across various regions of the United States. The hospital-level antibiotic use was measured as days of therapy (DOT) per 1,000 days present (DP).

The study was not able to determine specific links to individual antibiotic classes but to the use of high-risk antibiotics as a whole, except for cephalosporins, which were significantly correlated with hospital-acquired CDI ($r = 0.23$; P less than .01).

The overall correlation of high-risk antibiotic use and hospital-acquired CDI was 0.22 ($P = .003$). Higher correlation was observed in teaching hospitals ($r = 0.38$; $P = .002$) versus nonteaching hospitals ($r = 0.19$; $P = .055$), according to the researchers. The authors attributed this to the possibility of teaching hospitals dealing with more elderly and sicker patients.

After adjusting for significant confounders, the use of high-risk antibiotics was still independently associated with significant risk for hospital-acquired CDI. "For every 100-day increase of DOT per 1,000 DP in high-risk antibiotic use, there was a 12% increase in [hospital-acquired] CDI (risk ratio, 1.12; 95% [confidence interval], 1.04-1.21; $P = .002$)," according to the authors. This translated to four additional hospital-acquired CDI cases with every 100 DOT increase per 1,000 DP.

"Using a large and current dataset, we found an independent impact of hospital-level high-risk antibiotic use on [hospital-acquired] CDI even after adjusting for confounding factors such as community CDI pressure, proportion of patients aged 65 years or older, average length of stay, and hospital teaching status," the researchers concluded.

Funding was provided by Nabriva Therapeutics, an antibiotic development company. Four of the authors are full-time employees of Becton Dickinson, which sells diagnostics for infectious diseases, including CDI, and one author was an employee of Nabriva Therapeutics.

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SOURCE: Tabak YP et al. Infect Control Hosp Epidemiol. 2019 Sep 16.doi: 10.1017/ice.2019.236.

A quarter of ICU admissions due to substance abuse

BY CALEB RANS
MDedge News

FROM THE JOURNAL *CHEST* ▪
Nearly a quarter of resources used by the intensive care unit (ICU) are for substance abuse–related admissions, according to results from a retrospective chart review.

The abuse of illicit drugs topped substance abuse–related ICU stays, accounting for 13% of total admissions, which represented 11% of total charges.

"We conducted a study to provide updated data on ICU utilization and costs related to licit and illicit abuse at a large county hospital," wrote Donald Westerhausen, MD, of Indiana University, Indianapolis, and colleagues. The findings were reported in Chest.

The single-center study comprised 594 patients who were admitted for prescription, alcohol, or illicit drug use between May 2017 and October 2017. The team used laboratory data, in addition to medical history, to define substance abuse–related admissions.

A total of 611 admissions occurred during the 6-month study period. The researchers collected information on patient demographics, hospital charges, insurance coverage, and other clinical parameters.

After analysis, they found that patients admitted for substance abuse were generally younger than were those admitted for other reasons (44 years vs. 59 years; *P* less than .001). In addition, patients were more often male (64% vs. 48%), had greater mortality (14%), and experienced longer hospital stays (median, 6 days).

In total, 25.7% of ICU admissions were related to substance abuse, which comprised 23.1% of charges. In particular, 9.5% and 2.9% of admissions were related to alcohol use and prescription drugs, which represented 7.6% and 4.2% of total charges, respectively.

"Polysubstance abuse was the most frequent subcategory of illicit and prescription drug admissions," the researchers wrote.

Andrei Malov/Thinkstock

They acknowledged two limitations of the study: the short duration and single-center design. Future studies should account for seasonal differences in ICU admissions, they noted.

"Identifying and accurately describing the landscape of this current health crisis will help us take appropriate action in the future," they concluded.

No funding sources were reported. The authors did not disclose any conflicts of interest.

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SOURCE: Westerhausen D et al. Chest. 2019 Sep 5. doi: 10.1016/j.chest.2019.08.2180.

Procalcitonin can be useful to rule out bacterial infection

BY M. ALEXANDER OTTO
MDedge News

SEATTLE – Procalcitonin, a marker of bacterial infection, rises and peaks sooner than C-reactive protein (CRP), and is especially useful to help rule out invasive bacterial infections in young infants and pediatric community-acquired pneumonia due to typical bacteria, according to a presentation at the Pediatric Hospital Medicine meeting.

It's "excellent for identifying low-risk patients" and has the potential to decrease lumbar punctures and antibiotic exposure, but "the specificity isn't great," so there's the potential for false positives, said Russell McCulloh, MD, a pediatric infectious disease specialist at the University of Nebraska Medical Center, Omaha.

There was great interest in procalcitonin at the meeting; the presentation room was packed, with a line out the door. It's used mostly in Europe at this point. Testing is available in many U.S. hospitals, but a large majority of audience members, when polled, said they don't currently use it in clinical practice, and that it's not a part of diagnostic algorithms at their institutions.

Levels of procalcitonin, a calcitonin precursor normally produced by the thyroid, are low or undetectable in healthy people, but inflammation, be it from infectious or noninfectious causes, triggers production by parenchymal cells throughout the body.

Levels began to rise as early as 2.5 hours after healthy subjects in one study were injected with bacterial endotoxins, and peaked as early as 6 hours; CRP, in contrast, started to rise after 12 hours, and peaked at 30 hours. Procalcitonin levels also seem to correlate with bacterial load and severity of infection, said Nivedita Srinivas, MD, a pediatric infectious disease specialist at Stanford (Calif.) University (J Pediatr Intensive Care. 2016 Dec;5[4]:162-71).


M. Alexander Otto/MDedge News

(From left) Dr. Marie Wang, Dr. Russell McCulloh, and Dr. Nivedita Srinivas spoke in Seattle.

The presenters focused their talk on community acquired pneumonia (CAP) and invasive bacterial infections (IBI) in young infants, meaning essentially bacteremia and meningitis.

Different studies use different cutoffs, but a procalcitonin below, for instance, 0.5 ng/mL is "certainly more sensitive [for IBI] than any single biomarker we currently use," including CRP, white blood cells, and absolute neutrophil count (ANC). "If it's negative, you're really confident it's negative," but "a positive test does not necessarily indicate the presence of IBI," Dr. McCulloh said (Pediatrics. 2012 Nov;130[5]:815-22).

"Procalcitonin works really well as part of a validated step-wise rule" that includes, for instance, CRP and ANC; "I think that's where its utility is. On its own, it is not a substitute for you examining the patient and doing your basic risk stratification, but it may enhance your decision making incrementally above what we currently have," he said.

Meanwhile, in a study of 532 children a median age of 2.4 years with radiographically confirmed CAP, procalcitonin levels were a median of 6.1 ng/mL in children whose pneumonia was caused by *Streptococcus pneumoniae* or other typical bacteria, and no child infected with typical bacteria had a level under 0.1 ng/mL. Below that level, "you can be very sure you do not have typical bacteria pneumonia," said Marie Wang, MD, also a pediatric infectious disease specialist at Stanford (J Pediatric Infect Dis Soc. 2018 Feb 19;7[1]:46-53).

As procalcitonin levels went up, the likelihood of having bacterial pneumonia increased; at 2 ng/mL, 26% of subjects were infected with typical bacteria, "but even in that group, 58% still had viral infection, so you are still detecting a lot of viral" disease, she said.

Prolcalcitonin-guided therapy – antibiotics until patients fall below a level of 0.25 ng/ml, for instance – has also been associated with decreased antibiotic exposure (Respir Med. 2011 Dec;105[12]:1939-45).

The speakers had no disclosures. The meeting was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

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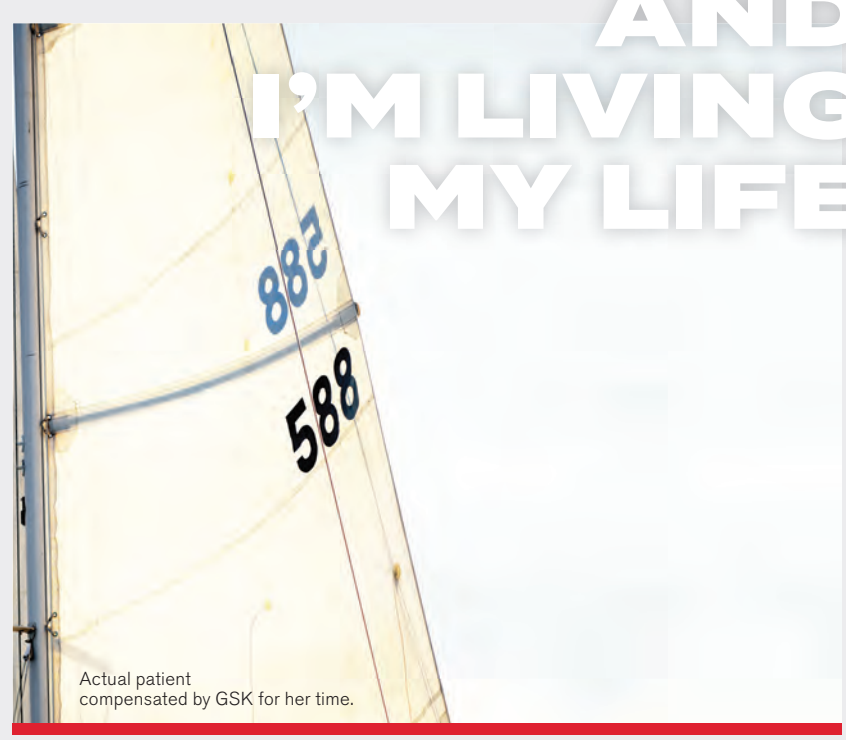
NUCALA is indicated for the add-on maintenance treatment of patients 6 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.



#1 prescribed biologic indicated for severe eosinophilic asthma*— 38,000 patients and counting[1†]

*Source: IQVIA - NPA™ audit: 12 mo. TRX data ending 4/19 (All rights reserved).

†December 2015 to April 2019 data sourced from IQVIA and GSK. Claims data based on total number of unique patients who had at least one claim for NUCALA in the United States. Not all patients remained on therapy. Individual results may vary.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred with NUCALA compared to none with placebo. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage

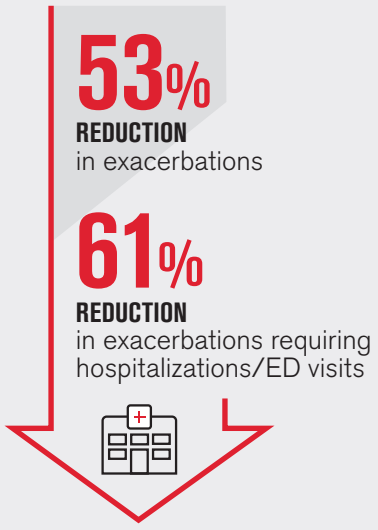
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms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

Parasitic (Helminth) Infection

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

Choose NUCALA:

Powerful Protection From Exacerbations[2‡]



Powerful Reduction in OCS Dose[3]

Lasting Evidence[4]

Only anti-interleukin 5 (IL-5) with a

4.5-year

open-label study that evaluated safety and efficacy

MENSA (Trial 2)[2]: 32-week study comparing NUCALA 100 mg to placebo, each added to SOC in 576 patients aged ≥12 years with severe eosinophilic asthma (SEA). **Primary Endpoint Results:** Frequency of exacerbations. NUCALA: 0.83/year, placebo: 1.74/year; *P*<0.001). **Secondary Endpoint Results:** Frequency of exacerbations requiring hospitalization and/or ED visit; NUCALA: 0.08/year; placebo: 0.20/year; *P*=0.02.

SIRIUS (Trial 3)[3]: 24-week study comparing NUCALA 100 mg to placebo in 135 patients aged ≥12 years with SEA receiving prednisone 5-35 mg (or equivalent) per day and regular use of high-dose ICS and 1 other controller. **Primary Endpoint Results:** Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control vs placebo; *P*=0.008.

COLUMBA[4]: 4.5-year open-label study assessing the safety, immunogenicity, and efficacy of NUCALA 100 mg added to asthma controller therapy in 347 patients aged ≥12 years with SEA.

‡ Worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalizations and/or emergency department (ED) visits; for patients on maintenance oral/systemic corticosteriods, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

Standard of care (SOC)=regular treatment with high-dose inhaled corticosteroids (ICS) and at least 1 other controller with or without oral corticosteroids (OCS).

Learn more at **KnowNucalaHCP.com**

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasms, 3% (<1%).

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

USE IN SPECIFIC POPULATIONS

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

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207. **3.** Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371:1189-1197. **4.** Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol.* 2019;143(5):1742-1751.

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

MPLJRNA190008 September 2019
Produced in USA.

Nucala
(mepolizumab)
Injection 100 mg/mL

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use
The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE
1.1 Maintenance Treatment of Severe Asthma
NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype.
Limitation of Use: NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS
NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster
Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

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

5.5 Parasitic (Helminth) Infection
Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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

6.1 Clinical Trials Experience in Severe Asthma
Adult and Adolescent Subjects Aged 12 Years and Older
A total of 1,327 subjects with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT #01000506; Trial 2, NCT #01691521; and Trial 3, NCT #01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.
The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Subjects with Severe Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects receiving mepolizumab 75 mg IV compared with 2 subjects in the placebo group.
Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.
Injection Site Reactions: Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.
Long-term Safety: Nine hundred ninety-eight subjects received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.
Pediatric Subjects Aged 6 to 11 Years
The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 subjects with severe asthma aged 6 to 11 years. Subjects received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Subjects received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 subjects received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for subjects aged 6 to 11 years was similar to that observed in subjects aged 12 years and older.

6.3 Immunogenicity
In adult and adolescent subjects with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.
The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.4 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. 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 NUCALA or a combination of these factors.
Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS
Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.
Risk Summary: The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and 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 mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 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 Embryofetal 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 mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an area under the curve [AUC] basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys.
Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.
In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation
Risk Summary
There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.
Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT #01691521) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.

(continued on next page)

8 USE IN SPECIFIC POPULATIONS *(cont'd)*
Use of NUCALA in children aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT #02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg SC every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC *[see Clinical Pharmacology (12.3) of full prescribing information]*.
The efficacy of NUCALA in children aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]*.
The safety and efficacy in pediatric patients aged younger than 6 years with severe asthma have not been established.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 46) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to adult subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.
Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.
Advise the patient to read the FDA-approved patient labeling (Patient Information).
Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.
Not for Acute Symptoms or Deteriorating Disease
Inform patients that NUCALA 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 NUCALA.
Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.
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.
Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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Many institutions exceed recommended CT scan radiation doses during lung cancer screening

BY ERIK GREB
MDedge News

A significant proportion of institutions that perform low-dose CT scan for lung cancer screening exceed the radiation dose levels that guidelines recommend, according to a study published in JAMA Internal Medicine.

Various institutional characteristics, such as allowing any radiologist to establish CT scan protocols, are associated with a greater likelihood of using higher radiation doses. "Dose optimization practices may benefit from being tailored to specific practice types, as well as different organizational structures, to have a higher likelihood of meeting dose guidelines," wrote Joshua Demb, PhD, MPH, a cancer epidemiologist at the University of California, San Diego, and colleagues.

Lung cancer screening benefits patients when low-dose CT scan is used, but not when high-dose CT scan is used, because radiation from higher doses may cause as many cancers as are detected by screening. The Centers for Medicare & Medicaid Services require institutions to use low-dose techniques and participate in a dose registry to be reimbursed for lung cancer screening. The American College of Radiology recommends that lung cancer screening scans have a volume CT dose index (CTDIvol) of 3 mGy or lower and an effective dose (ED) of 1 millisieverts (mSv) or lower.

A prospective study of registry data

Dr. Demb and colleagues conducted a study to describe CT scan radiation doses for lung cancer screening in current practice and to identify the factors that explain variation in doses between institutions. They prospectively collected lung cancer screening examination dose metrics from 2016 to 2017 at U.S. institutions participating in the University of California, San Francisco, International Dose Registry. Eligible institutions performed a minimum of 24 lung cancer screening scans during the study period. At baseline, the investigators surveyed institutions about their characteristics (for example, how they perform and oversee CT scans). Dr. Demb and colleagues estimated mixed-effects linear and logistic regression models using forward variable selection. They conducted their analysis between 2018 and 2019.

The researchers chose four outcome measures. The first was mean CTDIvol, reflecting the average radiation dose per slice. The second was mean ED, reflecting the total dose received and estimated future cancer risk. The third was the proportion of CT scans using radiation doses above ACR benchmarks. The fourth was the proportion of CT scans using radiation doses above the 75th percentile of registry doses (CTDIvol greater than 2.7 mGy and ED greater than 1.4 mSv).

Institutional characteristics and radiation dose

Dr. Demb and colleagues collected data from 72 institutions about 12,529 patients undergoing CT scans for lung cancer screening. Approximately 58% of patients were men, and the patients' median age was 65 years. The mean CTDIvol, adjusted for patient size, was 2.4 mGy. The mean ED for lung cancer screening, adjusted for chest diameter, was 1.2 mSv.

A total of 15 institutions (21%) had a median adjusted CTDIvol value higher than the ACR guideline, and 47 (65%) had a median adjusted ED higher than the ACR guideline. Approximately 18% of CT scans had a CTDIvol higher than guidelines, and 50% had an ED higher than ACR guidelines.

Institutions that permitted any radiologist to establish CT scan protocols had 44% higher mean CTDIvol and 27% higher mean ED, compared with institutions that restricted who could establish protocols. Institutions that permitted any radiologist to establish protocols also had higher odds of conducting examinations that exceeded ACR CTDIvol guidelines (odds ratio, 12.0) and of being in the 75th percentile of the registry CTDIvol (OR, 19.0) or ED (OR, 8.5) values.

In contrast, having lead radiologists establish CT scan protocols resulted in lower odds of using doses that exceeded ACR ED guidelines (OR, 0.01). Employing external, rather than internal, medical physicists was associated with increased odds of exceeding ACR CTDIvol guidelines (OR, 6.1). Having medical physicists establish protocols was associated with decreased odds of exceeding the 75th percentile of the registry CTDIvol (OR, 0.09) values. Institutions that updated protocols as needed, rather than annually, had 27% higher mean CTDIvol.

"Although we cannot establish causality in this observational study, our results suggest that considering these factors (for example, allowing only lead radiologists to establish protocols) could have a meaningful impact on dose, and could be important areas to develop interventions to optimize doses of CT protocols" the investigators wrote.

The Patient Centered Outcomes Research Institute and the National Institutes of Health supported this research. The authors reported no conflicts of interest.

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SOURCE: Demb J et al. JAMA Intern Med. 2019 Sep 23. doi: 10.1001/jamainternmed.2019.3893.

Molecular profiling a must in advanced NSCLC

BY NEIL OSTERWEIL
MDedge News

All patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) should undergo molecular testing for targetable mutations and for tumor expression of the programmed death–ligand 1 (PD-L1) protein, authors of a review of systemic therapies for NSCLC recommend.

Their opinion is based on evidence showing that 5-year overall survival rate for patients whose tumors have high levels of PD-L1 expression now exceeds 25%, and that patients with ALK-positive tumors have 5-year overall survival rates over 40%. In contrast, 5-year survival rates for patients with metastatic NSCLC prior to the 21st century were less than 5%, according to Kathryn C. Arbour, MD, and her colleagues of Memorial Sloan Kettering Cancer Center.

"Improved understanding of the biology and molecular subtypes of non–small cell lung cancer have led to more biomarker-directed therapies for patients with metastatic disease. These biomarker-directed therapies and newer empirical treatment regimens have improved overall survival for patients with metastatic non–small cell lung cancer," they wrote in JAMA.

The authors reviewed published studies of clinical trials of medical therapies for NSCLC, including articles on randomized trials, nonrandomized trials leading to practice changes or regulatory approval of new therapies for patients with locally advanced or metastatic NSCLC, and clinical practice guidelines.

Their review showed that approximately 30% of patients with NSCLC have molecular alterations predictive of response to treatment, such as mutations in EGFR, the gene encoding for epidermal growth factor receptor; rearrangements in the ALK (anaplastic lymphoma kinase) and ROS1 genes; and mutations in BRAF V600E.

Patients with somatic activating mutations in EGFR, which occur in approximately 20% of those with advanced NSCLC, have better progression-free survival when treated with an EGFR-target tyrosine kinase inhibitor such as gefitinib, compared with cytotoxic chemotherapy.

The review was supported in part by a grant from the National Cancer Institute to Memorial Sloan Kettering. Dr. Arbour reported serving as a consultant to AstraZeneca and nonfinancial research support from Novartis and Takeda. Dr. Riely reported grants and nonfinancial support from Pfizer, Roche/Genentech/Chugai, Novartis, Merck, and Takeda; a patent pending for an alternative dosing of erlotinib for which he has no right to royalties; and payments from the National Comprehensive Cancer Network to participate in a committee overseeing solicitation and selection of grants to be awarded by AstraZeneca.

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SOURCE: Arbour KC et al. JAMA. 2019;322(8):764-74.

Prior antibiotic use lowers checkpoint inhibitor response and survival

BY BIANCA NOGRADY
MDedge News

Prior antibiotic use may be associated with a reduced treatment response to checkpoint inhibitors, and worse outcomes, in patients with cancer, according to investigators.

In a prospective cohort study, researchers followed 196 patients with cancer who were treated with immune checkpoint inhibitors in routine clinical practice.

A total of 22 patients had been treated with a 7-day or less course of broad-spectrum beta-lactam–based antibiotics in the 30 days prior to starting immune checkpoint inhibitor therapy, and 68 patients were concurrently taking broad-spectrum beta-lactam–based antibiotics with their checkpoint inhibitor therapy.

The analysis revealed that prior antibiotic therapy was associated with nearly a 100% greater likelihood of poor response to checkpoint inhibitor therapy (*P* less than .001) and significantly worse overall survival (2 vs. 26 months). Patients who had been on prior antibiotic therapy were also more likely to stop checkpoint inhibitor therapy because their disease had progressed, and were more likely to die of progressive disease while on checkpoint inhibitors.

However, concurrent antibiotic use did not appear to affect either treatment response to checkpoint inhibitors or overall survival.

The most common indication for both prior and concurrent antibiotic use was respiratory tract infections. Researchers examined whether cancer type might play a role in contributing to the association; for example, chronic airway disease in lung cancer might mean higher likelihood of antibiotic use but also lower treatment response and survival.

They found that the association between prior antibiotic therapy and overall survival was consistent across the 119 patients with non–small cell lung cancer, the 38 patients with melanoma, and the 39 patients with other tumor types.

The association was also independent of the class of antibiotic used, the patient's performance status, and their corticosteroid use.

"Broad-spectrum ATB [antibiotic] use can cause prolonged disruption of the gut ecosystem and impair the effectiveness of the cytotoxic T-cell response against cancer, strengthening the biologic plausibility underlying the adverse effect of ATB therapy on immunotherapy outcomes," wrote David J. Pinato, MD, from Imperial College London, and coauthors in JAMA Oncology.

Addressing the question of whether comorbidities might be the mediating factor, the authors pointed out that the use of antibiotics during checkpoint inhibitor therapy – which was a potential indicator of patients' status worsening during treatment – was not associated with reduced response to treatment or lower overall survival.

"Although provision of cATB [concurrent antibiotic] therapy appears to be safe in the context of immunotherapy, clinicians should carefully weigh the pros and cons of prescribing broad-spectrum ATBs prior to ICI [immune checkpoint inhibitor] treatment," they wrote.

The study was supported by the Imperial College National Institute for Health Research Biomedical Research Centre, the Imperial College Tissue Bank, the Imperial Cancer Research U.K. Centre, the National Institute for Health Research, and the Wellcome Trust Strategic Fund. Two authors reported receiving grant funding and personal fees from the pharmaceutical sector unrelated to the study.

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SOURCE: Pinato DJ et al. JAMA Oncol. 2019 Sep 12. doi: 10.1001/jamaoncol.2019.2785.

NOTE CORRECTION: In the Critical Care Commentary "Changing clinical practice to maximize success of ICU airway management" in the August issue of *CHEST Physician*, please note a correction to the following sentence on page 27: The American College of Chest Physicians (CHEST) Difficult Airway Course faculty also initially recommended to not use NMB because of the high risk of failure to ventilate/oxygenate.

Most practices not screening for five social needs

BY ALICIA GALLEGOS
MDedge News


Wavebreakmedia/Thinkstock

A minority of physician practices and hospitals are screening patients for five key social needs that are associated with health outcomes, a study found.

Lead author Taressa K. Fraze, PhD, of the Dartmouth Institute for Health Policy and Clinical Practice in Lebanon, N.H., and colleagues conducted a cross-sectional survey analysis of responses by physician practices and hospitals that participated in the 2017-2018 National Survey of Healthcare Organizations and Systems. The investigators evaluated how many practices and hospitals reported screening of patients for five social needs: food insecurity, housing instability, utility needs, transportation needs, and experience with interpersonal violence. The final analysis included 2,190 physician practices and 739 hospitals.

Of physician practices, 56% reported screening for interpersonal violence, 35% screened for transportation needs, 30% for food insecurity, 28% for housing instability, and 23% for utility needs, according to the study published in JAMA Network Open.

Among hospitals, 75% reported screening for interpersonal violence, 74% for transportation needs, 60% for housing instability, 40% for food insecurity, and 36% for utility needs. Only 16% of physician practices and 24% of hospitals screened for all five social needs, the study found, while 33% of physician practices and 8% of hospitals reported screening for no social needs. The majority of the overall screening activity was driven by interpersonal violence screenings.

Physician practices that served more disadvantaged patients, including federally qualified health centers and those with more Medicaid revenue were more likely to screen for all five social needs. Practices in Medicaid accountable care organization contracts and those in Medicaid expansion states also had higher screening rates. Regionally, practices in the West had the highest screening rates, while practices in the Midwest had the lowest rates.

Among hospitals, the investigators found few significant screening differences based on hospital characteristics. Ownership, critical access status, delivery reform participation, rural status, region, and Medicaid expansion had no significant effects on screening rates, although academic medical centers were more likely to screen patients for all needs compared with nonacademic medical centers.

The study authors wrote that doctors and hospitals may need more resources and additional processes to screen for and/or to address the social needs of patients. They noted that practices and hospitals that did not screen for social needs were more likely to report a lack of financial resources, time, and incentives as major barriers.

To implement better screening protocols and address patients' needs, the investigators wrote that doctors and hospitals will need financial support. For example, the Centers for Medicare & Medicaid Services should consider expanding care management billing to include managing care for patients who are both at risk or have clinically complex conditions in addition to social needs.

Dr. Fraze and three coauthors reported receiving grants from the Agency for Healthcare Research and Quality during the conduct of the study. Dr. Fraze also reported receiving grants from the Robert Wood Johnson Foundation during the conduct of the study and receiving grants as an investigator from the 6 Foundation Collaborative, Commonwealth Fund, and Centers for Disease Control and Prevention. One coauthor reported receiving grants from the National Institute on Aging/National Institutes of Health during the conduct of the study.

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SOURCE: Fraze TK et al. JAMA Netw Open. 2019 Sep 18. doi: 10.1001/jamanetworkopen.2019.11514.

VIEW ON THE NEWS

Needed: Strategies for overcoming screening barriers

While momentum for social risk screening is growing nationally, the recent study by Fraze et al. illustrates that screening across multiple domains is not yet common in clinical settings, wrote Rachel Gold, PhD, of Kaiser Permanente Center for Health Research Northwest in Portland, Ore.

In an editorial accompanying the study, Dr. Gold and coauthor Laura Gottlieb, MD, an associate professor of family and community medicine at the University of California, San Francisco, wrote that a critical finding of the study is that reimbursement is associated with uptake of social risk screening (JAMA Network Open. 2019 Sep 18. doi: 10.1001/jamanetworkopen.2019.11513). Specifically, the analysis found that screening for social risks is more common in care settings that receive some form of payment to support such efforts, directly or indirectly.

"This finding aligns with other research showing that altering incentive structures may enhance the adoption of social risk screening in health care settings," Dr. Gold and Dr. Gottlieb wrote. "But these findings are just a beginning. Disseminating and sustaining social risk screening will require a deep understanding of how best to structure financial and other incentives to optimally support social risk screening; high-quality research is needed to help design reimbursement models that reliably influence adoption."

Further research is needed not only to explain challenges to the implementation of social risk screening, but also to reveal the best evidence-based methods for overcoming them, the authors wrote. Such methods will likely require a range of support strategies targeted to the needs of various health care settings.

"Documenting social risk data in health care settings requires identifying ways to implement such screening effectively and sustainably," Dr. Gold and Dr. Gottlieb wrote. "These findings underscore how much we still have to learn about the types of support needed to implement and sustain these practices."

Dr. Gold reported receiving grants from the National Institutes of Health during the conduct of the study. Dr. Gottlieb reported receiving grants from the Robert Wood Johnson Foundation, the Commonwealth Fund, Kaiser Permanente, Episcopal Health Foundation, the Agency for Healthcare Research and Quality, St. David's Foundation, the Pritzker Family Fund, and the Harvard Research Network on Toxic Stress outside the submitted work.

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EKOS™ Therapy

A SAFER INTERVENTION FOR INTERMEDIATE HIGH-RISK PE.[1,2]

2 mg tPA dose in 2-hour treatment.[1]

The data are clear: systemic lytic increases risk of ICH. EKOS therapy delivers a low-dose thrombolytic to the core of the clot via ultrasonic waves, so risk decreases, but efficacy doesn't.

To learn more visit www.bostonscientific.com

1 Victor F. Tapson. The OPTALYSE PE Trial JACC: Cardiovascular Interventions Jul 2018; 11(14): 1401-1410; DOI: 10.1016/j.jcin.2018.04.008

2 Konstantinides, MD, et al, "Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism" Journal of the American College of Cardiology; vol 69, pp.1536-1544, 2017.

FROM THE PRESIDENT

Wisdom of our crowd

BY CLAYTON T. COWL, MD, MS, FCCP

About a year ago, I had the opportunity to don the honorary regalia of the American College of Chest Physicians as its 81st President. On that memorable day on the dais in San Antonio, I used the example of James Surowiecki's book, "The Wisdom of Crowds: Why the Many Are Smarter than the Few and How Collective Wisdom Shapes Business, Economics, Societies, and Nations" to explain how we would use the collective wisdom of our members, our committee and NetWork members, and our talented association staff to build and shape CHEST over the coming year. For those of you not familiar with this concept, Surowiecki, a business columnist for New Yorker, outlines the concept that large groups of people are actually smarter than an elite few at solving the problems of an organization, fostering innovation, collectively coming to wise decisions, or even predicting the future. In channeling the lessons from the book, it has become obvious that listening to our members and partners, rather than trying to make all decisions from the top down, has been an effective method for coming to wise decisions about the strategy and operation of CHEST. Now that it's already time to hand the responsibility of the organization as President over to my friend and colleague Dr. Stephanie Levine, I've reflected on actually how effectively we have listened and how smart the collective crowd has been in moving the success of CHEST forward.

We heard from members that it was difficult to know how to get involved and what happens at the highest leadership levels of the organization. This prompted the development of podcasts dubbed "The Inside Scoop," recorded live approximately every 2 months and features various leaders of the organization with an informal way for members to better understand how to become involved in CHEST activities and to feel the pulse of activity of the association between the time the annual meeting ends and the next one begins.

The crowd informed us that communication at the Board of Regents level could be better. To address this, regular communications were sent out to the Board of Regents to update them on activities and discussion of issues between scheduled board meetings, as well as providing board members the opportunity to have access to the minutes of phone calls of the "5Ps," calls that included the Immediate Past President, President-Elect, President-Designate, and current President of the association, as well as the CHEST Foundation President.

We were told by members through focus groups and surveys, then again told by experts we invited to the June board meetings from education, business, design, and venture capital sectors (and who were naïve to CHEST as an association) that we needed to double down on virtual educational offerings to learners across the health-care delivery team and to revamp the information technology infrastructure. To that end, a digital

Dr. Clayton T. Cowl

strategy work group was convened with expertise in information technology, social media, and marketing to inventory all digital assets of the College and make recommendations for not just improvement, but for a complete transformation of digital technology created and promulgated by CHEST. The board then approved a budget of nearly $1 million to upgrade and rebuild the user experience within CHEST's digital environment, including its learning management system. We also opened a multimedia studio at CHEST headquarters, increased the numbers of serious educational gaming opportunities at the annual meeting, and are developing a line of serious game platforms that will allow for "edutainment" opportunities for our members and other learners around the world using various digital platforms.

"The collective wisdom of our members, talented clinicians and researchers, and colleagues in industry has provided incredibly valuable input to the CHEST leadership team. You have spoken, and we have been listening. Thanks to each of you who have reached out to me during this year as President."

Colleagues from around the world reminded us that 20% of CHEST membership was international and that our strategic plan included an international strategy. Thanks to the support of our colleagues around the world, we were able to enjoy a tremendously successful CHEST Congress in Bangkok, Thailand, in April, and a smaller regional meeting in June in Athens, Greece. Efforts of the Governance Committee have reshaped the structure of international representation, making it more relevant and allowing its members to have a stronger voice to the Board of Regents. Plans are underway for the next CHEST Congress in June 2020 in Bologna, Italy, to be held in collaboration with the Italian Chapter of CHEST in that country.

In an era when the majority of association annual meetings across multiple specialties is driving toward parity with similar looks, marketing, formats, and expectations, we listened to the needs and desires of attendees of last year's meeting and have improved CHEST 2019 in New Orleans even more. With the most simulation courses ever delivered at an annual meeting, more serious game opportunities, CHEST Challenge finals, a new innovation competition called "FISH Bowl," and even a medical escape room, CHEST volunteer leaders and organization staff have worked hard to provide a world class meeting that has a different look and feel from all the others. Plus, the crowd also told us that having CME and MOC credit available for the entire meeting was another variable that was desired, and has now been achieved.

The wisdom of the proverbial crowd of membership has spoken in terms of the need for philanthropic efforts in our specialty. The CHEST Foundation has responded by awarding tens of thousands of dollars to our members to recognize cutting-edge research, community service efforts, and, in addition, has allowed dozens of providers early on in training or in their career to attend the annual meeting with the help of travel grants.

CHEST guidelines continue to be updated and new ones created based on input from expert panel teams. The *CHEST* journal submission process, review turnaround times, and quality of manuscripts have improved each year thanks to useful feedback from authors and readers. Publications such as *CHEST Physician* are modified each year based upon feedback from our readers. Critiques from the board review courses have been the driving force keeping live learning formats and the electronic SEEK board preparation questions current and accurate when the science is constantly changing.

Truly, the collective wisdom of our members, talented clinicians and researchers, and colleagues in industry has provided incredibly valuable input to the CHEST leadership team. You have spoken, and we have been listening. Thanks to each of you who have reached out to me during this year as President. Traveling to four continents this past year to better understand the needs of members who are clinicians, educators, researchers, and caregivers positioned in each geographic region has been enlightening, educational, and transformative for me and my family. Your meaningful feedback, keen insights, and passion for outstanding patient care, impactful educational experiences, and life-changing research have helped to push CHEST to a higher level of excellence and to offer unparalleled experiences for our members to ultimately provide the very best care to patients.

E-cigarette-associated respiratory diseases: Ask your patients about vaping substances

BY SANDRA G. ADAMS, MD, MS, FCCP

E-cigarettes arrived in the U.S. market between 2005 and 2007. Vaping via e-cigarettes involves inhaling substances such as nicotine, flavorings, chemicals, and, sometimes, marijuana and/or other substances deep into the lungs. While the use of these devices is prevalent, the long-term effects are not known. We, as clinicians, need to specifically ask our patients about their use of substances via e-cigarettes because of alarming cases of severe, life-threatening respiratory illnesses recently being reported throughout the United States in young, otherwise healthy, individuals.

Dr. Adams

As of September 17, 2019, over 539 cases have been reported to the Centers for Disease Control and Prevention (CDC), where young, healthy people from 38 states and one US territory were hospitalized with severe respiratory disease. There have been at least seven confirmed deaths* and approximately one-third of those who survived required aggressive support with intubation and mechanical ventilation. The number of reported cases is rapidly rising (from 215 possible cases on August 27, 2019). The common theme in these cases is that every patient reported using an e-cigarette product within 90 days of the onset of symptoms, and most within the prior 2 weeks. By definition, other etiologies of respiratory failure, such as infections, collagen vascular, immunologic diseases, and malignancies were excluded.

Between 90% and 98% of patients presented to the hospital with respiratory symptoms, such as shortness of breath, cough, hemoptysis, and/or chest pain. The most common reported e-cigarette product exposure among these case patients is tetrahydrocannabinol, THC (in approximately 80% to 85%); however, some used only nicotine-based products (15% to 20%). In addition, approximately 45% to 50% reported using THC and nicotine-based products. One concerning fact that requires special attention is that some affected patients initially presented with nonrespiratory complaints, such as GI symptoms of nausea, vomiting, and/or diarrhea; constitutional symptoms such as fever (up to 104°F), fatigue, and/or weight loss; and neurologic symptoms such as headaches and even seizures. Many of these symptoms preceded the respiratory symptoms by up to 2 weeks. Therefore, a few of these patients initially presented without significant respiratory symptoms and with normal chest radiographs – but progressed over days to weeks to acute hypoxemic respiratory failure.

Up to 75% of the affected patients who ultimately required hospitalization for e-cigarette-associated respiratory disease initially presented to a primary care clinic or ED and were sent home due to nonspecific signs and symptoms, which mimic common viral illnesses. Therefore, it is critical for all health-care professionals to have a high clinical suspicion for e-cigarette-associated respiratory disease, particularly while more data are being gathered. When suspected, the CDC recommends asking patients about specific substances inhaled, the manufacturer, where the products/cartridges were obtained, type of device(s) used, and method used (ie, aerosolization, dabbing, dripping, etc).

The most common types of imaging and pathologic patterns attributed to e-cigarette use reported to date include lipoid pneumonia, diffuse alveolar damage, acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH), acute eosinophilic pneumonia, hypersensitivity pneumonitis, and organizing pneumonia. The most common patterns on imaging include basilar-predominant consolidation and ground-glass opacities with areas of subpleural sparing. In addition, approximately 10% to 15% of the reported cases had a spontaneous pneumothorax, pneumomediastinum, and/or associated pleural effusions. Bronchoscopy specimens, such as bronchoalveolar lavage (BAL) and transbronchial biopsies (TBBx), were often but not always obtained. In patients who underwent bronchoscopy, many were found to have lipid-laden alveolar macrophages. These findings were discovered by staining fresh (ie, those not placed in fixative) specimens from BAL and/or TBBx for lipids with oil red O or another stain to specifically detect fat within the samples. Other etiologies of these radiographic/pathologic patterns and conditions should be excluded, as listed above.

The clinical course varies widely among these reported cases of vaping and e-cigarette-associated respiratory diseases. A minority of the reported patients spontaneously improved, and others required significant supportive care – from supplemental oxygen to complete support with ECMO. Some were treated with systemic corticosteroids with a wide range of responses and with various dosages: from prednisone of 0.5 to 1 mg/kg up to pulse-dose steroids with 1 g methylprednisolone for 3 days with a slow taper.

The information and data reported about these e-cigarette-associated respiratory diseases are clearly evolving quickly and vary from center to center and state to state. All suspected cases should be reported to your state health department. Similar to other inhalational injuries, it is critical to monitor these patients following recovery from the acute illness to help determine the long-term pulmonary effects and clinical courses of these individuals. Offering assistance and treatment for addiction is also important in these patients to help reduce their chances of recurrent respiratory problems from ongoing exposure to these substances in e-cigarettes. The bottom line is that cases of e-cigarette-associated respiratory diseases are increasing rapidly throughout the United States. Therefore, we should all be vigilant about asking our patients about their use of these substances and providing clear and strong messages for each of our patients to avoid vaping any substances through e-cigarettes.

Dr. Adams is Professor of Medicine, Pulmonary/Critical Care Division, Distinguished Teaching Professor, UT Health San Antonio; Staff Physician, South Texas Veterans Health Care System, San Antonio, Texas

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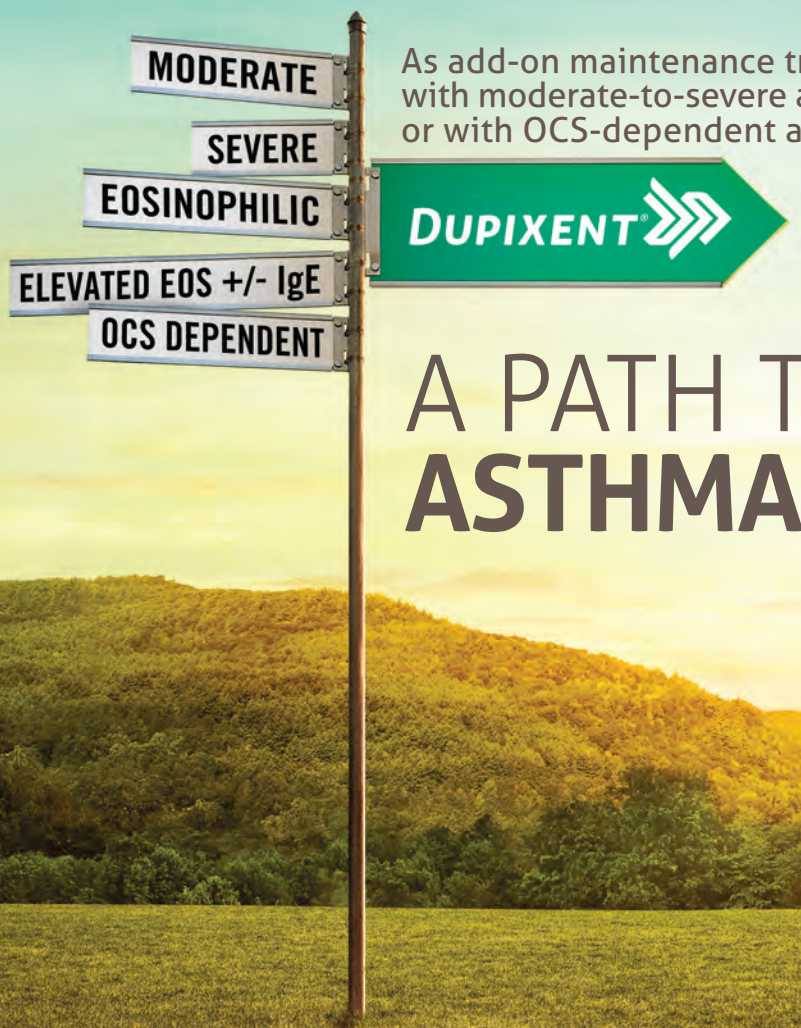
***As the vaping statistics are changing daily, the reported numbers in this report are as of September 17, 2019.**



As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

A PATH TO **ASTHMA CONTROL**

A NOVEL BIOLOGIC THAT INHIBITS IL-4 AND IL-13 SIGNALING, TWO OF THE SOURCES OF INFLAMMATION IN ASTHMA[1,a]

[a] **The mechanism of dupilumab action in asthma has not been established.**

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with EGPA have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

LEARN MORE AT *DUPIXENTASTHMAHCP.COM*

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **81%**

REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24[1,b]

- **71% REDUCTION** with DUPIXENT 200 mg + SOC (n=65) vs placebo + SOC (n=68) (0.30 vs 1.04; rate ratio: 0.29 [95% CI: 0.11, 0.76])
- **81% REDUCTION** with DUPIXENT 300 mg + SOC (n=64) vs placebo + SOC (n=68) (0.20 vs 1.04; rate ratio: 0.19 [95% CI: 0.07, 0.56])

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL**

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12[1]

- **430 mL IMPROVEMENT** with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL])
- **390 mL IMPROVEMENT** with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL])

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation with DUPIXENT. 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) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

TRIAL 1: 24-WEEK STUDY–776 adults (≥18 years) with moderate-to-severe asthma on a standard of care of medium- or high-dose ICS and a LABA were randomized to either DUPIXENT 200 mg Q2W[c] + SOC (n=150), DUPIXENT 300 mg Q2W[d] + SOC (n=157), or placebo + SOC (n=158). Subjects enrolled in Trial 1 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. DUPIXENT was administered as an add-on to background asthma treatment. **Primary endpoint:** Mean change from baseline to Week 12 in FEV_1 in patients with baseline eosinophils ≥300 cells/µL. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.[e] **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose FEV_1 at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[b] Severe exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
[c] With 400 mg loading dose.
[d] With 600 mg loading dose.
[e] Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LSM, least squares mean; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION WITH DUPIXENT[1]

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 430 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 390 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

~68% OF THE TOTAL IMPROVEMENT IN FEV_1 SEEN AT WEEK 2 WITH DUPIXENT 200 mg + SOC (Trial 1 ≥300 cells/µL)[2]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in patients with asthma are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL[1,3]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

70%

REDUCTION IN OCS DOSE

(median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs **42%** (median 50%) with placebo + SOC (n=107)

86% OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107)

IMPROVE LUNG FUNCTION AND REDUCE SEVERE EXACERBATIONS WITH THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS, REGARDLESS OF PHENOTYPE[b]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

59%
REDUCTION

IN ANNUALIZED RATE OF SEVERE EXACERBATIONS
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63])

220 mL
IMPROVEMENT

IN PRE-BRONCHODILATOR FEV_1
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL])

TRIAL 3: 24-WEEK STUDY–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107); the baseline mean OCS dose was 11 mg in the DUPIXENT group and 12 mg in the placebo group. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Additional secondary endpoints:** Annualized rate of severe exacerbation events during the 24-week treatment period; and mean change from baseline to Week 24 in FEV_1. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV_1 at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/μL.

[a] Intention-to-treat (ITT) population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).
[b] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.
[c] With 600 mg loading dose.

Please see brief summary of full Prescribing Information on the following pages.

References: 1. DUPIXENT Prescribing Information. **2.** Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. **3.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485.

SANOFI GENZYME

REGENERON

DUP.19.08.0282

DUPIXENT® (dupilumab) injection, for subcutaneous use Rx Only
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia.

Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program, as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. 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.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*

6.1 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.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, nonfatal myocardial infarctions [MI], and nonfatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described that follow, with the incidence of antibodies in other studies or to other products, may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had

neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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 an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level, which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT 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 DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in 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 (5.5)]*.

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ENVIRONMENTAL SCAN

Drivers of change in education, content delivery, and career advancement

BY THERESE BORDEN
MDedge News

Keeping up to date and maintaining currency on developments in medicine are a routine part of medical practice, but the means by which this is accomplished are changing rapidly. Training, maintenance of certification, continuing education, mentoring, and career development will all be transformed in the coming years because of new technology and changing needs of physicians. Traditional learning channels such as print media and in-person courses will give way to options that emphasize ease of access, collaboration with fellow learners, and digitally optimized content.

Education and content delivery

The primary distribution channels for keeping medical professionals current in their specialty will continue to shift away from print publications and expand to digital outlets including podcasts, video, and online access to content.[1] Individuals seeking to keep up professionally will increasingly turn to resources that can be found quickly and easily, for example, through voice search. Content that has been optimized to appear quickly and with a clear layout adapted to a wide variety of devices will most likely be consumed at a higher rate than resources from well-established organizations that have not transformed their continuing education content. There is already a growing demand for video and audiocasts accessible via mobile device.[2]

John D. Buckley, MD, FCCP, professor of medicine and vice chair for education at Indiana University, Indianapolis, sees the transformation of content delivery as a net plus for physicians, with a couple of caveats. He noted, "Whether it is conducting an in-depth literature search, reading/streaming a review lecture, or simply confirming a medical fact, quick access can enhance patient care and advance learning in a manner that meets an individual's learning style. One potential downside is the risk of unreliable information, so accessing trustworthy sources is essential. Another potential downside is that, while accessing the answer to a very specific question can be done very easily, this might compromise additional learning of related material that used to occur when you had to read an entire book chapter to answer your question. Not only did you answer your question, you learned a lot of other relevant information along the way."

Online learning is now a vast industry and has been harnessed by millions to further professional learning opportunities. Massive Open Online Courses (MOOCs) are free online courses available for anyone to enroll.[3] MOOCs have been established at Harvard, MIT, Microsoft, and other top universities and institutions in subjects like computer science, data science, business, and more. MOOCs are being replicated in conventional universities and are projected to be a model for adult learning in the coming decade.[4]

Dr. Buckley

Another trend is the growing interest in microlearning, defined as short educational activities that deal with relatively small learning units utilized at the point where the learner will actually need the information.[5]

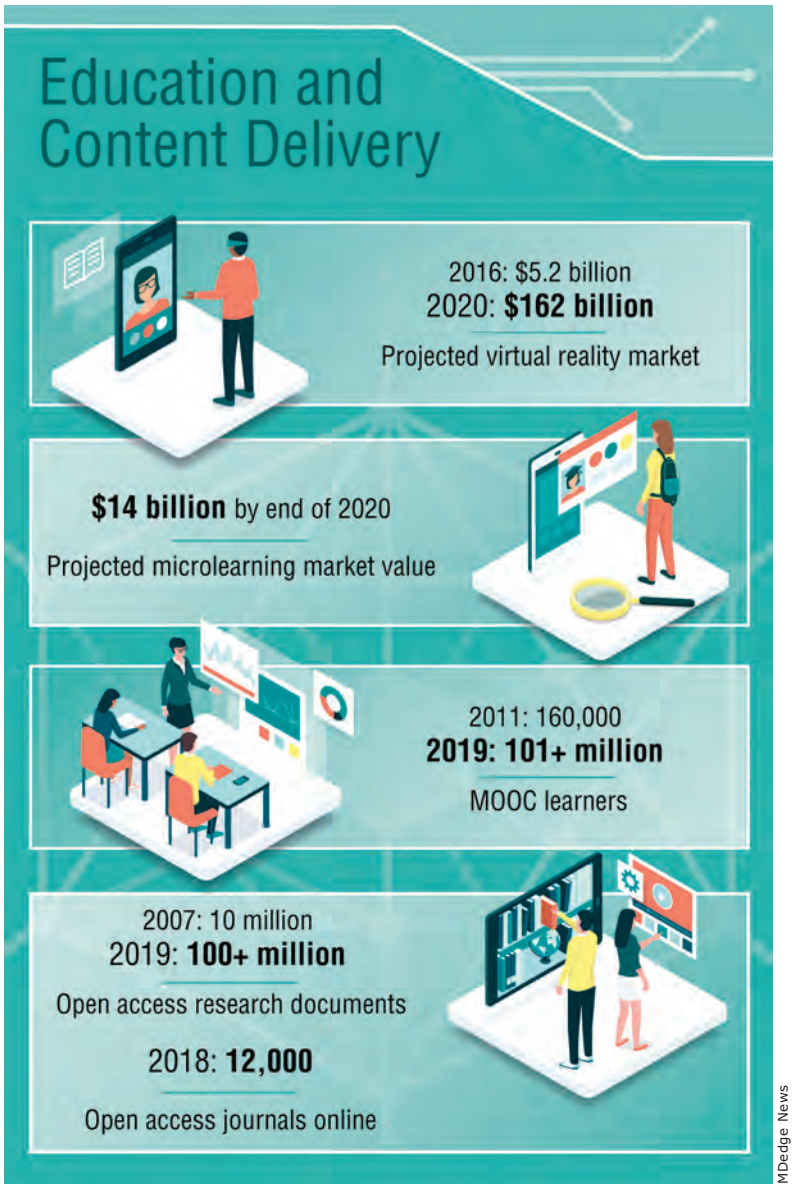
Dr. Buckley sees potential in microlearning for continuing medical education. "It is unlikely that microlearning would be eligible for CME currently unless there were a mechanism for aggregating multiple events into a substantive unit of credit. But the ACCME [Accreditation Council for Continuing Medical Education] has been very adaptive to various forms of learning, so aggregate microlearning for CME credit may be possible in the future." He added that the benefits of rapid and reliable access to specific information from a trusted source are significant, and the opportunities for microlearning for chest physicians are almost limitless. "Whether searching for the most updated review of a medical topic, or checking to see if your ICU patient's sedating medication can cause serotonin syndrome, microlearning is already playing a large role in physician education, just less formal than what's been used historically," he said.

Institutions for which professional development learning modules are an important revenue stream will increasingly be challenged to compete with open-access courses of varying quality.

A key trend identified in 2018 is accelerating higher-education technology adoption and a growing focus on measured outcomes and learning.[5] Individuals are interested in personalized learning plans and adaptive learning systems that can provide real-time assessments and immediate feedback. It is expected that learning modules and curricula will be most successful if they are easily accessed, attractively presented, and can incorporate immediate feedback on learning progress. Driving technology adoption in higher education in the next 3-5 years will be the proliferation of open educational resources and the rise of new forms of interdisciplinary studies. As the environment for providing and accessing content shifts from pay-to-access to open-access, organizations will need to identify a new value proposition if they wish to grow or maintain related revenue streams.[6]

The implications of these changes in demand are profound for creators of continuing education content for medical professionals. Major investment will be needed in new, possibly costly platforms that deliver high-quality content with accessibility and interactive elements to meet the demands of professionals, the younger generation in particular.[7]

The market will continue to develop new technology to serve continuing education needs and preferences of users, thus fueling competition among stakeholders. With the proliferation of free and low-cost online and virtual programs, continuing education providers may experience a negative impact on an important revenue stream if they don't identify a competitive advantage that meets the needs of tomorrow's workforce. However, educational programs and courses that use artificial intelligence, virtual reality, and augmented reality to enhance the learning experience are likely to experience higher levels of use in the coming years.[8]



MDedge News

Workforce diversity and mentoring

A global economy requires organizations to seek a diverse workforce. Diversity can also lead to higher levels of profitability and employee satisfaction. As such, it will be essential for organizations to increase opportunities for individuals from diverse backgrounds to join the workforce. Creating a diverse workforce will mean removing barriers of time and location to skill building through online learning opportunities and facilitation of interdisciplinary career paths.

A critical piece of the emerging model of career development will be mentoring. Many professionals in today's workforce view mentoring as an opportunity to gain immediate skills and knowledge quickly and effectively. Mentoring has evolved from pairing young professionals with seasoned veterans to creating relationships that match individuals with others who have the skills and knowledge they desire to learn about – regardless of age and experience. Institutions striving to develop a diverse workforce will need many individuals to serve as both mentors and mentees. When searching for solutions to work-related challenges, individuals will increasingly turn to knowledge management and collaboration systems (virtual mentoring) that provide them with the opportunity to match their needs in an efficient and effective manner.

Dr. Buckley values peer-to-peer mentoring as a means of accessing and sharing niche expertise among colleagues, but he acknowledges the difficulties in incorporating it into everyday practice. "The biggest obstacles are probably time and access. More and more learners and mentors are recognizing the tremendous value of effective mentorship, so convincing people is less of an issue than finding time," he said.

Mentorship will continue to play a central role in the advancement of one's career, yet women and minorities find it increasingly difficult to match with a mentor within the workplace. These candidates are likely to seek external opportunities. Individuals will evaluate the experience, opportunities for career advancement, and the level of diversity and inclusion when seeking and accepting a new job.

Dr. Buckley sees both progress and remaining challenges in reducing barriers to underrepresented groups in medical institutions. "There continues to be a need for ongoing training to help individuals and institutions recognize and eliminate their barriers and biases, both conscious and subconscious, that interfere with achieving diversity and inclusion. Another important limitation is the pipeline of underrepresented groups that are pursuing careers in medicine. We need to do more empowerment, encouragement, and recruitment of underrepresented groups at a very early stage in their education if we ever expect to achieve our goals."

Future challenges

The transformations described above will require a large investment by physicians aiming to maintain professional currency, by creators of continuing education content, and by employers seeking a diversified workforce. All these stakeholders have an interest in the future direction of continuing education and professional training. The development of new platforms for delivery of content that is easily accessible, formatted for a wide variety of devices, and built with real-time feedback functions will require a significant commitment of resources.

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Note: Background research performed by Avenue M Group.

CHEST Inspiration is a collection of programmatic initiatives developed by the American College of Chest Physicians leadership and aimed at stimulating and encouraging innovation within the association. One of the components of CHEST Inspiration is the Environmental Scan, a series of articles focusing on the internal and external environmental factors that bear on success currently and in the future. See "Envisioning the Future: The CHEST Environmental Scan," *CHEST Physician*, June 2019, p. 44, for an introduction to the series.

This month in the journal *CHEST*®

Editor's picks

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

ORIGINAL RESEARCH

The Saint Georges Respiratory Questionnaire definition of chronic bronchitis may be a better predictor of COPD exacerbations compared to the classic definition.
By Dr. V. Kim, et al.

Confocal laser endomicroscopy (CLE) as a guidance tool for pleural biopsies in malignant pleural mesothelioma.
By Dr. L. Wijmans, et al.

Association of Angiotensin Modulators With the Course of Idiopathic Pulmonary Fibrosis.
By Dr. M. Kreuter, et al.

Age-Stratified National Trends in Pulmonary Embolism Admissions.
By Dr. E. D. Pauley, et al.

COMMENTARY

Solving the Opioid Crisis: Respiratory Depression by Opioids as Critical Endpoint.
By *Dr. G. Montandon and Dr. A. S. Slutsky.*

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2019 Education Calendar

November 7 - 9
Extracorporeal Support for Respiratory and Cardiac Failure in Adults

November 14 - 16
Critical Care Ultrasound: Integration Into Clinical Practice

November 22 - 23
Comprehensive Pleural Procedures

December 5 - 7
Ultrasonography: Essentials in Critical Care

December 13 - 14
Advanced Critical Care Echocardiography Board Review Exam Course

Coding changes coming soon

BY MICHAEL NELSON, MD, FCCP
CHEST Physician Editorial Board

There may be some positive changes coming to evaluation and management (E/M) services effective January 1, 2021. In the proposed calendar year 2020 Physician Fee Schedule (CY 2020 PFS), the Centers for Medicare & Medicaid Services (CMS) suggested a number of coding, payment, and documentation changes for office/outpatient E/M visits, Current Procedural Terminology (CPT®) codes **99201-99215**. A summary of these changes include:

- Separate payment for the five levels of office/outpatient E/M visit CPT codes, as revised by the CPT Editorial Panel effective January 1, 2021. This would include deletion of CPT code **99201** (Level 1 new patient office/outpatient E/M visit) and adoption of the revised CPT code descriptors for CPT codes **99202-99215**;
- Elimination of the use of history and/or physical exam to select among code levels;
- Choice of time or medical decision making to decide the level of office/outpatient E/M visit (using the revised CPT interpretive guidelines for medical decision making);
- Payment for prolonged office/outpatient E/M visits using the revised CPT code for such services, including separate payment for new CPT code **99XXX** and deletion of Healthcare Common Procedure Coding System (HCPCS) code **GPRO1** (extended office/outpatient E/M visit) that was previously finalized for 2021;
- Revise the descriptor for HCPCS code **GPC1X** and delete HCPCS code **GCG0X**; and
- Increase in value for HCPCS code **GPC1X** and allowing it to be reported with all office/outpatient E/M visit levels.


Dr. Nelson

These changes are predicted to result in a simplification of physician documentation and a redistribution of payments favoring providers who deliver primary care or care to more complex patients.

These changes were recommended by CMS to improve payment accuracy, reduce the administrative burden, and better reflect the current practice of medicine. These changes are predicted to result in a simplification of physician documentation and a redistribution of payments favoring providers who deliver primary care or care to more complex patients.

In CY 2019 PFS, CMS proposed to pay a single (blended) rate for office/outpatient visits 2-4, but due to comments from stakeholders, including specialty societies, CMS proposed to accept alternate recommendations by AMA/CPT. These recommendations include using medical decision making or time to

Continued on following page

TABLE 1: Comparison of Current Office/Outpatient E/M Services Code Set vs CY2021 Prolonged Services Code

CPT code	Current time	Current RVU	Proposed time	Proposed RVU
99201	17	0.48	NA	NA
99202	22	0.93	22	0.93
99203	29	1.42	40	1.6
99204	45	2.43	60	2.6
99205	67	3.17	85	3.5
99211	7	0.18	7	0.18
99212	16	0.48	18	0.70
99213	23	0.97	30	1.30
99214	40	1.50	49	1.92
99215	55	2.11	70	2.8
99XXX	NA	NA	15	0.61

MDedge News

CRITICAL CARE COMMENTARY

Should PEEP be titrated based on esophageal pressures?

BY ALICE GALLO DE MORAES, MD, AND RICHARD A. OECKLER, MD, PHD

Application of basic physiology principles at bedside has changed the approach to the treatment of patients with acute respiratory distress syndrome (ARDS) and refractory hypoxemia.

Current standard of care for patients with ARDS includes a low tidal volume ventilation strategy (6 mL/kg of ideal body weight), keeping plateau pressures below 30 cm H_2O (Brower RG, et al. *N Engl J Med.* 2000;342[18]:1301), driving pressures below 15 cm H_2O and adequate positive end-expiratory pressures (PEEP) to keep the alveoli open without overdistension (Villar J, et al. *Crit Care Med*. 2006;34[5]:1311). However, at this time, despite the awareness of the importance of this intervention, there is no consensus regarding the best method to determine ideal PEEP at the individual patient level.

A thorough understanding of the basic physiologic concepts regarding respiratory pressures is of paramount importance to be able to formulate an opinion. The transpulmonary pressure (or lung distending pressure) is the gradient caused by the difference between alveolar (PA) and pleural pressure (PPL). In order to prevent lung collapse at end-expiration, PA must remain higher than PPL such that the gradient remains outward, preventing end-expiratory collapse and atelectotrauma. To accomplish that, it is necessary to know the end-expiratory PA and PPL. Esophageal balloon pressures (PES) represent central thoracic pressures, but, despite positional and regional variations, they are a good surrogate for average "effective" PPL (Baedorf KE, et al. *Med Klin Intensivmed Notfmed.* 2018;113[Suppl 1]:13).

Dr. Gallo de Moraes

Dr. Oeckler

Understanding that the value of the PES represents a practical PPL makes it easier to appreciate the potential usefulness of an esophageal balloon to titrate PEEP. The objective of PEEP titration is to prevent de-recruitment, maintain alveolar aeration, and improve the functional size of aerated alveoli. If the applied PEEP is lower than the PPL, the dependent lung regions will collapse. On the other hand, if PEEP is higher than the PPL, the lung would be overdistended, causing barotrauma and hemodynamic compromise.

The question is: Should we use esophageal balloons?

Yes, we should.

A single center randomized control trial (EPVent) compared PEEP titration to achieve a positive PL vs standard of care lung protective ventilation (Talmor D, et al. *N Engl J Med.* 2008;359:2095). The PEEP titration group used significantly higher levels of PEEP, with improved oxygenation and lung compliance. However, there was no significant difference in ventilator-free days or mortality between the groups.

Obese patients are also likely to benefit from PEEP titration guided by an esophageal balloon, as they often have higher levels of intrinsic PEEP. Therefore, the application of higher levels of PEEP to compensate for the higher levels of intrinsic PEEP may help reduce work of breathing and prevent tidal recruitment-de-recruitment and atelectasis. Additionally, low to negative transpulmonary pressures measured using the actual values of PES in obese patients and obese animal models predicted lung collapse and tidal opening and closing (Fumagalli J, et al. *Crit Care Med.* 2017;45[8]:1374).

It is useful to remember that the compliance of the respiratory system (Crs) is the total of the sum of the compliance of the chest wall (Ccw) and the lung compliance (CL). In obese patients, Ccw has a much more significant contribution to the total Crs, and the clinician should be really

Continued on page 61

Continued from previous page

determine the level of a visit, rather than the schema that was based on history and physical exam and outlined in the 1995/1997 guidelines. This resulted in elimination of CPT code **99201** and changes to the descriptors of **99202-99215**. These codes were resurveyed by the Relative Value Update Committee (RUC) resulting in new values and times. (See Table 1).

One can see that there has been an incremental increase in time and value for most codes. When selecting a code based upon time, there is a range that is defined for each code,and additional information about the codes, including the descriptors and ranges, can be found on the AMA website https://www.ama-assn.org/cpt-evaluation-and-management.

For CPT codes **99205** and **99215** (level 5 codes), an add-on code has also been proposed that would account for additional time spent above the new levels defined in the codes. The descriptor for CPT **99XXX** (the final numbers have not yet been assigned) reads *Prolonged office or other outpatient evaluation and management service(s) (beyond the total time of the primary procedure which has been selected using total time), requiring total time with or without direct patient contact beyond the usual service, on the date of the primary service; each 15 minutes (List separately in addition to codes* **99205**, **99215** *for office or other outpatient Evaluation and Management services*). **99XXX** is similar to CPT add-on code **99292** in that it may be used multiple times for a single encounter. This is illustrated in Table 2.

TABLE 2: Total Proposed Practitioner Times for Office/Outpatient E/M Visits When Time Is Used to Select Visit Level

Total time	CPT code
Established Patient Office/Outpatient E/M Visit	
40-54 minutes	99215
55-69 minutes	99215 ×1 and 99XXX ×1
70-84 minutes	99215 ×1 and 99XXX ×2
85 or more minutes	99215 ×1 and 99XXX ×3 or more for each additional 15 minutes
New Patient Office/Outpatient E/M Visit	
60-74 minutes	99205
75-89 minutes	99205 ×1 and 99XXX ×1
90-104 minutes	99205 ×1 and 99XXX ×2
105 or more minutes	99205 ×1 and 99XXX ×3 or more for each additional 15 minutes

MDedge News

However, **99XXX** is only used with level 5 codes. It will replace HCPCS code **GPRO1**, which had been finalized in the CY 2019 PFS. The proposed code will have a value of 0.61 RVU.

Finally, there is a proposal to revise the descriptor for HCPCS code **GPC1X** and eliminate HCPCS code **GCG0X**. The new descriptor for **GPC1X** *Visit complexity inherent to evaluation and management associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient's single, serious, or complex chronic condition. (Add-on code, list separately in addition to office/outpatient evaluation and management visit, new or established)* is being updated to simplify the coding and, with the elimination of **GCG0X**, to remove the perception that the code is primary care or specialty specific. The value of **GPC1X** is also being increased to 0.33 RVU.

It must be made clear that these changes are proposals only, and CMS is still reviewing stakeholder and public comments. Any actual changes will not be codified until publication of the CY2020 PFS later this year. Additional information regarding the proposed rule can be found by accessing https://federalregister.gov/d/2019-16041.

Instead of choosing an ICS/LABA,

START BREAKING TRADITION

Start appropriate symptomatic patients with COPD on ANORO for dual bronchodilation

The GOLD 2019 Report

- **Continues to emphasize the role of LAMA/LABA for patients with COPD**[1]
- **Does not include ICS/LABA as initial treatment for many patients**[1]

ANORO was studied in patients with moderate or worse COPD.

INDICATION

ANORO is for the maintenance treatment of patients with COPD. ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information

CONTRAINDICATIONS

- ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or with hypersensitivity to umeclidinium, vilanterol, or any of the excipients.
- Use of a long-acting beta$_2$-adrenergic agonist (LABA) without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma.

WARNINGS AND PRECAUTIONS

- The safety and efficacy of ANORO in patients with asthma have not been established. ANORO is not indicated for the treatment of asthma. Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. Available data do not suggest an increased risk of death with use of LABA in patients with COPD.
- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.
Please see Brief Summary of Prescribing Information for ANORO ELLIPTA following this ad.

START WITH ANORO FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION VS AN ICS/LABA[2]

Nearly 2x the lung function improvement vs ADVAIR[2]

LS mean change from baseline in weighted mean FEV_1 (0-24 hours) on Day 84

1.8x IMPROVEMENT

Study DB2114930[2]

74-mL Difference (*P*<0.001)
ANORO **165 mL (n=353)**
ADVAIR **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101-mL Difference (*P*<0.001)
ANORO **213 mL (n=349)**
ADVAIR **112 mL (n=348)**

Studied in patients with moderate to severe COPD (GOLD 2 or 3).[2]

What would almost 2x the lung function improvement mean for your patients?

Learn more at StartWithANORO.com

Description of studies[2,3]: The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of ADVAIR DISKUS 250 mcg/50 mcg were evaluated in 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

Primary endpoint: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LS=least squares.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO should not be used more often or at higher doses than recommended or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO if such reactions occur.

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors as increased systemic exposure to vilanterol and cardiovascular adverse effects may occur. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- ANORO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Please see additional Important Safety Information for ANORO ELLIPTA on the previous pages.
Please see Brief Summary of Prescribing Information for ANORO ELLIPTA following this ad.

References: 1. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. 2019 report. www.goldcopd.org. Accessed November 27, 2018. **2.** Donohue JF, Worsley S, Zu C-Q, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015; 109(7):870-881. **3.** Data on file, GSK.

Visit StartWithANORO.com

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

ANORO ELLIPTA was developed in collaboration with INNOVIVA

UCVADVT190009 August 2019
Produced in USA.

BRIEF SUMMARY

ANORO ELLIPTA
(umeclidinium and vilanterol inhalation powder), for oral inhalation use

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
ANORO ELLIPTA is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
Important Limitations of Use
ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma. The safety and efficacy of ANORO ELLIPTA in asthma have not been established.
4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full prescribing information]*.
Use of a long-acting beta$_2$-adrenergic agonist (LABA) without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma *[see Warnings and Precautions (5.1)]*. ANORO ELLIPTA is not indicated for the treatment of asthma.
5 WARNINGS AND PRECAUTIONS
5.1 Serious Asthma-Related Events—Hospitalizations, Intubations, Death
The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established.
ANORO ELLIPTA is not indicated for the treatment of asthma *[see Contraindications (4)]*.
Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted.
Available data do not suggest an increased risk of death with use of LABA in patients with COPD.
5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting Beta$_2$-agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full prescribing information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction, non-fatal acute myocardial infarction, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/25 mcg (n = 4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n = 4,134), and 2.2 per 100 patient-years for ANORO ELLIPTA (n = 2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving fluticasone furoate/umeclidinium/vilanterol, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving ANORO ELLIPTA.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients.
In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.
6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Serious asthma-related events–hospitalizations, intubations, death. LABA, such as vilanterol (one of the active ingredients in ANORO ELLIPTA), as monotherapy (without ICS) for asthma increase the risk of asthma-related events. ANORO ELLIPTA is not indicated for the treatment of asthma [*see Warnings and Precautions (5.1)*].
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and two 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials
The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trial 1, NCT #01313650 and Trial 2, NCT #01313637); N = 1,532 and N = 1,489, respectively) and 2 active-controlled trials (Trial 3, NCT #01316900 and Trial 4, NCT #01316913); N = 843 and N = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).
Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.
Table 1. Adverse Reactions with ANORO ELLIPTA with ≥1% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %	Placebo (n = 555) %
Infections and infestations				
Pharyngitis	2	1	2	<1
Sinusitis	1	<1	1	<1
Lower respiratory tract infection	1	<1	<1	<1
Gastrointestinal disorders				
Constipation	1	<1	<1	<1
Diarrhea	2	<1	2	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	2	<1	2	1
Muscle spasms	1	<1	<1	<1
Neck pain	1	<1	<1	<1
General disorders and administration site conditions				
Chest pain	1	<1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence <1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trials
In a long-term safety trial (Trial 5, NCT #01316887), 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions observed with a frequency of ≥1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.
6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of ANORO ELLIPTA. 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 ANORO ELLIPTA or a combination of these factors.
Cardiac Disorders
Palpitations.
Eye Disorders
Blurred vision, glaucoma, increased intraocular pressure.
Immune System Disorders
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.
Nervous System Disorders
Dysgeusia, tremor.
Psychiatric Disorders
Anxiety.
Renal and Urinary Disorders
Dysuria, urinary retention.
Respiratory, Thoracic, and Mediastinal Disorders
Dysphonia, paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women to inform a drug-associated risk. *(See Clinical Considerations.)* In animal reproduction studies, umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effects on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the maximum recommended human daily inhaled dose (MRHDID). Vilanterol administered via inhalation to pregnant rats and rabbits produced no fetal structural abnormalities at exposures approximately 70 times the MRHDID. *(See Data.)*

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

Clinical Considerations

Labor and Delivery: There are no human studies evaluating the effects of ANORO ELLIPTA, umeclidinium, or vilanterol during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of ANORO ELLIPTA during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data

Animal Data: The combination of umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with umeclidinium and vilanterol individually.

Umeclidinium: In separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species.

In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods with no evidence of effects on offspring development at doses up to approximately 26 times the MRHDID (on an AUC basis at maternal subcutaneous doses up to 60 mcg/kg/day).

Vilanterol: In separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 450 times, respectively, the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 70 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

8.2 Lactation

Risk Summary

There is no information available on the presence of umeclidinium or vilanterol in human milk, the effects on the breastfed child, or the effects on milk production. Umeclidinium was detected in the plasma of offspring of lactating rats treated with umeclidinium suggesting its presence in maternal milk. *(See Data.)* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANORO ELLIPTA and any potential adverse effects on the breastfed child from umeclidinium or vilanterol or from the underlying maternal condition.

Data

Subcutaneous administration of umeclidinium to lactating rats at ≥60 mcg/kg/day resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl <30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for the individual components, umeclidinium and vilanterol, as described below.

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and at inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately equivalent to the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

ANORO ELLIPTA is not indicated for the treatment of asthma. Inform patients that LABA, such as vilanterol (one of the active ingredients in ANORO ELLIPTA), when used alone (without ICS) for asthma increase the risk of asthma-related hospitalization or asthma-related death.

Not for Acute Symptoms

Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with ANORO ELLIPTA without healthcare provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and contact their healthcare provider right away.

Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

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PULMONARY PERSPECTIVES®

The emerging role of quantitative CT scans in ILD

BY SAMANTHA D'ANNUNZIO, MD; CHRISTINE NAYAR, MD; AND NINA PATEL, MD, FCCP

The role of imaging for interstitial lung disease (ILD) is of paramount importance. With the growth of high resolution chest computed tomography (HRCT) imaging techniques, we are able to visualize nuances between individual ILDs more critically.

HRCT is an essential component of an initial ILD evaluation and also has become part of the armamentarium of tools used for routine management of these patients. The technology of HRCT scans has evolved over the years, most recently with the advent of quantitative HRCT (qCT). The technology employs texture-based classification, which identifies and quantifies different radiographic findings. The arrival of qCT scanning has been slowly emerging as a new player in the ILD world. What exactly is qCT, and what role can, and will, it serve for our ILD patients?

Quantitative CT scanning was introduced in the 1980s, but only within the last 15 years has its use for ILD taken form. Human interpretation of CT scanning is fraught with subjectivity, based on the interpreting radiologist's training, experience, and individual visual perception of images. This can result in significant variability in radiographic interpretations and, ultimately, affects a patient's diagnosis, disease monitoring, treatment, and prognosis. Semiquantitative visual scoring by radiologists is highly variable, especially in areas with limited availability of chest radiologists. qCT employs an automated histogram signature technique that utilizes density and texture-based analysis of the lung parenchyma.

Utilizing machine learning from pathologically confirmed datasets, computer programs were trained with specialized thoracic radiologists to distinguish some commonly found radiographic abnormalities into four major groups: ground glass, reticular, honeycombing, and emphysema. In addition, these categories are quantified and spatially depicted on an analysis (Bartholmai, et al. *J Thorac Imaging*. 2013;28[5]:298).

The technology employs texture-based classification, which identifies and quantifies different radiographic findings.

Various computer programs have been built to streamline the process and expedite the interpretation of an individual's HRCT scan. The more commonly familiar program, CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings), has been used in multiple research studies of qCT in ILD and IPF. Each patient's CT scan is uploaded to the program, and a breakdown of the patient's lungs into each category is presented. Not only is each abnormality quantified and precisely defined, it is also color-coded by segments to help with visual interpretation by the physician.

The benefit of qCT lies not only in the automated, objective evaluation of interstitial lung disease, but also in its possible use in prognostication and mortality prediction. Neither use has been fully validated as of yet. However, growing evidence shows a promising role in both realms. Thus far, there have been some studies correlating PFT data with qCT findings.

A follow-up study of the Scleroderma Lung Study II examined qCT changes over 24 months and correlated those findings with PFTs and patient-reported outcomes. Patients in this study were either treated with cyclophosphamide (CYC) for 1 year/placebo 1 year vs mycophenolate mofetil (MMF) for 2 years. A large portion of patients receiving CYC or MMF had a significant correlation between improved or stable qCT scores and their FVC and TLC. Neither CYC nor MMF was superior in qCT scores, aligning with the findings of the study, which showed noninferiority of MMF compared with CYC (Goldin, et al. *Ann Am Thorac Soc*. 2018 Nov;15[11]:1286). Interestingly, the improvement of ground glass is often viewed by physicians as positive, since this finding is typically thought of as active inflammation. However, if qCT determines that the fibrosis score actually increases over time, despite an improvement in ground glass, this may more accurately reflect the development of subtle fibrosis that is not easily appreciated by the human eye (Goldin, et al. *Ann Am Thorac Soc.* 2018 Nov;15[11]:1286). In this context, it is feasible that parenchymal changes occur prior to deterioration on PFTs. Diffusing capacity for carbon monoxide (DLCO) correlates largely with the extent of lung involvement on qCT, but DLCO is not a specific biomarker in predicting severity of ILD (ie, because pHTN or anemia can confound DLCO). Forced vital capacity (FVC) in certain diseases may also confound CT correlation (ie, muscle weakness or extrathoracic restriction from skin disease in systemic sclerosis). The usefulness of PFT data as a clinical endpoint in research studies may be replaced by qCTs more consistent and precise detection of disease modification.

IPF has been an interesting area of exploration for the role of qCT in disease monitoring and possible prognostication. It is known that the presence of honeycombing on HRCT is asso-

Continued on following page

Continued from page 55

interested in the CL. At the bedside, esophageal manometry can be very useful to distinguish the contribution of CL and Ccw to the total Crs.

No, we shouldn't.

Another randomized controlled trial (EPVent-2), by the same group, compared PEEP titration guided by esophageal pressure with empirical PEEP titration, in patients with moderate to severe ARDS (Beitler JR, et al. *JAMA*. 2019;321[9]:846). The primary outcomes of interest, death, and mechanical ventilator-free days through day 28 were not different between the groups.

Additionally, placement of an esophageal balloon is challenging and operator-dependent. The balloon portion of the esophageal catheter should be positioned in the lower third of the esophagus, behind the heart. Catheter placement is typically performed by inserting it into the stomach to a depth of about 60 cm, and gently pressing on the abdomen and observing a sudden increase in pressure on the ventilator screen. It is then withdrawn to about 40 cm, while looking for cardiac oscillations and pressure change (Talmor D, et al. *N Engl J Med.* 2008;359:2095). One can see how easily it would be to insert the esophageal balloon incorrectly. A misplaced balloon won't provide accurate PES and can potentially cause harm.

Final answer: It depends on each individual patient.

Arguments for and against using an esophageal balloon to titrate PEEP in patients with ARDS and refractory hypoxemia are ongoing. Even the two most cited and applied trials on the matter (EPVent and EPVent-2) reported contradictory results. However, when analyzed in depth, both showed better oxygenation with the use of esophageal balloon. EPVent had improvement in oxygenation as its primary endpoint, and it was significant in the esophageal balloon group. EPVent-2 had oxygenation goals, in the form of need for rescue therapies for refractory hypoxemia, as secondary endpoints. Nonetheless, the patients in the esophageal balloon group in EPVent-2 required prone positioning less frequently, had lower use of pulmonary vasodilators, and a lower rate of ECMO consultations. Even though those trials did not show a mortality benefit, both showed an oxygenation benefit.

The ideal single tool that would indicate the "perfect "PEEP for each patient remains to be described. Until then, PEEP titration guided by a combination of ARDSnet PEEP tables, while maintaining a plateau pressure below 30 cm H_2O and considering a driving pressure below 15 cm H_2O should be a clinician's goal. In patients in the extremes of height and body weight, and/or with conditions that would increase intra-abdominal pressure, such as ascites, a well-placed esophageal balloon while patient is supine might be beneficial.

The truth of the matter is, PEEP should be titrated by a trained intensivist in conjunction with the multidisciplinary ICU team, at patients' bedside taking into consideration each individual's unique physiologic and pathophysiologic characteristics at that moment.

Dr. Gallo de Moraes is Assistant Professor of Medicine, and Dr. Oeckler is Assistant Professor of Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, Minnesota.

CHEST NETWORKS

Robotic-assisted bronchoscopy. PARDS. Vaping alert. PR and COPD.

Interventional Chest/ Diagnostic Procedures

Emergence of robotic-assisted bronchoscopy for the diagnosis of peripheral lung lesions

The diagnostic chest medicine community saw exciting advances in technology for diagnosis of peripheral lung lesions (PLL) with the recent FDA approval of two robotic-assisted bronchoscopy systems (RBS): the Monarch Platform from Auris Health (2018) and the Ion system from Intuitive Surgical (2019). Small pilot studies of 15 (Monarch) and 29 (Ion) subjects, respectively, demonstrated safety and feasibility of biopsy and diagnosis of PLL using RBS (Rojas-Solano, et al. J *Bronchol Intervent Pulmonol*. 2018;25:168; Fielding et al. *Respiration.* 2019;98[2]:142). While these studies were not powered to evaluate diagnostic yield, they suggested the potential for improved yields over current technologies.

Current bronchoscopic modalities for diagnosis of PLL include electromagnetic navigation bronchoscopy, radial endobronchial ultrasound, and fluoroscopic guidance, all of which have favorable safety profiles but have been plagued by a wide range in diagnostic yields (38% to 88%) (Eberhardt R, et al. *Am J Respir Crit Med.* 2007;176[1]:36; Ost DE, et al. *Am J Respir Crit Care Med.* 2016;193[1]:68). Despite the discordant history of efficacy of PLL sampling modalities, they have gained widespread adoption due to the increasing need to access the periphery. That said, many operators have been left wanting, making new technologies attractive options despite a lack of data. The emergence of RBS may present an opportunity to change the way we approach bronchoscopic procedures, making what was a manual procedure into one that is machine-assisted and, perhaps, improving our accuracy of repetition. The robotic age of lung medicine is an exciting proposition, however, it is paramount that we pursue a robust evidence-based strategy with multicentered clinical trials and move beyond the limitations of registry data in order to carefully embrace these new technologies.

Christina MacRosty, DO
Incoming Fellow-in-Training Member
Jason Akulian, MD, MPH, FCCP
Steering Committee Member

Pediatric Chest Medicine

PARDS: A new definition

Pediatric Acute Respiratory Distress Syndrome (PARDS) is a multifactorial clinical syndrome associated with high morbidity and mortality in children. It is caused by disruption of the alveolar epithelial–endothelial permeability barrier leading to accumulation of protein-rich fluid in the alveoli and surfactant degradation. These changes result in a restrictive lung disease characterized by hypoxemia, radiographic opacities, decreased FRC, and lung compliance and increased physiologic dead space. Resolution usually occurs after several weeks, with potential development of fibrosis. The most common cause of ARDS in children is viral respiratory infection, although associated with many underlying conditions, including pneumonia, sepsis, trauma, burns, pancreatitis, inhalation, transfusion, and cardiopulmonary bypass.


Dr. Rao

In 2015, an international panel of experts convened the Pediatric Acute Lung Injury Consensus Conference (PALICC) to establish new definitions and guidelines for PARDS. The 2015 PALICC definition broadens to include any new parenchymal infiltrate(s) and allows use of pulse oximetry to avoid underestimating ARDS prevalence in children. It also allows utilization of the oxygenation index (OI) and oxygenation saturation index (OSI) rather than the PaO_2/Fio_2 (P/F) ratio to assess hypoxemia (PARDS: consensus. *Pediatr Crit Care Med.* 2015;16[5]:428; Orloff et al. *Pediatr Allergy Immunol Pulmonol.* 2019;32[2]:35).

In a follow-up international, prospective, cross-sectional, observational study across 27 countries, the PALICC definition identified more children as having PARDS than the Berlin definition. The PALICC PARDS severity groupings improved mortality risk stratification. The PALICC PARDS framework appears to be a better tool for future epidemiologic and therapeutic research among children with PARDS (Khemani et al. *Lancet Respir Med.* 2019;7[2]:115).

Harish Rao, MD
Steering Committee Member

EIGHT* people have died! Need action now

Pediatricians nationwide have raised the alarm as the numbers of middle- and high-school students who are vaping continues to skyrocket. The National Youth Tobacco survey (2018) showed a 78% increase in e-cigarette use in high school students with a 48% increase in middle school students between 2017-2018. Now considered a public health crisis with hundreds of cases of severe respiratory illnesses and eight deaths linked to vaping, our physicians, legislators, educators, and respiratory health organizations are joining forces to curb its use in adolescents.

The American College of Chest Physicians has long supported regulation of e-cigarettes, joining the Forum of International Respiratory Societies in a position statement

Continued on following page

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ciated with increased mortality. Patients with a progressive fibrotic ILD have similar mortality rates to those with IPF (Adegunsoye, et al. *Ann Am Thorac Soc.* 2019 May;16[5]:580). The ability to correlate radiographic findings with mortality could potentially become an important marker of clinical deterioration, especially in those patients who are unable to perform PFTs. In addition, it can also be beneficial in those with co-existent emphysema, since PFTs may be confounded by this overlap. Nakagawa and colleagues proposed a computer-aided method for qCT analysis of honeycombing in patients with IPF. The algorithm for the qCT analysis also has specific parameters to exclude emphysematous lesions on imaging. The %honeycomb area (HA) was correlated with a composite physiologic index derived from PFTs (calculated from FEV_1, FVC and DLCO). This tool can accurately quantify the percentage of honeycombing and aid in monitoring IPF. Using this protocol, Nakagawa was able to demonstrate a significant correlation with 3-year mortality, with a marked difference found when using a cutoff value of 4.8% (Nakagawa, et al. *Plos One.* 2019 Mar; 14[3]:e0214278). Furthermore, patient survival in IPF has been compared against the CALIPER program and PFTs. Mortality for patients was significantly associated with pulmonary vessel volume (PVV), an innovative tool that quantified the volume of the pulmonary artery and veins, which may become a new parameter used for disease monitoring. Using qCT in addition to PFTs provides more tangible evidence to help monitor patients with IPF, guide treatment decisions, and plan for transplant or palliative care. The growing use of PVV in qCT has yet to be fully elucidated, but it does have a promising role (Jacob, et al. *Eur Respir J.* 2017;49[1]. doi: 10.1183/13993003.01011-2016).

Despite the positive outlook for qCT, there are major issues that limit its widespread use. During the image acquisition process, there is a lack of consistency and quality control, stemming from multiple different manufacturers of CT scan machines, reconstitution methods, radiation doses, and noise or inspiratory efforts of patients. The Radiologic Society of North America (RSNA) is attempting to fix this issue by creating a standardized protocol for collecting images used for qCT (Castillo-Saldana, et al. *J Thorac Imaging.* 2019 Aug 7. doi: 10.1097/RTI.0000000000000440). In order to move forward with adaptation of qCT, a standardized approach and handling of images needs to be created.

Quantitative CT is an exciting new prospect for the care of patients with ILD. As these patients, and their management, become more complex, expanding the toolbox for physicians is much needed. It will be fascinating to see how the role of qCT takes shape over the coming years.

Dr. D'Annunzio is with Westmed Medical Group, Rye, NY; Dr. Nayar is a Pulmonary/Critical Care Fellow at NYU School of Medicine; and Dr. Patel is with Columbia University Medical Center.

Continued from previous page

recommending bans on flavored e-cigarettes and restricting use in areas where children are present.

The Administration announced this week its intention to " clear the market " of all flavored e-cigarettes. Sweet and fruit flavorings are known to entice adolescents to try e-cigarettes while the variety and ability to choose their own combinations of flavors continues to bring teens back again and again. We know that the brain continues to develop into our mid-twenties, causing teens to be more vulnerable to the addictive properties of nicotine.

Dr. Cataletto

Increasing numbers of exposures in adolescents and the severity of vaping-related illnesses have prompted states to take a proactive approach to keep e-cigarettes out of the hands of children. Michigan was the first state to ban the sale of flavored e-cigarettes online and in brick and mortar stores with compliance to take effect within the next 30 days. Other states are expected to follow suit.

Legislation is an important step in our efforts to curb vaping and protect our children.

Mary Cataletto MD, FAAP, FCCP
NetWork Chair

*As the vaping statistics are changing daily, the reported numbers in this report are as of September 20, 2019.

Pulmonary Physiology, Function, and Rehabilitation

Pulmonary rehab and COPD

The introduction of pulmonary rehabilitation (PR) into the care of a patient with COPD can be a life-changing intervention. It has not only been shown to significantly improve symptoms, daily function, and quality of life – but also reduce the risk of acute exacerbation (Spruit et al. *Am J Respir Crit Care Med*. 2013;188[8]:e13).

Dr. Gartman

However, the referral rate for PR is extremely low, and many patients with COPD, despite having high symptom burdens, may be unaware of its existence.

Unfortunately, this problem is worsened by PR program availability and proximity, with recent estimates suggesting that there are only 831 PR centers in the US for 24 million patients with COPD (Bhatt. *Ann Am Thorac Soc*. 2019;16[1]:55).

As a result, there is an immediate need to explore alternative strategies that enable patients to realize the benefits of PR outside of a facility-based program (Rochester, et al. *Am J Respir Crit Care Med*. 2015;192[11]:1373).

Recently, there have been many proposals for adapting PR programs to accommodate the maximum number of participants; these have included home-, telehealth- or internet-based programs, and low-impact exercise (eg, yoga or tai-chi) regimens.

While these interventions may benefit our patients with COPD, current data do not support that they are a replacement for or replicate the robust outcomes of a formal PR program. It is important that in the process of expanding the availability of "pulmonary rehab," we do not dilute the process as to limit its returns. Significant attention is being paid to developing novel program designs that utilize technology and nonfacility-based programs – and in the end, there will be a balance struck between beneficial outcomes, program personalization, and proper patient selection for a given regimen.

Eric Gartman, MD, FCCP
Steering Committee Member

Thoracic Oncology

A new era in lung cancer diagnostics: Robotic-assisted bronchoscopy

Lung cancer screening leads to increased detection of early stage lung cancer (LC). The majority of nodules detected are peripherally located.

Dr. Patel

Image-guided bronchoscopic modalities, including radial probe endobronchial ultrasound (r-EBUS) and electromagnetic navigation bronchoscopy (ENB), allow diagnosis of peripheral nodules with a low rate of complications. Although a meta-analysis of image-guided bronchoscopic procedures reported a diagnostic yield of 70% (Wang Memoli JS, et al. *Chest*. 2012;142[2]:385), the diagnostic yield remains inferior to CT-guided biopsy. Robotic-assisted bronchoscopy (RAB) with four-way steering, 180 degrees of deflection in any direction, and better access to peripheral airways may improve the diagnostic yield. Two FDA-approved platforms are commercially available. The Monarch System, (Auris Health) has a 3.2-mm outer diameter and a 1.2-mm working channel. Results from an ongoing prospective, multicenter study in 24 patients revealed successful localization of targeted lesions in 92%, with no significant adverse events (Chen, et al. *Am J Respir Crit Care Med*. 2019;199:A7304/NCT03727425; Clinical Trials. 2019. https://clinicaltrials.gov/ct2/show/NCT03727425).

The Ion Endoluminal System (Intuitive Surgical) has a 3.5-mm outer diameter and a 2.0-mm working channel. Preliminary data revealed 96.6% of target lesions were successfully reached, and no adverse events (Fielding et al. *Chest*. 2017;152[4]:A858). A prospective, multicenter randomized trial is currently ongoing (Clinical Trials. 2019. https://clinicaltrials.gov/ct2/show/NCT03893539).

The aim of bronchoscopic procedures is to safely and effectively diagnose early stage LC. RAB shows a great deal of potential in the future of LC diagnostics.

Priya Patel, MD
Fellow-in-Training Member
Adnan Majid, MD
NetWork Member

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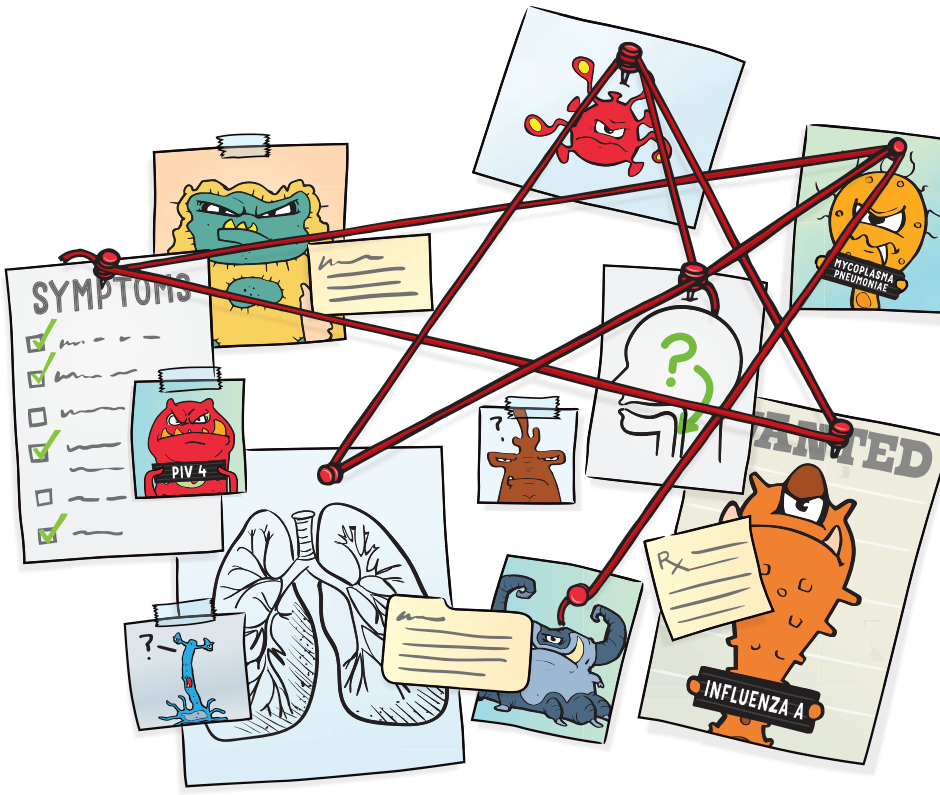

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