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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

klebercordeiro/Getty Images

Sleep insufficiency costs billions in lost productivity worldwide

BY JEFF CRAVEN
MDedge News

The United States loses 1.23 million working days and up to $411 billion per year because of insufficient sleep in workers, and the problem extends to a substantial economic toll and increased health-related costs in other countries worldwide, according to a cross-country comparative analysis.

"Our study shows that the effects from a lack of sleep are massive. Sleep deprivation not only influences an individual's health and well-being but has a significant impact on a nation's economy, with lower productivity levels and a higher mortality risk among workers," Marco Hafner, a research leader at RAND Europe and the report's main author, stated in a press release.

Mr. Hafner and his colleagues analyzed data from 62,366 employees from the Britain's Healthiest Workplace competition during 2015 and 2016 to determine factors affecting lack of sleep.

The investigators found that individuals who were overweight or obese slept an average of 2.5 minutes to 7 minutes less each day, compared with people at a healthy body mass index. Smoking was identified as a factor associated with insufficient sleep, and people who smoke slept 5 fewer minutes per day, com-

SLEEP // *continued on page 6*

Shared decision making falls short for lung cancer screening

BY BIANCA NOGRADY
MDedge News

A small study of discussions between clinicians and patients about lung cancer screening with low-dose computed tomography has highlighted a lack of shared decision making and information about potential harms.

"Our findings are consistent with increasingly robust evidence that patients, members of the public, and clinicians tend to overestimate the benefits and underestimate the harms of medical interventions, including treatments, tests, or screening tests," wrote Alison T. Brenner, PhD, and her colleagues at the University of North Carolina at Chapel Hill, in a presentation of the findings in JAMA Internal Medicine.

The researchers transcribed conversations between 14 patients – who were eligible for lung cancer screening because of their age – and their primary care or pulmonary care physicians. They found that not one physician adequately explained false positives or their consequences, such as the possibility of

SCREENING // *continued on page 7*

INSIDE HIGHLIGHT

CHEST KEYNOTE

Reflections on a lifetime practicing chest medicine

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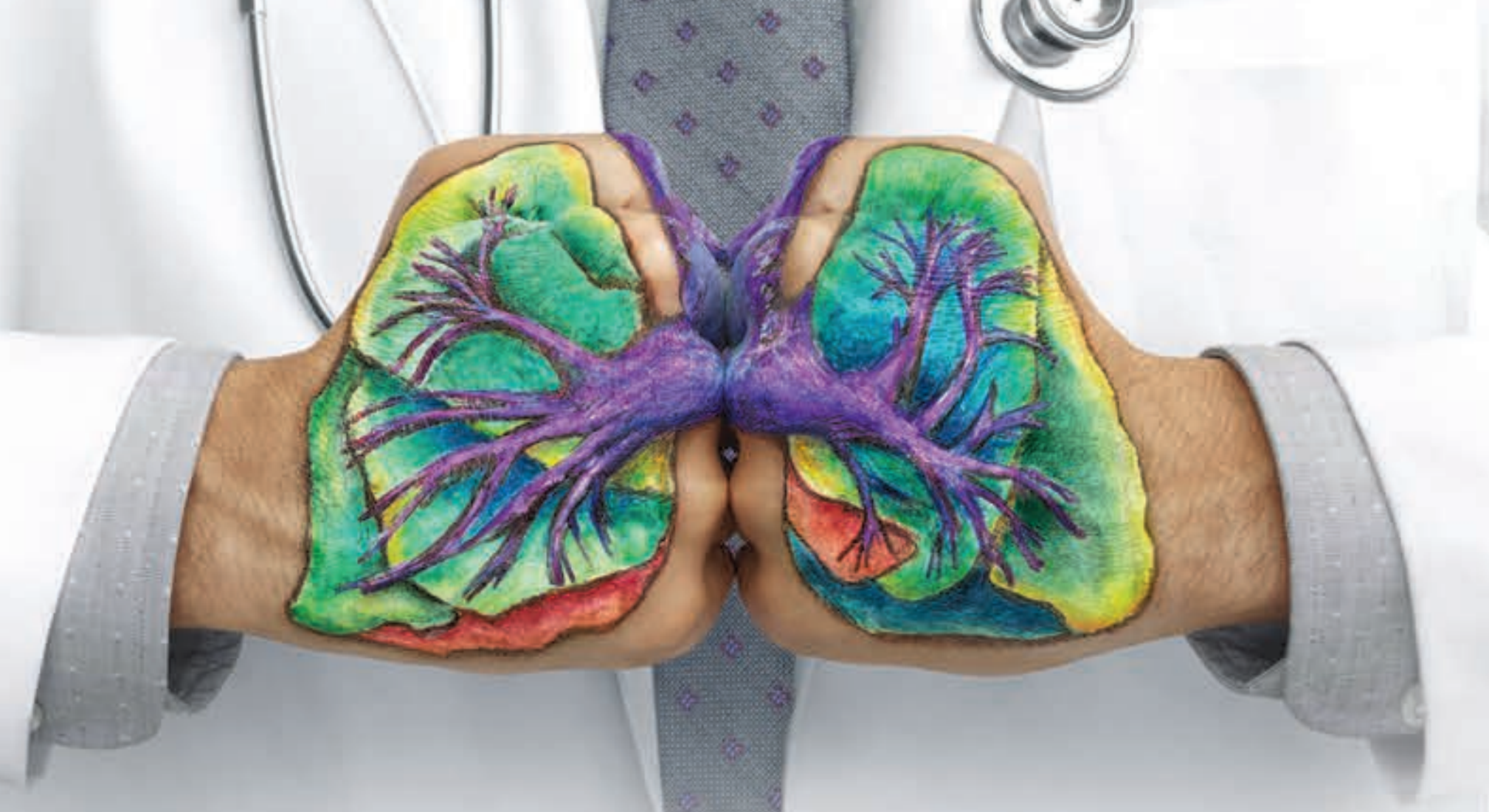

Indication

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

Select Important Safety Information

Elevated liver enzymes: Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3× ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels prior to initiating Esbriet, then monthly for the first 6 months, and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with placebo patients (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, compared with 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications 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 reductions of Esbriet are 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]

STUDIED IN A RANGE OF PATIENTS

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[‡]

WORLDWIDE PATIENT EXPERIENCE

More than 37,000 patients have taken pirfenidone worldwide[4§]

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

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

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when using 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. October 2017. **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. 2016.

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]**

†In clinical trials, serious adverse reactions, including elevated liver enzymes, 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

CMS proposes cutting required EHR documentation

BY GREGORY TWACHTMAN
MDedge News

Doctors could spend less time with their EHRs under Medicare's proposed physician fee schedule for 2019.

The sweeping proposal also would improve Medicare telemedicine opportunities and update portions of the Quality Payment Program and the Medicare Shared Savings Program, according to documents posted online July 12. There would also be more opportunities to be paid for telemedicine services under the proposed rule, released by the Centers for Medicare & Medicaid Services online and scheduled for publication July 27 in the Federal Register.

"We are streamlining the system of office E&M codes and reducing the requirements for documentation," CMS Administrator Seema Verma

said during a July 12 press conference.

The proposal would condense all four levels of E&M coding to one level, with one payment – there would no longer be higher payments provided for high levels.

While the change could reduce payments to specialists who generally bill only at the highest level for E&M visits, that difference should be made up in the additional time physicians should have to see patients, according to a fact sheet on the proposed physician fee schedule.

"We estimate that this proposal would save approximately 51 hours of clinic time per clinician per year," Ms. Verma said, or an additional 500 years of time available for patient care across the system.

The proposed schedule also would expand list of services that qualify for telemedicine payments and would add payments for virtual check-ins via phone or other communication technologies such as Skype, paying clinicians for time spent reviewing patient photos submitted via text or e-mail.

More time savings could come from proposed reductions to the documentation required qualify for bonus payments under the Merit-Based Incentive Payment System (MIPS) track of the Quality Payment Program.

CMS proposes to remove 34 process measures that are considered to be low value or low priority, Ms. Verma said, noting that most physicians are doing these measures but seeing no meaningful difference in the performance that would differentiate payment under the program.

"We estimate that this proposal would save approximately 51 hours of clinic time per clinician per year."

The proposed update continues on with the MyHealthEData initiative by supporting greater patient access to their individual health records. Ms. Verma said that the agency will "reward providers that offer interoperability and provide patients access to their health information."

While the proposal would not change most of the thresholds for participating MIPS – physicians still would be exempted if they bill Medicare $90,000 or less annually and see 200 or fewer Medicare patients – they also would be exempted if they perform 200 or fewer services under Medicare fee schedule. However, the agency is proposing for the first time to allow physicians to opt-in to the MIPS program if they are prepared to meet the program's requirements, according to a fact sheet on the proposed changes to QPP.

CMS also is proposing changes to how it pays for new drugs administered in the physician office under Medicare Part B. The proposal would reduce reimbursement for drugs that have not yet been on the market long enough to establish an average sales price from wholesale acquisition cost (WAC) plus 6% to WAC plus 3%, potentially saving money for both patients and Medicare.

The agency also asked for information related to price transparency as part of the proposal. It is looking for perspectives on whether providers and suppliers can and should be required to provide charge and payments information, for health care services and out-of-pocket costs, as well as what data elements would be most useful to consumers to promote price shopping.

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Sleep deficit is a global problem // continued from page 1

pared with nonsmokers. People who had more than two sugary drinks per day slept an average of 3.4 minutes less per day, compared with those who consumed less or no sugary drinks. The authors noted people who performed 120 minutes of physical activity or less per day and people with a medium to high risk of mental health problems slept an average of 2.6 minutes and 17.2 minutes less each day, respectively.

Regarding workplace-associated factors for insufficient sleep, the investigators found lack of choice in their work routine was associated with 2.3 minutes less sleep per day, and those who worked irregular hours slept 2.7 minutes less per day on average; people with workplace stress and unrealistic time pressures slept 8 minutes less per day on average.

Commuters slept 9.3 minutes less per day if they had a 30- to 60-minute commute to work, while those who had a commute longer than 60 minutes slept 16.5 minutes less per day.

Commuters slept 9.3 minutes less per day if they had a 30- to 60-minute commute to work, while those who had a commute longer than 60 minutes slept 16.5 minutes less per day than people with shorter commutes.

Mr. Hafner and his colleagues also found the following personal and sociodemographic factors were associated with insufficient sleep:

- People who had financial concerns slept 10 minutes less per day, compared with people who did not have financial concerns.
- Unpaid care was associated with an average of 5 minutes less sleep per day.
- People with dependent children under 18 years old in the same household slept an average of 4.2 minutes less daily.
- Men slept 9 minutes less per day, compared, with women.
- Never being married was associated with sleeping an average of 4.8 minutes less per day, while people who were separated from their partner slept an average of 6.5 minutes less per day.

"At first glance, the estimates of minutes of sleep lost due to the various factors outlined above may seem small," the investigators wrote in their report. The loss of sleep for each factor can a few minutes. "However, it is important to stress that the estimates represent the effect on sleep duration of each single factor, holding all other factors constant."

That lost sleep can significantly affect a person's health, the authors noted. Sleeping less than 6 hours per night was associated with a 13% increased risk in all-cause mortality and a person sleeping between 6 hours and 7 hours per night had a 7% increased risk of all-cause mortality, compared with people who

Continued on following page

VIEW ON THE NEWS

David A. Schulman, MD, FCCP, comments: We have long known about the adverse health effects of sleep deprivation, including an increased risk of diabetes, hypertension, and cardiovascular disease. More overtly, sleep deprivation has been clearly associated with increased accident risk, both vehicle-related and on-the-job. While disease-related sleep loss (such as that due to insomnia, sleep apnea, or restless legs syndrome) often leads affected patients to seek medical counsel and therapy, the far more common behavioral and lifestyle contributors to sleep deprivation (including extended work hours, shift work, and irregular sleep schedules) are often the result of personal choices, and, thus, far more rarely end up in our offices in search of treatment. The analysis published by Hafner and RAND Europe demonstrates the significant impact that such decisions can make when examined on the national level. Although it is unlikely that such data will inspire individuals to make better choices in terms of their sleep habits, it is quite possible that these results will lead to a call-to-action by corporations, if not the country as a whole, as any temporal or financial investment in improving the sleep of our population may well be more than paid back by the resulting benefits to productivity.

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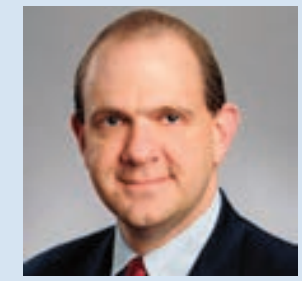

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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Little time spent on discussing screening trade-offs // *continued from page 1*

additional imaging and invasive diagnostic procedures, nor did any discuss the potential for diagnosis and treatment of cancer that would not have affected the individual during his or her lifetime (overdiagnosis).

Researchers used a 12-item scoring system for physician behaviors, with 0-4 points allocated to each item. The items included telling patients there was more than one way to deal with the identified problem, explaining the pros and cons of the available options, exploring patients' fears and concerns, and offering the patient clear opportunities to ask questions.

Mean scores for each item ranged from 0 to 0.79. Two conversations met the baseline skill criteria – a score of two points – for one item each, two other conversations met the baseline skill criteria for two items. But for 8 of the 12 items, not one conversation achieved even a baseline skill score. The mean total visit length was 13:07 minutes, and the mean time spent discussing lung cancer screening (LCS) was 0:59 minute (range, 0:16-2:19 minutes).

"Although experts disagree on how well the existing evidence suggests an overall net benefit of LCS, consensus has emerged on the importance of shared decision making," wrote the investigators. Current U.S. Preventive Services Task Force recommendations stress that lung cancer screening should not occur without a shared decision-making process, including a thorough discussion of benefits and harms.

The authors said that, while their study was small, it did raise concerns that shared decision making in practice is a long way from what is recommended by the guidelines.

"The fact that the main drivers of harms from LCS (false positives and their sequelae, as well as overdiagnosis) were not adequately explained by physicians is troubling," they wrote. "However, these findings are consistent with other evidence that discussions between patients and physicians regarding preference-sensitive cancer screening decisions are imbalanced with respect to explaining the pros and cons."

Based on these findings, the authors called for urgent discussions between clinical leaders, policy makers, and researchers about how to involve patients more meaningfully in discussions about lung cancer screening.

"Until more is known, we believe that guideline and policy makers should not assume that recommending SDM [shared decision making] for cancer-screening decisions with a 'tenuous balance of benefits and harms,' like LCS, will protect patients who would value avoiding screening harms."

The study was supported by the North Carolina Translational and Clinical Sciences Institute and the National Cancer Institute. No conflicts of interest were declared.

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SOURCE: Brenner A T et al. JAMA Intern Med. 2018; Aug 13. doi: 10.1001/jamainternmed.2018.3054.

VIEW ON THE NEWS

Lack of shared decision making 'disappointing'

The results of this first real-world study of the U.S. Preventive Services Task Force recommendations on lung cancer screening – which comes 4 years after the recommendations were made – are disappointing. Even the highest-scoring conversations made no mention of possible harms, such as a 98% false-positive rate, additional testing, and the small increased cancer risk from radiation.

Despite the small sample size, there is no reason to suspect these conversations are atypical. It may be that limited time, lack of education about shared decision making, and a lack of emphasis on the importance of discussing the potential harms and benefits of cancer screening play a role in the lack of shared decision making.

Rita F. Redberg, MD, is from the department of medicine in the division of cardiology at the University of California, San Francisco, and the editor of JAMA Internal Medicine. These comments are taken from an accompanying editorial (JAMA Int Med. 2018 Aug 13. doi: 10.1001/jamainternmed.2018.3527). Dr. Redberg chaired the April 2014 Medicare Evidence Development & Coverage Advisory Committee meeting on lung cancer screening.

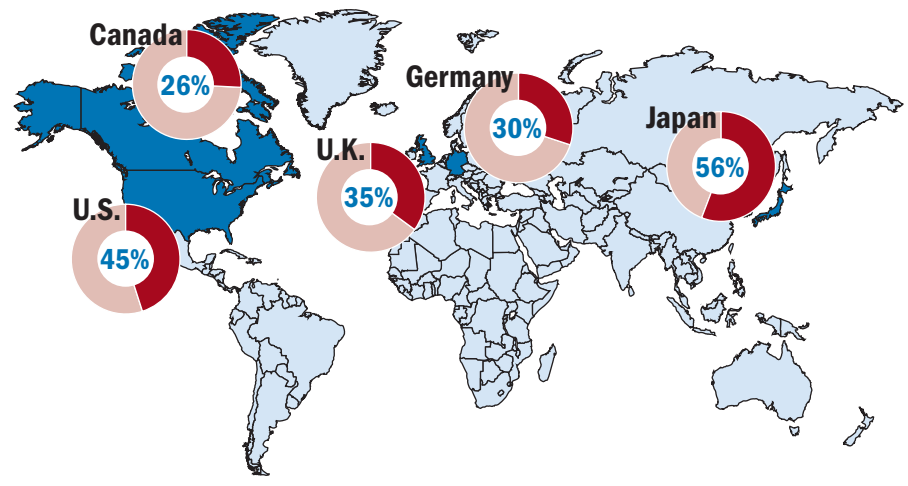
Continued from previous page

slept between 7 hours and 9 hours per night.

Insufficient sleep can also affect workplace productivity, with factors such as absenteeism and presenteeism (working while tired) affecting performance at work because of loss of sleep. There was a 1.5% higher productivity loss among people sleeping between 6 hours and 7 hours of sleep per night, compared with people who slept between 7 hours and 9 hours a night, which the authors estimated would cost an employer 6 working days per year for a person sleeping less than 6 hours per night.

In the United States, the authors reported 1.23 million working days (9.9 million working hours) are lost per year because of lack of sleep. They studied four other member countries in the Organisation for Economic Co-operation and Development and found similar results: Japan loses 0.6 million working days (4.8 million working hours) per year, the United Kingdom loses 207,224 working days (1.6 million working hours), Germany loses 209,024 working days (1.6 million working hours), and Canada loses 78,861 working days (630,886 working hours) annually because of insufficient sleep among workers. In total, the report estimates lack of sleep costs approximately $680 billion for these countries.

Percentage of adults averaging less than 7 hours of sleep



Note: Based on data for 1,501 respondents to a 2013 National Sleep Foundation survey.
Source: RAND Corporation

MDEDGE NEWS

The authors encouraged individuals, employers, and countries to adopt policies that would lessen the economic impact of insufficient sleep and improve sleep outcomes.

For individuals, recommendations included setting a consistent wake-up time, limiting electronic devices before sleep, limiting intake of substances such as caffeine, alcohol, and nicotine prior to sleep, and increasing physical activity. Employers were encouraged to recognize the benefits that getting a full night's sleep has for their employees, adopt routines that improve their employees' sleep outcomes, and limit use of electronic devices outside office hours. Public health authorities were encouraged to create awareness campaigns and activities supporting sleep-related help and implementing more efficient public schedules such as delayed school starting times.

"Improving individual sleep habits and duration has huge implications, with our research showing that simple changes can make a big difference," Mr. Hafner stated in a press release. "For example, if those who sleep under 6 hours a night increase their sleep to between 6 and 7 hours a night, this could add $226.4 billion to the U.S. economy."

The authors report no relevant conflicts of interest.

SOURCE: Hafner M et al. RAND Corporation.

Next-gen sputum PCR panel boosts CAP diagnostics

BY BRUCE JANCIN
MDedge News

NEW ORLEANS – A next-generation lower respiratory tract sputum polymerase chain reaction (PCR) film array panel identified etiologic pathogens in 100% of a group of patients hospitalized for community-acquired pneumonia, Kathryn Hendrickson, MD, reported at the annual meeting of the American College of Physicians.

The investigational new diagnostic assay, the BioFire Pneumonia Panel, is now under Food and Drug Administration review for marketing clearance. It offers great potential for targeted therapy along with reduced overuse of antibiotics in patients with community-acquired pneumonia (CAP), observed Dr. Hendrickson, an internal medicine resident at Providence Portland (Ore.) Medical Center. The new product is designed to complement the currently available respiratory panels from BioFire.

"Rapid-detection results in less empiric antibiotic use in hospitalized patients. When it's FDA approved, this investigational sputum PCR panel will simplify the diagnostic bundle while improving antibiotic stewardship," she observed.

She presented a prospective study of 63 patients with CAP hospitalized at the medical center, all of whom were evaluated by two laboratory methods: the hospital's standard bundle of diagnostic tests and the new BioFire film array panel. The purpose was to determine if there was a difference between the two tests in the detection rate of viral and/or bacterial pathogens as well as the clinical significance of any such differences; that is, was there an impact on days of treatment and length of hospital stay?

Traditional diagnostic methods detect an etiologic pathogen in at best half of hospitalized CAP patients, and the results take too much time. So Providence Portland Medical Center adopted as its standard

COURTESY CDC

diagnostic bundle a nasopharyngeal swab and a BioFire film array PCR that's currently on the market and can detect nine viruses and three bacteria, along with urine antigens for *Legionella sp*. and *Streptococcus pneumoniae*, nucleic acid amplification testing for *S. pneumoniae* and *Staphylococcus aureus*, and blood and sputum cultures. In contrast, the investigational panel probes for 17 viruses, 18 bacterial pathogens, and seven antibiotic-resistant genes; it also measures procalcitonin levels in order to distinguish between bacterial colonization and invasion.

The new BioFire Pneumonia Panel detected a mean of 1.4 species of pathogenic bacteria in 79% of patients, while the standard diagnostic bundle detected 0.7 species in 59% of patients. The investigational panel identified a mean of 1.0 species of viral pathogens in 86% of the CAP patients; the standard bundle detected a mean of 0.6 species in 56%.

All told, any CAP pathogen was detected in 100% of patients using the new panel, with a mean of 2.5 different pathogens identified. The standard bundle detected any pathogen in 84% of patients, with half as many different pathogens found, according to Dr. Hendrickson.

A peak procalcitonin level of 0.25 ng/mL or less, which was defined as bacterial colonization, was associated with a mean 7 days of treatment, while a level above that threshold was associated with 11.3 days of treatment. Patients with a peak procalcitonin of 0.25 ng/mL or less had an average hospital length of stay of 5.9 days, versus 7.8 days for those with a higher procalcitonin indicative of bacterial invasion.

The new biofilm assay reports information about the abundance of 15 of the 18 bacterial targets in the sample, the investigators didn't find this bacterial quantitation feature to be substantially useful in distinguishing bacterial colonization from invasion.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments:

The busy ICU where I work has almost daily admissions of patients with severe pneumonia. Teaching points on rounds with the residents focus on the facts that we can identify a causative organism less than half of the time; that initial, immediate, empiric broad-spectrum antibiotics are needed in patients with pneumonia and sepsis; and that tapering antibiotics to organism-specific therapy when a causative organism is identified is associated with improved outcomes. A rapid and accurate diagnostic test in our patients with pneumonia would be a welcome tool as we would be able to optimize our antibiotic regimens, implement good antibiotic stewardship, and provide better care for our patients.

Dr. Hendrickson reported no conflicts regarding the study, which was supported by BioFire Diagnostics.

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FDA approves first EpiPen and EpiPen Jr. generic

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved the first generic EpiPen and EpiPen Jr. autoinjector for the emergency treatment of allergic reactions, including anaphylaxis, for adults and children weighing more than 33 pounds, according to an announcement from the agency.

"Today's approval of the first generic version of the most widely prescribed epinephrine autoinjector in the U.S. is part of our longstanding commitment to advance access to lower cost, safe, and effective generic alternatives once patents and other exclusivities no longer prevent approval," FDA commissioner Scott Gottlieb, MD, said in the release.

Manufactured by Teva Pharmaceuticals USA, the two strengths of the generic versions are 0.3 mg and 0.15 mg.

The FDA has previously approved other epinephrine autoinjectors, which include brand-name products and so-called "authorized generic" versions of Epi-Pen and Adrenaclick.

An authorized generic "is made under the brand name's existing drug application using the same formulation, process, and manufacturing facilities that are used by the brand name manufacturer. The labeling or packaging is, however, changed to remove the brand name or other trade dress. In some cases, a company may choose to sell an authorized generic at a lower cost than the brand-name drug product," according to the FDA statement.

The FDA has previously approved other epinephrine autoinjectors, which include brand-name products and so-called "authorized generic" versions of Epi-Pen and Adrenaclick.

"Complex" generics – those that, as with this generic, include both a drug and a delivery device – face a tougher path to approval because the FDA has to evaluate and approve both components.

"We remain committed to doing our part to provide scientific and regulatory clarity for sponsors seeking to develop complex generics, as well as prioritize the approval of medicines with little or no generic competition, as part of our overarching effort to remove barriers to generic development and market entry of critically important medicines," Dr. Gottlieb explained. "This approval means patients living with severe allergies who require constant access to life-saving epinephrine should have a lower-cost option, as well as another approved product to help protect against potential drug shortages."

Side effects of epinephrine autoinjectors include anxiety, restlessness, palpitations, nausea, and weakness; rarely, serious skin and soft-tissue infections after use of epinephrine autoinjectors have been reported.

cpalmer@mdedge.com

NOW APPROVED
TO REDUCE COPD EXACERBATIONS

See the following pages for
IMPACT *TRIAL*
Infor**M**ing the **PA**thway of **C**OPD **T**reatment

For appropriate patients with COPD

LESS TO TAKE. MORE TO TAKE IN.

TRELEGY—the only once-daily triple therapy (ICS/LABA/LAMA) for COPD delivered in a single inhaler

ICS=inhaled corticosteroid; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

INDICATION

TRELEGY is for maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for reducing exacerbations in patients with a history of exacerbations. TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- TRELEGY is not for the treatment of asthma. LABA monotherapy for asthma increases the 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. 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.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Patient Information, for TRELEGY following this ad.

gsk | INNOVIVA

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

IMPACT TRIAL

INFORMING THE PATHWAY OF COPD TREATMENT

A landmark study for patients with a history of COPD exacerbations

10,000+ PATIENTS

Symptomatic patients with at least 1 COPD exacerbation in the last year while on maintenance medication[1,2*]

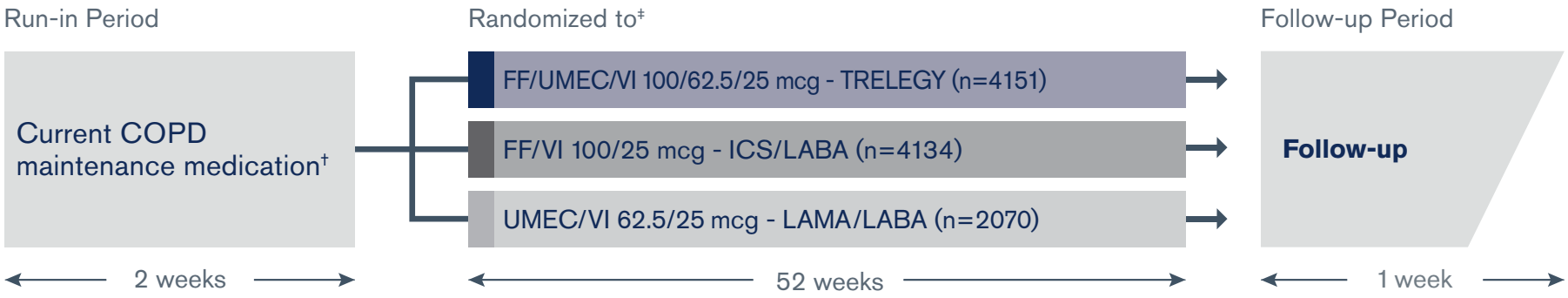
52-WEEK STUDY

A randomized, double-blind, 3-arm, parallel group; primary endpoint measured was the annual rate of moderate to severe exacerbations

1ST AND ONLY

First and only trial to study the efficacy and safety of triple therapy vs an ICS/LABA and vs a LAMA/LABA in an exacerbating COPD population

DESIGNED TO REFLECT CLINICAL PRACTICE



Exacerbation severity criteria: Moderate if treatment with systemic corticosteroids and/or antibiotics was required and severe if hospitalization was required.

*Eligible patients were symptomatic with a postbronchodilator percent predicted FEV_1 <50% and a history of 1 or more moderate or severe exacerbations within the previous year, or with a postbronchodilator percent predicted FEV_1 of 50% to 80% and a history of 2 or more moderate exacerbations or 1 severe exacerbation in the previous year. At screening, patients (mean age: 65 years) had a mean postbronchodilator percent predicted FEV_1 of 45.5% and a mean postbronchodilator FEV_1/FVC ratio: 0.47.

†Current maintenance medications included ICS + LABA + LAMA, ICS + LABA, LAMA + LABA, LAMA, and other.

‡Each delivered once daily via the ELLIPTA inhaler.

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol.

IMPORTANT SAFETY INFORMATION (cont'd)

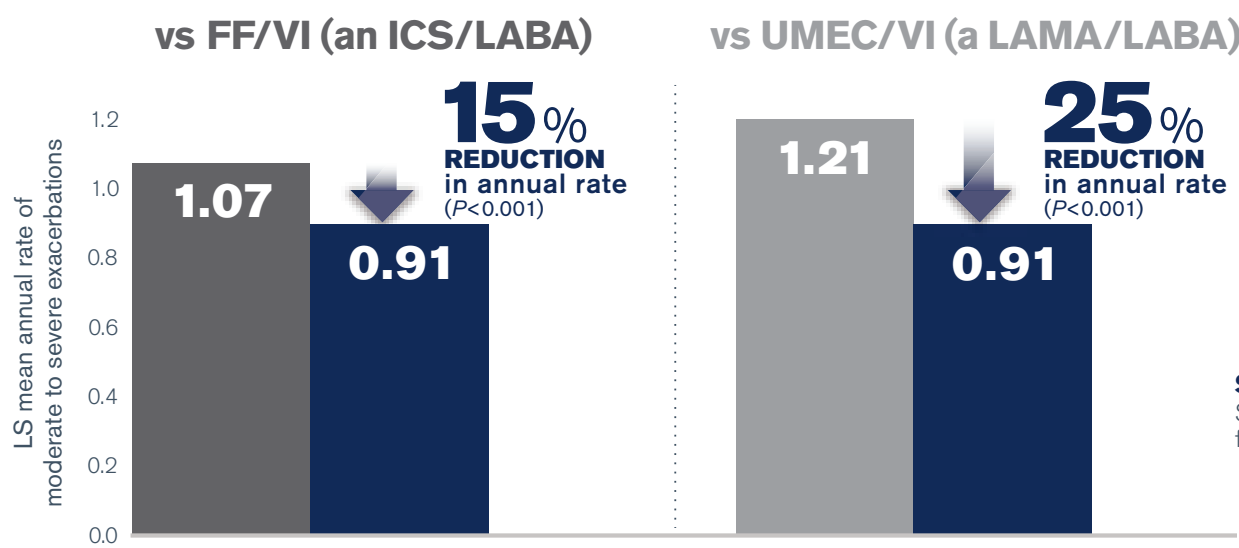
WARNINGS AND PRECAUTIONS (cont'd)

- TRELEGY 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.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA 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.
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of inhaled corticosteroids, like fluticasone furoate.

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Patient Information, for TRELEGY following this ad.

In the landmark IMPACT TRIAL, TRELEGY was proven the most effective treatment for reducing moderate to severe exacerbations vs FF/VI (an ICS/LABA) and vs UMEC/VI (a LAMA/LABA)

PRIMARY ENDPOINT: ANNUAL RATE OF MODERATE TO SEVERE EXACERBATIONS



STUDY DESCRIPTION
See previous page for description

UMEC/VI is not approved for the reduction of COPD exacerbations.

LS=least squares.

Prescribe TRELEGY—the only once-daily triple therapy (ICS/LABA/LAMA) for COPD delivered in a single inhaler

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.

Learn more about the *IMPACT TRIAL* at TrelegyMD.com

TRELEGY ELLIPTA
(fluticasone furoate, umeclidinium, and vilanterol inhalation powder)

For appropriate patients on COPD maintenance medication who need improvement in lung function or reduction in exacerbations

Prescribe TRELEGY

ONE INHALER | ONCE DAILY | ONE CO-PAY*

***One co-pay is not a guarantee of coverage or lower out-of-pocket costs for patients than alternative treatments. Formulary status and patient out-of-pocket costs may vary, may be up to the prescription's retail cost, and are subject to change.**

TRELEGY does not replace a rescue inhaler.

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, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of inhaled corticosteroids or inhaled anticholinergics; therefore, monitoring is warranted.
- 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.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo + FF/VI) reported in two 12-week clinical trials with umeclidinium + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).
- Additional adverse reactions (≥1% incidence) reported in subjects taking TRELEGY in a 52-week trial included upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

DRUG INTERACTIONS

- TRELEGY 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 TRELEGY with other anticholinergic-containing drugs, as this may lead to an increase in anticholinergic adverse effects.

USE IN SPECIFIC POPULATIONS

- Use TRELEGY with caution in patients with moderate or severe hepatic impairment, as fluticasone furoate systemic exposure may increase by up to 3-fold. Monitor for corticosteroid-related side effects.

Please see additional Important Safety Information for TRELEGY on the previous pages.
Please see Brief Summary of Prescribing Information, including Patient Information, following this ad.

References: 1. Data on file, GSK. **2.** Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple vs dual therapy in patients with COPD [published online April 18, 2018.]. *N Engl J Med*. doi:10.1056/NEJMoa1713901.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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TRELEGY ELLIPTA
(fluticasone furoate, umeclidinium, and vilanterol inhalation powder)

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation

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

1 INDICATIONS AND USAGE

TRELEGY is indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. TRELEGY ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use

TRELEGY is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of TRELEGY is contraindicated in the following conditions: severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

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

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When 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.

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

5.2 Deterioration of Disease and Acute Episodes

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

TRELEGY should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. TRELEGY 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 TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 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.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If TRELEGY 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 re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of TRELEGY beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of TRELEGY and Use With Other Long-acting Beta$_2$-agonists

TRELEGY 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 TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with TRELEGY. When such an infection develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while treatment with TRELEGY continues, but at times therapy with TRELEGY may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

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

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was <1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.

In a 52-week trial of subjects with COPD (N=10,355), the incidence of pneumonia was 8% for TRELEGY ELLIPTA (n=4,151), 7% for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 5% for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Fatal pneumonia occurred in 12 of 4,151 patients (0.35 per 100 patient-years) receiving TRELEGY ELLIPTA, 5 of 4,134 patients (0.17 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (0.29 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (<0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression

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

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

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

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

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

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses

Continued on next page

of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

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

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

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY 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 TRELEGY *[see Contraindications (4)]*.

5.12 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, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY 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 *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

TRELEGY, like other sympathomimetic amines, 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 (MI), non-fatal acute MI, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for TRELEGY ELLIPTA (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 umeclidinium/vilanterol 62.5 mcg/25 mcg (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 TRELEGY ELLIPTA, 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 umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 86 subjects receiving placebo, 80 subjects receiving fluticasone furoate 100 mcg, and 90 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

5.13 Reduction in Bone Mineral Density

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

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY 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 (eg, 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. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and/or cataracts.

5.15 Worsening of Urinary Retention

TRELEGY, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (eg, 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.

5.16 Coexisting Conditions

TRELEGY, 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.

5.17 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 medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

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

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

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 safety of TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol and a 52-week long-term trial of TRELEGY ELLIPTA compared with the fixed-dose combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol *[see Clinical Studies (14)]*.

Trials 1 and 2

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based on the two 12-week trials.

Continued on next page

Table 1. Adverse Reactions With Umeclidinium + Fluticasone Furoate/Vilanterol With ≥1% Incidence and More Common Than Placebo + Fluticasone Furoate/Vilanterol (Trials 1 and 2)

Adverse Reaction	Umeclidinium + Fluticasone Furoate/ Vilanterol (n=412) %	Placebo + Fluticasone Furoate/ Vilanterol (n=412) %
Nervous system disorders		
Headache	4	3
Dysgeusia	2	<1
Musculoskeletal and connective tissue disorders		
Back pain	4	2
Respiratory, thoracic, and mediastinal disorders		
Cough	1	<1
Oropharyngeal pain	1	0
Gastrointestinal disorders		
Diarrhea	2	<1
Infections and infestations		
Gastroenteritis	1	0

Trial 3 - Long-term Safety Data

A 52-week trial (Trial 3) evaluated the long-term safety of TRELEGY ELLIPTA compared with the fixed-dose combinations of fluticasone furoate/vilanterol 100 mcg/25 mcg and umeclidinium/vilanterol 62.5 mcg/25 mcg. A total of 10,355 subjects with COPD with a history of moderate or severe exacerbations within the prior 12 months were randomized (2:2:1) to receive TRELEGY ELLIPTA, fluticasone furoate/vilanterol, or umeclidinium/vilanterol administered once daily in a double-blind clinical trial (mean age: 65 years, 77% white, 66% male across all treatments) *[see Clinical Studies (14)]*.

The incidence of adverse reactions in the long-term trial were consistent with those in Trials 1 and 2. However, in addition to the adverse reactions shown in Table 1, adverse reactions occurring in ≥1% of the subjects treated with TRELEGY ELLIPTA (n=4,151) for up to 52 weeks also included upper respiratory tract infection, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, oral candidiasis *[see Warnings and Precautions (5.4)]*, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), 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, 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, 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 beta-agonists with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY or its individual components, fluticasone furoate, umeclidinium, and vilanterol, in pregnant women to inform a drug-associated risk.

Clinical Considerations

Labor and Delivery: TRELEGY should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol, or from the underlying maternal condition.

8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. In Trial 3, 2,265 subjects aged 65 years and older, of which 565 subjects were aged 75 years and older, were administered TRELEGY ELLIPTA. 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

TRELEGY has not been studied in subjects with hepatic impairment. Information on the individual components is provided below.

Fluticasone Furoate/Vilanterol

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

Umeclidinium

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]*.

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

TRELEGY contains fluticasone furoate, umeclidinium, and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to TRELEGY. Treatment of overdosage consists of discontinuation of TRELEGY 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 Fluticasone Furoate

Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 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 1000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.3 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 (eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use *of full prescribing information*).

Not for Acute Symptoms

Inform patients that TRELEGY 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,

Continued on next page

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation *(cont'd)*

short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication 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 TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other LABA.

Local Effects

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (ie, oral) antifungal therapy while still continuing therapy with TRELEGY, but at times therapy with TRELEGY may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that TRELEGY may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRELEGY.

Paradoxical Bronchospasm

As with other inhaled medicines, TRELEGY can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue TRELEGY and contact their healthcare provider right away.

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY 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 TRELEGY.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects

Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (eg, 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 develop.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develop.

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.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

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TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

Dupilumab succeeds in reducing asthma exacerbations

BY MICHELE G. SULLIVAN
MDedge News

Among patients with moderate to severe asthma, dupilumab reduced exacerbations by almost 50%, while also allowing glucocorticoid-treated patients to cut their use of that medication by 70%, with no increased risk of exacerbation.

The pair of placebo-controlled studies – Liberty Asthma Quest and Liberty Asthma Venture – also showed treatment-associated stability in forced expiratory volume in 1 second (FEV_1) evidence of lung remodeling among those who took the antibody, Mario Castro, MD, of Washington University, St. Louis, and his colleagues reported in the New England Journal of Medicine.

By week 12, FEV_1 it had already increased by 0.32 L, they said. "An analysis of the postbronchodilator FEV_1 slope showed a loss of lung function in patients who received placebo and no loss in those who received dupilumab, findings that suggest a potential effect of dupilumab on airway remodeling," wrote Dr. Castro and his colleagues. "The slope analysis showed that patients who received placebo lost, on average, approximately 40 mL annually, which is consistent with data from other cohorts of patients with asthma."

Dupilumab is an anti–interleukin-4 alpha antibody that blocks both IL-4 and IL-13. The Quest trial examined efficacy and safety of two doses (200 mg and 300 mg every 2 weeks), compared with placebo in patients with uncontrolled asthma. Venture examined efficacy and safety of 300 mg or placebo as add-on therapy for patients with severe asthma who were taking glucocorticoids.

Liberty Asthma Quest

This 52-week study randomized 1,902 patients with severe, uncontrolled asthma to placebo or dupilumab 200 mg or 300 mg every other week. The primary endpoints were annual rate of severe asthma exacerbations and the change in FEV_1 by week 12. The study also looked at these endpoints in patients whose baseline eosinophil count was greater than 300 per mm^3.

Patients were a mean of 48 years old with a mean baseline FEV_1 of about 1.75 L (about 58% of the predicted normal value). They had a mean of two exacerbations per year and an average eosinophil count of about 350 per mm^3.

Both doses outperformed placebo in all endpoints. Among those taking 200 mg, the annual relapse rate was 0.46 versus 0.87 among those taking placebo – a significant 47.7% risk reduction. Among those taking 300 mg, the exacerbation rate was 0.52 versus 0.97; this translated to a significant 46% risk reduction.

The response rate was even greater among those with an eosinophil count greater than 300 per cubic millimeter: 0.37 for 200 mg and 0.40 for 300 mg versus the placebo rates of 1.08 and 1.24. This translated to risk reductions of 65.8% and 67.4%, respectively.

By week 12, FEV_1 had significantly increased by 0.32 L in the 200-mg group and by 0.34 L in the 300-mg group, compared with nonsignificant increases among those taking placebo.

Patients with the high eosinophil counts experienced the greatest benefits, with FEV_1 increasing by a mean of 0.43 L at 12 weeks in the 200-mg group and by 0.47 L in the 300-mg group, significantly better than either placebo comparator.

Liberty Asthma Venture

In this study, the effect of dupilumab on glucocorticoid use among 210 patients with severe asthma was examined. Patients were randomized to add-on dupilumab 300 mg every 2 weeks for 24 weeks. Glucocorticoids were tapered downward from weeks 4 to 20. The primary endpoints were percent reduction in glucocorticoid dose at week 24, and the percentage of patients who experienced a reduction of at least 50% in glucocorticoid dose.

Oral glucocorticoid use decreased by a mean of 70.1% in the active group, compared with 41.9% in the placebo group, a statistically significant difference, Klaus F. Rabe, MD, of Christian Albrechts University, Kiel, Germany, and his coauthors wrote in the New England Journal of Medicine. The median change was even better: a 100% reduction in the active group and 50% reduction in the placebo group.

By week 24, 80% of those taking dupilumab had decreased their glucocorticoid intake by at least 50%, compared with 50% of the placebo group reaching this goal. The glucocorticoid dose was less than 5 mg/day in 69% of the dupilumab group, compared with 33% of the placebo group.

Like Quest, Venture showed a treatment advantage among patients with high baseline eosinophil count. "The magnitude of the effect was largest in patients with a higher eosinophil count at baseline," the investigators wrote. "… The odds ratios [a 50% glucocorticoid reduction] for dupilumab versus placebo were 6.59 among patients with 300 or more cells per cubic millimeter at baseline and 2.91 among those with less than 300 cells per cubic millimeter at baseline."

In a fully adjusted model at week 24, 48% of the patients in the dupilumab group were able to stop oral glucocorticoids entirely, compared with 25% of the placebo group.

Dupilumab was also associated with a significant 59% reduction in severe annual asthma exacerbations. FEV_1 among the active group was 0.22 L better than that in the placebo group at week 24.

Both trials were funded by Sanofi and Regeneron. Dr. Castro has received grant support from Sanofi. Dr. Rabe has received consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, and Teva Pharmaceutical Industries.

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SOURCES: Castro M et al. N Engl J Med. 2018;378:2486-96; Rabe KF et al. N Engl J Med. 2018;378:2475-85.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Patients with asthma have benefited over the last several decades from the emphasis placed on daily therapy with anti-inflammatory agents and long-acting bronchodilators. In particular, the use of inhaled corticosteroids on a daily basis has led to dramatic improvements in exacerbation rates, symptom relief, and quality of life. However, there are still many patients who remain inadequately controlled despite optimal regimens, and who continue to be at risk for adverse outcomes. The future is bright, as novel treatments are on the horizon, which may change the nature of our practice in regards to asthma patients. Although it is still too early to be certain, dupilumab may be one of the treatments that represents a true breakthrough in asthma therapy.

Ivacaftor approved for patients aged 1-2 years

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved Kalydeco (ivacaftor) for the treatment of patients aged 12 to less than 24 months who have cystic fibrosis that is caused by any of 10 mutations in the CFTR gene and is responsive to the drug, the drug's developer announced.

The drug was approved for patients aged 6 years and older in 2012 and in patients aged 2-5 years in 2015 and is the only approved drug that treats the underlying cause of cystic fibrosis rather than its symptoms.

The approval is based on the ongoing phase 3, open-label ARRIVAL trial (NCT02725567), which is assessing the drug's safety in children aged 12 months to less than 24 months. The trial's investigators have found that its safety profile in this age group is consistent with that seen in older children and adults. Most adverse events were mild to moderate; the most common (occurring in more than 30% of patients) were cough, pyrexia, elevated aspartate aminotransferase, elevated alanine aminotransferase, and runny nose. The trial found that, after 24 weeks of treatment, the mean sweat chloride levels decreased from 104.1 mmol/L (n = 14) to 33.8 mmol/L (n = 14).

Ivacaftor is contraindicated in patients taking certain antibiotics, seizure medications, or other medications; risk of drug interaction – affecting either the performance of ivacaftor or that of the other medication – is also a concern. Patients should inform their doctors if they are pregnant, planning to become pregnant, or breastfeeding; have liver or kidney problems; or drink grapefruit juice or eat grapefruit or Seville oranges. There also is a risk of high liver enzymes or cataracts. Ivacaftor is available in 150-mg tablets for adults and pediatric patients aged 6 years and older and in 50-mg and 75-mg granules for younger patients. Full prescribing information can be found on the FDA website.

Ivacaftor was approved for patients aged 6 years and older in 2012 and in patients aged 2-5 years in 2015 and is the only approved drug that treats the underlying cause of cystic fibrosis rather than its symptoms.

Lumacaftor/ivacaftor indication for younger children

The FDA has expanded the indication for Orkambi (lumacaftor/ivacaftor) to include patients who are aged as young as 2 years with cystic fibrosis (CF), according to its manufacturer, Vertex Pharmaceuticals. Specifically, the drug is meant to treat the most common underlying cause of CF – having two copies of the F508del-CFTR mutation – and is the first drug to treat it.

The approval is based on a phase 3, two-part, open-label, multicenter study that assessed various doses in patents aged 2-5 years. The study demonstrated safety and tolerability in that age group equivalent to that seen in older patients. The drug is expected to be available for this age group within 2-4 weeks of this approval.

Available as oral granules in two doses for weight-based dosing (either lumacaftor 100 mg/ivacaftor 125 mg or lumacaftor 150 mg/ivacaftor 188 mg), the compound targets the defective chloride channels responsible for CF; the two halves work together to increase the number of chloride channels on cell surfaces and also improve their function.

Orkambi should be prescribed only for patients with CF who have the dual F508del-CFTR mutation; it is not indicated for other types of CF. Patients should not take this drug if they are taking drugs such as rifampin, phenytoin, triazolam, or cyclosporine because of possible drug interactions. It can also lead to worsening liver function and elevated blood liver enzymes, increased blood pressure, or cataracts. The most common side effects include breathing problems, nausea, fatigue, and rash.

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Theophylline not effective for COPD exacerbations

BY DOUG BRUNK
MDedge News

SAN DIEGO – For people with chronic obstructive pulmonary disease at high risk of exacerbation, the addition of low-dose theophylline to inhaled corticosteroids conferred no overall clinical benefit, results from a large trial funded by the UK found.

"Globally, theophylline was used for decades as a bronchodilator," one of the study authors, David B. Price, MB BChir, said at an international conference of the American Thoracic Society. "The problem is theophylline has a narrow therapeutic index, it requires some blood monitoring, and

Doug Brunk/MDedge News

Dr. David B. Price said, "If it worked, it would be wonderful; it would save the National Health Service a fortune."

it has been replaced by more effective inhaled bronchodilators. However, there has been a lot of discussion about whether low-dose theophylline has anti-inflammatory effects on its own and whether it increases sensitivity to inhaled steroids in COPD."

According to the 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, there is "limited and contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates," and its clinical relevance has "not yet been fully established." Dr. Price, a professor of primary care respiratory medicine at the University of Aberdeen (Scotland), and his associates hypothesized that the addition of low-dose theophylline to inhaled steroid therapy in COPD would reduce the risk of moderate to severe COPD exacerbations after 1 year of treatment. "If it worked, it would be wonderful; it would save the National Health Service a fortune," he said.

In a government-funded trial known as Theophylline With Inhaled Corticosteroids (TWICS), people aged 40 years and older with COPD on a drug regimen including inhaled corticosteroids with a history of at least two exacerbations treated with antibiotics and/or oral corticosteroids in the previous year were recruited in 121 U.K. primary and secondary care sites from January 2014 through August 2016. They were randomized to receive low-dose theophylline or placebo for 1 year. Theophylline dose (200 mg once/twice a day) was determined by ideal body weight and smoking status. Primary outcome was the number of participant-reported exacerbations in the 1-year treatment period treated with antibiotics and/

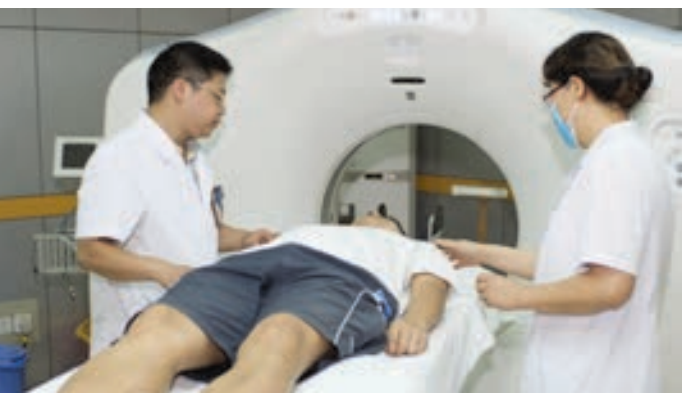
Continued on following page

More CT surveillance failed to increase NSCLC survival

BY MICHELE G. SULLIVAN
MDedge News

More frequent imaging didn't improve 5-year survival in patients with resected non–small cell lung carcinoma, even after researchers controlled for tumor histology and recurrence.

Compared with those followed every 3 months, the hazard ratio for 6-month follow-up with CT scanning was 1.16, and 1.06 for annual follow-up – a nonsignificant difference. Nor did more frequent imaging improve survival among the subgroup of patients who were cancer free 9 months after their surgery or among those who had recurrences, Timothy L. McMurry, PhD, and his colleagues reported in the Annals of Surgery. The paper was presented at the annual meeting of the American Surgical Association.



WINDCATCHER/THINKSTOCK

The results probably reflect the very poor survival rates of any patients who develop recurrent non–small cell lung cancer (NSCLC), wrote Dr. McMurry, a biostatistician at the University of Virginia, Charlottesville, and his coauthors.

"Surveillance recommendations need to be considered in the context of potential harms and benefits to patients and their caregivers," they said. "Follow-up imaging and office visits increase cost and can lead to patient anxiety. Although it seems intuitive that earlier detection of asymptomatic recurrence could improve outcomes, patients with recurrent NSCLC do very poorly … poor survival after recurrence helps explain why more intense surveillance after surgical resection was not associated with improvement in overall survival."

However, they noted, treatment advances for recurrent and metastatic disease may already be changing the outlook for these patients, "systemic therapy and targeted agents are demonstrating clinically significant survival benefits for small patient subgroups, which, in the future, may augment the benefits of early recurrence detection."

The team undertook this retrospective study – the largest of its kind in NSCLC patients – in light of current follow-up recommendations that are based almost solely on expert consensus, with low-level data.

"Because there is a paucity of high-quality data on NSCLC surveillance, practice guidelines are based on small retrospective analyses and expert opinion. This results in wide variation in practice including both underuse and overuse of surveillance services."

The study plumbed the National Cancer Database, extracting information on patients who underwent surgery for NSCLC stages I-III during 2006-2007. All had complete resection and negative margins. Patients were followed through 2012, or until they had a recurrence, a new primary cancer, or they died.

The cohort comprised 4,463 who were followed with CT imaging: 1,614 every 3 months, 1,999 every 6 months, and 850 annually. These intervals correspond to the three different major recommendations. The most common procedure was a lobectomy (about 80%). Patients with higher-stage cancers were significantly more likely to receive more frequent imaging. The regression model controlled for age, sex, comorbidities, tumor stage, and surgical procedure.

After 14 months, 3,552 patients (79.5%) were alive and cancer free. However, during the rest of the follow-up period, 11% developed a new primary cancer and 24% a recurrence of their lung cancer, with no between-group differences. The regression analysis showed no significant difference in recurrence related to surveillance interval, whether 6 months was compared with 3 months (hazard ratio, 1.16) or 1 year with 3 months (HR, 1.06).

Results were much the same for the subgroup of 3,165 who were alive and cancer free 9 months after surgery. In this group, 11% developed a new primary cancer and 29% a recurrence of their lung cancer, with similar numbers in each of the surveillance groups (HR, 1.12 for 6 months vs. 3 months).

Finally, a model including only those who had recurrence, new cancers, or were lost to follow-up within 14 months of surgery also showed no benefit for more frequent surveillance.

"More recent prerecurrence imaging was not associated with postrecurrence survival (HR, 1.02 per month since imaging), and patients who had gone more than 14 months without imaging were at no greater risk of death (HR, 1.01)," the investigators wrote. However, the data show that "at least annual CT surveillance is appropriate but that there is no benefit to more than biannual surveillance."

The authors reported no financial conflicts.

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SOURCE: McMurry TL et al. Ann Surg. 2018 Jul 12. doi: 10.1097/SLA.0000000000002955.

Continued from previous page

or oral corticosteroids. Participants were assessed six and 12 months after randomization. The study was powered to detect a 15% reduction in exacerbations and aimed to recruit 1,424 participants.

In all, 1,578 people were randomized: 791 to theophylline and 787 to placebo. Of these, primary outcome data were available for 98% of participants: 772 in the theophylline group and 764 in the placebo group, which amounted to 1,489 person-years of follow-up data. The mean age of patients was 68 years, 54% were male, 32% currently smoked, 80% were using inhaled corticosteroids/long-acting beta$_2$-agonists/long-acting muscarinic agents, and their mean FEV$_1$ was 51.7% predicted.

Slightly more than one-quarter of study participants (26%) ceased study medication. Dr. Price said that this was balanced between the theophylline and placebo groups and mitigated by over-recruitment and a high rate of follow-up.

He reported that there were 3,430 moderate to severe exacerbations: 1,727 in the theophylline group and 1,703 in the placebo group. The mean number of exacerbations in participants allocated to theophylline and placebo groups were essentially the same: 2.24 vs. 2.23. However, there were a fewer number of exacerbations that required hospitalization in the theophylline group, compared with the placebo groups (0.17 vs. 0.24, for an adjusted rate ratio of 0.72). Dr. Price was quick to point out that this finding applied to a relatively small number of study participants, about 3% overall.

"How you interpret this, I don't know," he said. "Our conclusion is that in the broad population there is no benefit [of low-dose theophylline], but maybe someone might want to study its use in frequent exacerbation patients who are getting hospitalized."

The study was funded by the National Institute for Health Research, United Kingdom. Dr. Price reported having no financial disclosures.

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SOURCE: Price, DB et al. Abstract 7709, ATS 2018.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: When I was a first-year resident in the mid-1980s, I developed an interest in pulmonary and critical care medicine. One couldn't be interested in this field at that time without knowing about theophylline. All of my outpatients with COPD were taking theophylline. I was taught that it had multiple benefits related to bronchodilation, augmented respiratory drive, and improved exercise tolerance. Theophylline had a critical care connection as well. I often cared for ICU patients admitted with theophylline toxicity. I learned about the practical aspects of a "narrow therapeutic window." Over the years, I came to believe that the data available didn't support the teachings that promoted theophylline's effectiveness, and I became wary of the drug's side effects. I haven't prescribed theophylline in many years. Recently, while working on a CHEST guideline concerning prevention of COPD exacerbations, I had a chance to review some data suggesting that theophylline might be of benefit in preventing these events. I wondered if there might be a role for this drug after all. But the current study from United Kingdom seems to indicate that theophylline at a low dose (to avoid adverse effects) is not effective in preventing COPD exacerbations in at-risk patients.

Nicotine preloading linked to reduced varenicline usage

BY LUCAS FRANKI
MDedge News

Nicotine preloading with patches 4 weeks before making a quit attempt was not significantly associated with smoking abstinence, mainly because of a decline in varenicline use, according to Paul Aveyard, PhD, and his associates at Nuffield Department of Primary Care Health Sciences, University of Oxford (England).

The primary study outcome, biochemically validated abstinence at 6 months, was achieved by 17.5% of the 899 people who preloaded with a 21-mg/24-hr nicotine patch for 4 weeks and by 14.4% of the 893 in the control group. After 1 year, 14.0% of people in the preloading group maintained long-term abstinence, compared with 11.3% in the control group. In addition, 35.5% of the preloading group and 32.3% of the control group achieved abstinence 4 weeks from baseline.

"Nicotine preloading with a 21-mg/24-hr nicotine patch for 4 weeks seems to be efficacious, safe, and well tolerated, but probably deters the use of varenicline, the most effective smoking cessation drug."

M1LOSLUZ/ISTOCKPHOTO

The unadjusted odds ratio for the effect of preloading at 6 months was 1.25 (95% confidence interval, 0.97-1.62; $P = .08$) and not statistically significant. However, when reduced varenicline usage in the preloading group was taken into account, the effect of preloading did reach statistical significance (OR, 1.34; 95% CI, 1.03-1.73; $P = .03$). Similar results were found at 1 year and at 4 weeks, where the preloading effect did not reach significance until adjusted for varenicline usage.

"Nicotine preloading with a 21-mg/24-hr nicotine patch for 4 weeks seems to be efficacious, safe, and well tolerated, but probably deters the use of varenicline, the most effective smoking cessation drug. If it were possible to overcome this unintended consequence, preloading could lead to a worthwhile increase in long-term smoking abstinence," the investigators concluded.

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SOURCE: Aveyard P et al. BMJ. 2018 Jun 13. doi: 10.1136/bmj.k2164.

Better adherence, shorter course with rifampin for TB

BY ANDREW D. BOWSER
MDedge News

Four months of rifampin is effective in prevention of active tuberculosis, with significantly higher adherence rates versus 9 months of isoniazid in adults and children, a pair of recent studies suggest.

In one randomized, open-label trial that included adults with latent *Mycobacterium tuberculosis* infection, the 4-month rifampin regimen was not inferior to the 9-month isoniazid regimen in preventing active tuberculosis, had better safety, and had a rate of treatment completion 15.1 percentage points higher than the comparator.

"This trial adds to the mounting evidence of benefits of rifamycin -containing regimens of 3 or 4 months' duration," investigators reported in the New England Journal of Medicine.

Isoniazid treatment has been associated with low rates of regimen completion because of the hepatotoxic effects, according to authors of the current studies comparing isoniazid to rifampin.

Similarly, in an open-label study in children with latent *M. tuberculosis* infection, the shorter rifampin regimen had comparable efficacy and safety, according to investigators, along with a rate of treatment completion 13.4 percentage points higher than the longer isoniazid regimen.

"Rifampin has the advantage of being a single-drug regimen with existing palatable formulations for children," reported authors of this companion study, also published in the journal.

Treatment challenges

Treating latent tuberculosis infection is central to the World Health Organization End TB Strategy and other tuberculosis elimination plans. An estimated 1.7 billion individuals, or about one-quarter of the global population, harbor latent tuberculosis infection, according to one recent estimate.

The WHO recommends treatment of latent tuberculosis infection, as well as for children under 5 years of age who are household contacts of individuals with tuberculosis. The recommended treatment is 6 or 9 months of isoniazid, with the longer duration being associated with better efficacy, previous studies have shown.

However, isoniazid treatment has been associated with low rates of regimen completion because of the hepatotoxic effects, according to authors of the current studies comparing isoniazid to rifampin.

The 4-month daily rifampin regimen has been associated with superior treatment adherence rates

and fewer hepatotoxic effects, compared with the 9-month isoniazid regimen in previous observational studies. Moreover, an earlier randomized trial including 679 men in Hong Kong demonstrated that 3 months of rifampin was superior to placebo and comparable to 6 months of isoniazid as tuberculosis prophylaxis.

Rifampin: Latest data

The adult trial just published in the New England Journal of Medicine demonstrates the efficacy and real-world effectiveness of the 4-month rifampin regimen versus the 9-month isoniazid regimen for prevention of active tuberculosis, according to lead

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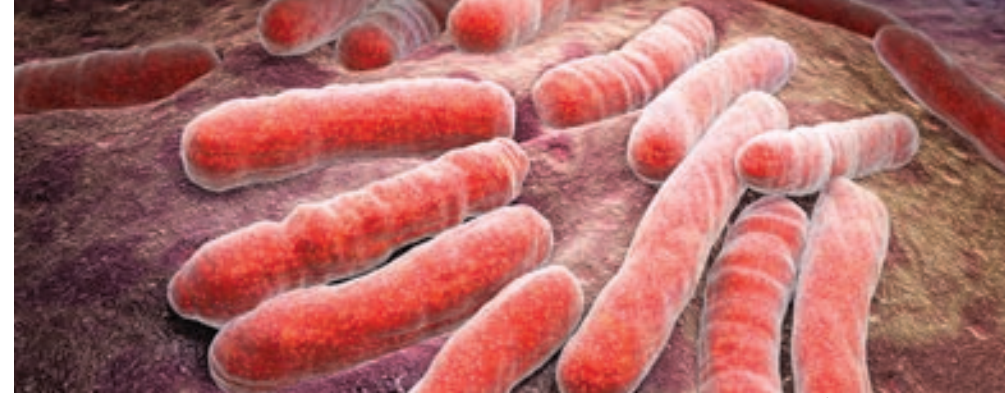

ILEXX/THINKSTOCK

Continued from previous page

author Dick Menzies, MD, of the Montreal Chest Institute at McGill University Health Centre.

The 4-month rifampin regimen is a "fundamental game-changer in TB prevention" based on its comparable efficacy is adults, along with improved safety and acceptability, Dr. Menzies said in a recent press release.

Dr. Menzies and his colleagues reported on 6,063 adults (aged 18 years or older) randomized to the 4-month rifampin or 9-month isoniazid regimen at trial sites in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea.

Treatment was completed by 78.8% of individuals in the rifampin arm, compared with 63.2% of patients in the isoniazid arm, for a difference of 15.1 percentage points (95% confidence interval, 12.7-17.4; *P* less than .001), the researchers reported.

Rifampin was not inferior to isoniazid in preventing tuberculosis, according to the report. In the per-protocol analysis, there were a total of five confirmed or clinically diagnosed cases of active tuberculosis in each of the trial arms. All active cases were treated successfully, including two cases that had demonstrated drug resistance, investigators added.

The rifampin group had consistently lower rates of grade 3–grade 5 adverse events, particularly hepa-

totoxic events, versus the isoniazid group, according to analyses outlined in the report.

"We believe this 4-month rifampin treatment should replace the 9 months on isoniazid for most people who need therapy for latent tuberculosis," said Dr. Menzies, a respirologist with the Montreal Chest Institute and a professor of medicine, epidemiology and biostatistics at McGill University, also in Montreal.

Experience in children

In the related study, reported by lead author Thierno Diallo, MD, of Hôpital National Ignace Deen, in Conakry, Guinea, along with Dr. Menzies, and their coauthors, 829 children were randomized to 4 months of rifampin or 9 months of isoniazid.

The study population included 79 children under 2 years, the age group that has the highest risk of life-threatening TB, Dr. Diallo and his colleagues wrote in their report.

Treatment was completed in 86.5% of all children randomized to rifampin, compared with 77.1% in the isoniazid arm (difference of 13.6 percentage points; 95% confidence interval, 7.9-19.3; *P* less than .001), according to the investigators.

Two active tuberculosis cases were diagnosed in the isoniazid group over 542 person-years of follow-up, versus no cases in the rifampin group over a similar follow-up period.

"Although the only cases of active tuberculosis were diagnosed in the isoniazid group, we cannot conclude that 4 months of rifampin was either superior or noninferior to 9 months of isoniazid for the prevention of active tuberculosis," the authors wrote.

"We believe this 4-month rifampin treatment should replace the 9 months on isoniazid for most people who need therapy for latent tuberculosis."

"However, since there were no cases of active tuberculosis in the rifampin group in our trial or among 434 children who received 3 months of once-weekly isoniazid plus rifapentine in another trial, we suggest that these shorter rifamycin containing regimens are effective," they added.

In contrast to the adult trial, safety profiles in this study were similar for rifampin and isoniazid, investigators said.

The lack of difference is side effects was possibly because of the differences in the pharmacokinetic activity of rifampin in younger patients, a topic that deserves further study, they concluded.

No potential conflicts of interest relevant to the studies were reported by Dr. Menzies, Dr. Diallo, or their coauthors.

Both studies were supported by grants from the Canadian Institutes of Health Research. The adult study was supported in part by a grant from the Australian National Health and Medical Research Council, while the companion study in children was supported in part by a grant from the Conselho Nacional de Pesquisa in Brazil.

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SOURCES: Menzies D et al. N Engl J Med. 2018 Aug 2;379(5):440-53; Diallo T et al. N Engl J Med. 2018 Aug 2;379(5):454-63.

Four syndromes suggest life-threatening PVL-positive *S. aureus* infection

BY BRUCE JANCIN
MDedge News

MALMO, SWEDEN – Methicillin-resistant *Staphylococcus aureus* gets the blame in the Americas as the main cause of a great wave of community-acquired severe invasive staphylococcal infections in children and adolescents during the past nearly 2 decades, but many European pediatric infectious disease specialists believe that Panton-Valentine leukocidin (PVL), a frequent co-traveler with MRSA, is the true bad actor.

"The American literature focused first on MRSA, but we've seen very similar, very severe cases with MSSA [methicillin-susceptible *S. aureus*] PVL-positive and MRSA PVL-positive infections," Pablo Rojo, MD, PhD, said at the annual meeting of the European Society for Paediatric Infectious Diseases.

"It is only because at the beginning there were so many MRSA cases in the States that they thought that was the driver of the disease. It is still unclear. There is still a discussion. But I wanted to bring you my opinion and that of many other authors that it's mostly PVL associated," added Dr. Rojo of Complutense University in Madrid.

He was senior author of a multinational European and Israeli prospective study of risk factors associated with the severity of invasive community-acquired *S. aureus* infections in children, with invasive infection being defined as hospitalization for an infection with *S. aureus* isolated from a normally sterile body site such as blood, bone, or cerebrospinal fluid, or *S. aureus* pneumonia. They identified 152 affected children, 17% of whom had severe community-acquired invasive *S. aureus*, defined by death or admission to a pediatric intensive care unit due to respiratory failure or hemodynamic instability.

The prevalence of PVL-positive *S. aureus* infection in the overall invasive infection group was 19%, while 8% of the isolates were MRSA. In a multivariate analysis, PVL positivity was independently associated with a fivefold increased risk of severe *S. aureus* infection, while MRSA was not associated with a significantly increased risk. The other independent risk factors for severe outcome were pneumonia, with an adjusted 13-fold increased risk, and leukopenia at admission, with an associated 18-fold risk (Clin Microbiol Infect. 2016 Jul;22[7]:643.e1-6).

Of note, the virulence of PVL stems from the pore-forming toxin's ability to lyse white blood cells. Because a leukocyte count is always available once a patient reaches the ED, severe leukopenia as defined by a count of less than 3,000 cells/mm^3 at admission becomes a useful early marker of the likely severity of any case of *S. aureus* invasive disease, according to Dr. Rojo.

He highlighted four key syndromes involving severe invasive *S. aureus* infection in previously healthy children and adolescents that entail a high likelihood of being PVL positive and should cause physicians to run – not walk – to start appropriate empiric therapy.The microbiologic diagnosis of PVL can be made by ELISA (enzyme-linked immunoassay) to detect the toxin in an *S. aureus* isolate, by a rapid monoclonal antibody test, or by polymerase chain reaction to detect PVL genes in an *S. aureus* isolate. But don't wait for test results to initiate treatment because these are high-mortality syndromes, he advised.

"My message to you is that you don't need to wait for a microbiological diagnosis or the results to come back from a sample you have sent to the reference lab in the main referral center. We can base our diagnosis and decision to treat on clinical grounds if we focus on these four very uncommon syndromes involving invasive *S. aureus* infection. I think if you have any child with these symptoms you have to manage them on the assumption that PVL is present," said Dr. Rojo, principal investigator of the European Project on Invasive *S. aureus* Pediatric Infections.

The four key syndromes

The four syndromes are severe *S. aureus* pneumonia, *S. aureus* bone and joint infections with multiple foci, *S. aureus* osteomyelitis complicated by deep vein thrombosis, and invasive *S. aureus* infection plus shock.

- **Severe *S. aureus* pneumonia.** Investigators at Claude Bernard University in Lyon, France, have done extensive pioneering work on severe PVL-positive *S. aureus* invasive infections in children. In an early paper, they highlighted the characteristics that distinguish severe PVL-positive pneumonia: It typically occurs in previously healthy children and adolescents without underlying comorbid conditions, and it is often preceded by a influenza-like syndrome followed by an acute severe pneumonia with hemoptysis. Mortality was very high in this early series, with nearly half of the patients being dead within the first several days after admission (Lancet. 2002 Mar 2;359[9308]:753-9).
- **Severe osteomyelitis.** Investigators at Baylor College of Medicine, Houston, were among the first to observe that osteomyelitis caused by PVL-positive strains of *S. aureus* are associated with more severe local disease, with multiple affected areas, bigger abscesses, a greater systemic inflammatory response, and more surgeries required compared with osteomyelitis caused by PVL-negative *S. aureus* (Pediatrics. 2006 Feb;117[2]:433-40).
- **Osteomyelitis with deep vein thrombosis.** When a child hospitalized for acute hematogenous osteomyelitis due to *S. aureus* develops difficulty breathing, that's a red flag for a severe PVL-positive infection involving deep vein thrombosis. Indeed, investigators at the Leeds (England) General Infirmary have reported that deep vein thrombosis in the setting of *S. aureus* osteomyelitis is associated with a greater than eightfold increased likelihood of a PVL-positive infection (Br J Hosp Med [Lond]. 2015 Jan;76[1]:18-24). Also, patients with PVL-positive osteomyelitis and deep vein thrombosis are prone to formation of septic emboli.
- **Osteomyelitis with septic shock.** The Lyon group compared outcomes in 14 pediatric patients with PVL-positive *S. aureus* osteomyelitis and a control group of 17 patients with PVL-negative disease. All 14 PVL-positive patients had severe sepsis and 6 of them had septic shock. In contrast, none of the controls did. Median duration of hospitalization was 46 days in the PVL-positive group, compared with 13 days in controls (Pediatr Infect Dis J. 2007 Nov;26[11]:1042-8).

Bruce Jancin/MDedge News

Dr. Pablo Rojo: 'We can base our diagnosis and decision to treat on clinical grounds if we focus on these four very uncommon syndromes involving invasive *S. aureus* infection.'

Treatment

No randomized trials exist to guide treatment, but Dr. Rojo recommends the protocol utilized by the Lyon group: a bactericidal antibiotic – vancomycin or a beta-lactam – to take on the *S. aureus*, coupled with a ribosomally active antibiotic – clindamycin or linezolid – to suppress the PVL toxin's virulence expression. The French group cites both *in vitro* and *in vivo* evidence that clindamycin and linezolid in their standard dosing have such an antitoxin effect (Clin Microbiol Rev. 2017 Oct;30[4]:887-917).

In addition, Dr. Rojo recommends utilizing any of the commercially available intravenous immunoglobulin (IVIG) products on the basis of work by investigators at Vanderbilt University in Nashville, Tenn., who have demonstrated that these products contain functional neutralizing antibodies against *S. aureus* leukocidins. This observation provides a likely explanation for anecdotal reports of improved outcomes in IVIG-treated patients with toxin-associated staphylococcal disease (Antimicrob Agents Chemother. 2017 Oct 24;61[11]. pii: e00968-17).

He reported having no financial conflicts.

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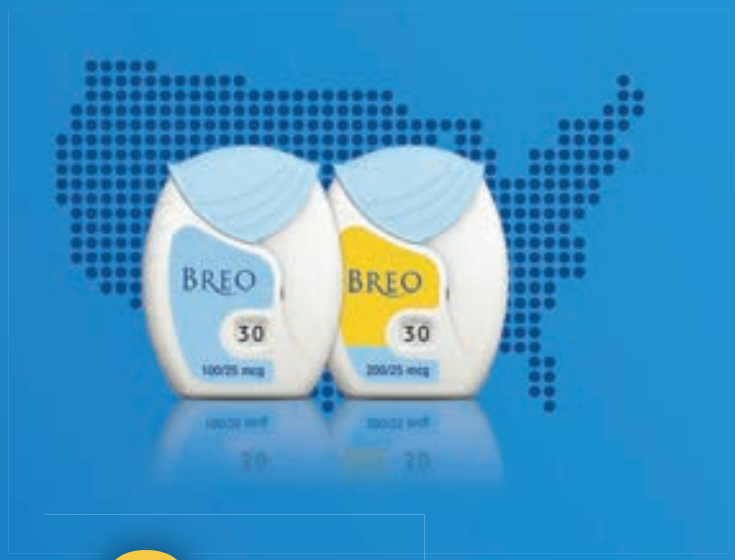

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One-hour sepsis bundle improved pediatric mortality

BY TED BOSWORTH
MDedge News

A bundle of blood cultures, broad-spectrum antibiotics, and intravenous fluid replacement reduces risk of in-hospital mortality among children with sepsis if all three forms of management are initiated within an hour, according to a cohort study published in JAMA.

When provided within 1 hour, none of individual components of the bundles were associated with a significant reduction of risk-adjusted, in-hospital mortality by themselves.

Although published guidelines already recommend prompt initiation of these three elements of care, a mandate created in New York in 2013 called for these interventions to be initiated in children within 1 hour of sepsis recognition. The newly published cohort study shows a mortality benefit when this is done.

In the study, which evaluated the impact of the bundle as well as each of the components in 1,179 pediatric patients with sepsis treated at 54 hospitals, the risk-adjusted odds ratio of in-hospital mortality was 0.59 ($P = .02$) among patients receiving the mandated protocol, compared with those who did not.

When provided within 1 hour, none of individual components of the bundles were associated with a significant reduction of risk-adjusted, in-hospital mortality by themselves. However, there were trends for benefit with blood cultures (OR, 0.73; $P = .1$) and broad-spectrum antibiotics (OR, 0.78; $P = .18$). There was no trend for administration of intravenous fluids (OR, 0.88; $P = .56$), for which the mandate

Continued on page 30

VIEW ON THE NEWS

Sepsis bundle completion may not be only reason for better outcomes

The data published by Evans et al. support a protocol approach to sepsis management in children as well as prompt delivery of the components outlined in the New York state mandate, according to an accompanying editorial written by Robert J. Vinci, MD, of Boston Medical Center, and Elliot Melendez, MD, of Johns Hopkins All Children's Hospital, St. Petersburg, Fla. However, it cannot be determined from this study whether it is prompt delivery of these three mandated components or a more rigorous approach to pediatric sepsis management that deserves the most credit for the mortality benefit.

"Organizations that undertake quality improvement initiatives may have systems of care that promote the bundle completion, which then leads to improved outcomes," they wrote. As a result, bundle completion may be a marker of expertise in managing critically ill children. They agreed that the data support the tested protocol, but they questioned whether this is sufficient.

"Organizations should be cautious about merely adopting a bundle of care without ensuring they have a universal culture of safety and quality that is adopted and supported from front-line clinical caregivers to organizational leaders and administrators," they stated.

Dr. Vinci and Dr. Melendez had no disclosures to report.

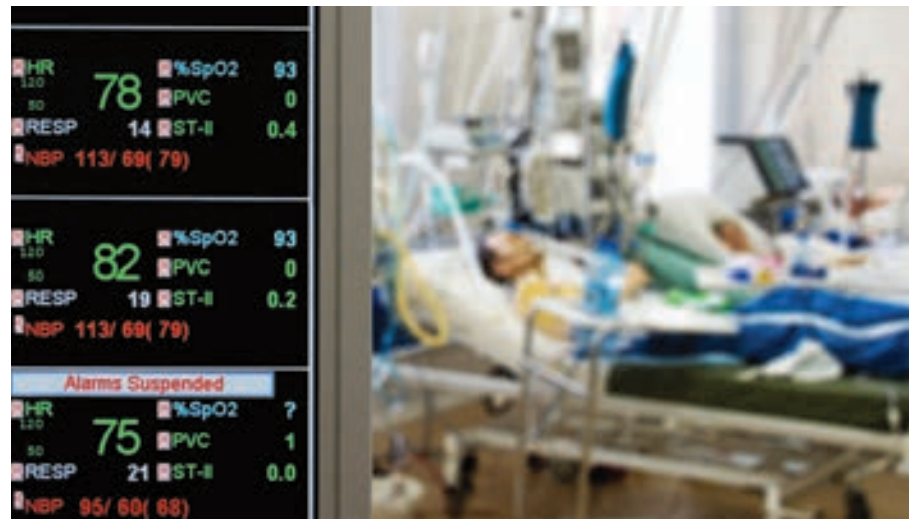
REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Do you know what's driving her **severe asthma?**

AstraZeneca

Better ICU staff communication with family may improve end-of-life decision making

BY MICHELE G. SULLIVAN
MDedge News



ANDREI MALOV/THINKSTOCK

A nurse-led support intervention for the families of critically ill patients did little to ease families' psychological symptoms, but it did improve their perception of staff communication and family-centered care in the intensive care unit.

The length of ICU stay was also significantly shorter and the in-unit death rate higher among patients whose families received the intervention – a finding that suggests difficult end-of-life choices may have been eased, reported Douglas B. White, MD, and his colleagues (N Engl J Med. 2018;378:2365-75).

"The intervention resulted in significant improvements in markers of the quality of decision making, including the patient- and family-centeredness of care and the quality of clinician-family communication. Taken together, these findings suggest that the intervention allowed surrogates to transition a patient's treatment to comfort-focused care when doing so aligned with the patient's values," wrote Dr. White of the University of Pittsburgh. "A previous study that was conducted in the context of advanced illness suggested that treatment that accords with the patient's preferences may lead to shorter survival among those who prioritize comfort over longevity."

"These findings suggest that the intervention allowed surrogates to transition a patient's treatment to comfort-focused care when doing so aligned with the patient's values."

The trial randomized 1,420 patients and their family surrogates in five ICUs to usual care, or to the multicomponent family-support intervention.

The primary outcome was change in the surrogates' scores on the Hospital Anxiety Depression Scale (HADS) at 6 months. The secondary outcomes were changes in Impact of Event Scale (IES; a measure of posttraumatic stress) the Quality of Communication (QOC) scale, quality of clinician-family communication measured by the Patient Perception of Patient Centeredness (PPPC) scale and the mean length of ICU stay.

The intervention was delivered by nurses who received special training on communication and other skills needed to support the families of critically ill patients. Nurses met with families every day and arranged regular meetings with ICU clinicians. A quality improvement specialist incorporated the family support into daily work flow.

In a fully adjusted model, there was no significant between-group difference in the 6-month HADS scores (11.7 vs. 12 points). Likewise, there was no significant difference between the groups in the mean IES score at 6 months.

Family members in the active group did rate the quality of clinician-family communication as significantly better, and they also gave significantly higher ratings to the quality of patient- and family-centered care during the ICU stay.

The shorter length of stay was reflected in the time to death among patients who died during the stay (4.4 days in the intervention group vs. 6.8 days in the control group), although there was no significant difference in length of stay among patients who survived to discharge. Significantly more patients in the intervention group died in the ICU as well (36% vs. 28.5%); however, there was no significant difference in 6-month mortality (60.4% vs. 55.4%).

The study was supported by an Innovation Award from the University of Pittsburgh Medical Center Health System and by the Greenwell Foundation. Dr. White reported having no financial disclosures

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SOURCE: White DB et al. N Engl J Med. 2018;378:2365-75.

Continued from page 28

specified 20 mL/kg.

Although 46.5% of patients received intravenous fluids, 62.8% received broad-spectrum antibiotics, and blood cultures were obtained in 67.7% of the children within 1 hour, only 24.9% were managed with the entire sepsis bundle. Across hospitals, the proportion of children completing the bundle ranged from 7.3% to 46.1%.

Bundle completion was more common in hospitals already treating a relatively high volume of pediatric patients and in those with pediatric specialty services, but the study authors noted that this was not a linear relationship. Rather, they called this association "hypothesis generating" and speculated that other factors might also be important.

The children in this cohort ranged in age from under 1 month to 17 years. Slightly more than half were aged 6 years or older and nearly one-third were older than 12 years. Nearly 45% had no comorbidities. Slightly more than one-third had a malignancy or were immunosuppressed.

None of the study authors reported any relevant financial relationships with industry.

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SOURCE: Evans IVR et al. JAMA. 2018 Jul 24. doi: 10.1001/jama.2018.9071.

VIEW ON THE NEWS

Glimpsing a path forward

Although the results by White and colleagues "cannot be interpreted as clinically directive," the study offers a glimpse of the path forward in improving the experience of families with critically ill loved ones, Daniela Lamas, MD, wrote in an accompanying editorial (N Engl J Med. 2018;378:2431-2).

The study didn't meet its primary endpoint of reducing surrogates' psychological symptoms at 6 months, but it did lead to an improved ICU experience, with better clinician communication. There was another finding that deserves a close look: In the intervention group, ICU length of stay was shorter and in-hospital mortality greater, although mortality among those who survived to discharge was similar at 6 months.

These findings suggest that the intervention did not lead to the premature death of patients who would have otherwise done well, but rather was associated with a shorter dying process for those who faced a dismal prognosis, according to Dr. Lamas.

"As we increasingly look beyond mortality as the primary outcome that matters, seeking to maximize quality of life and minimize suffering, this work represents an 'end of the beginning' by suggesting the next steps in moving closer to achieving these goals."

Dr. Lamas is a pulmonary and critical care doctor at Brigham & Women's Hospital and on the faculty at Harvard Medical School, Boston.

ILLUMINATEOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Elevated eosinophils are seen in the airways of approximately 50% of patients with severe asthma, and are a **direct cause of chronic inflammation**, which can lead to progressive damage in the airways.[1-3]

Patients with eosinophilic asthma (e-asthma) can experience frequent exacerbations requiring oral corticosteroid (OCS) use, emergency visits, or hospitalizations.[3,4,5] Use of OCS may leave patients susceptible to **steroid-associated adverse events and comorbidities**.[6]

Learn more about how testing patients for e-asthma can help inform clinical decision making at illuminatEOS.com

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AstraZeneca

Some PE patients don't require hospitalization

BY JENNIFER SMITH
MDedge News

FROM THE JOURNAL *CHEST*® ▪ A new study suggests that certain patients with acute pulmonary embolism (PE) may be better off receiving outpatient treatment.

Researchers tested outpatient anticoagulant therapy in 200 patients with PE with a low mortality risk. At 90 days of follow-up, there were no deaths or recurrences of venous thromboembolism (VTE), but one patient experienced major bleeding after a traumatic injury.

A majority of patients said they were satisfied with outpatient care.

Of the 146 patients who completed a satisfaction survey at 90 days, 89% said they would choose outpatient management if they had another PE in the future.

Joseph R. Bledsoe, MD, of Intermountain Medical Center in Salt Lake City, and his colleagues reported these results in *CHEST*®.

The researchers tracked patients who were treated for acute PE in five Intermountain Healthcare emergency departments from 2013 to 2016. The patients had to have a low mortality risk according to the Pulmonary Embolism Severity Index (score less than 86), echocardiography (no signs of right heart strain), and whole-leg compression ultrasound. Patients could not have deep vein thrombosis proximal to the popliteal vein, hypoxia, hypotension, hepatic failure, or renal failure. They had to be eligible for therapeutic anticoagulation and could not have any condition requiring hospitalization.

With these criteria, the researchers selected 200 patients. They were observed in the ED or hospital for 12-24 hours and then discharged with anticoagulant therapy. Patients received rivaroxaban (n = 149), enoxaparin transitioned to warfarin (n = 26), apixaban (n = 24), or enoxaparin alone (n = 1).

Results

The study's primary outcome was the 90-day composite rate of all-cause mortality, recurrent symptomatic VTE, and major bleeding. There were no deaths and no cases of recurrent VTE, but one patient did experience major bleeding at day 61 because of a traumatic thigh injury.

Within 7 days of study enrollment, there were 19 patients (9.5%) who returned to the ED and 2 patients (1%) who were admitted to the hospital. One patient with pulmonary infarct was admitted for pain control (day 2); the other was admitted for an elective coronary intervention (day 7) because of a positive cardiac stress test.

Within 30 days, 32 patients (16%) returned to the ED, and 5 (3%) were admitted to the hospital for events unrelated to their PE.

The study also showed that patients were largely satisfied with outpatient care. Of the 146 patients who completed a satisfaction survey at 90 days, 89% said they would choose outpatient management if they had another PE in the future.

"We found a large subset of patients with blood clots who'd do well at home; in fact, who probably did better at home," Dr. Bledsoe said. "When patients are sent home versus staying in the hospital, they're at lower risk of getting another infection. It's a lot less expensive, too."

Currently, the standard of care in the United States for acute PE is hospitalization for all patients. That's recommended, in part, because their overall mortality rate is 17%. However, the lower mortality rate among some appropriately risk-stratified patients suggests that at-home care, which has become the norm in some European countries, leads to better outcomes for those patients overall and less chance of a hospital-introduced infection, according to Dr. Bledsoe.

He added that similar research should be conducted outside of the Intermountain Healthcare system to confirm the results of this study.

The investigators reported no conflicts related to this study.

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SOURCE: Bledsoe JR et al. Chest. 2018 Aug;154(2):249-56.

Long-acting beta$_2$-agonists don't increase CV risk

BY CHRISTOPHER PALMER
MDedge News

Neither heart rate nor blood pressure worsened under long-term use of long-acting beta$_2$-agonists (LABAs) olodaterol or formoterol in patients with chronic obstructive pulmonary disease (COPD), according to a post hoc pooled analysis published in Pulmonary Pharmacology & Therapeutics.

The study was conducted by Stefan Andreas, MD, department of cardiology and pneumology, University Medical Centre Göttingen, and Lung Clinic Immenhausen, both in Germany. "Long-term effects of LABAs on basal heart rate and BP have not been previously investigated in a large patient cohort," the investigators wrote.

The analysis evaluated data from four studies and included a total of 3,104 patients with moderate to very severe COPD, which was defined as Global Initiative for Chronic Obstructive Lung Disease stage 2-4. Patients were randomized to either once-daily olodaterol (5 or 10 mcg), twice-daily formoterol (12 mcg), or placebo. Heart rate and blood pressure were measured before and after dosing at baseline and at four time points during the study: 6 weeks, 12 weeks, 24 weeks, and 48 weeks.

Short-term effects were seen around dosing, from before administration to after, although these changes were quantitatively small.

At all time points, the increases seen in the placebo group were greater than seen in the treatment groups; both systolic and diastolic blood pressure showed either slight decreases from or similarities with those seen at baseline, depending on time point. Short-term effects were seen around dosing, from before administration to after, although these changes were quantitatively small.

One limitation of the study is that it couldn't include patients with unstable COPD because of safety reasons; this prevents the findings from being more broadly generalizable. In addition, they noted, "caution is needed, particularly when interpreting data collected within the post-marketing period, which can be confounded by a greater number of patients receiving active or new treatment due to having higher severity disease and having not responded well to other treatments."

They reported personal fees from various industry entities, such as Novartis, AstraZeneca, and GlaxoSmithKline. Some also reported receiving personal fees from or working for Boehringer Ingelheim, which funded the work.

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SOURCE: Andreas S et al. Pulm Pharmacol Ther. 2018 Aug 2. doi: 10.1016/j.pupt.2018.08.002.

Patch-based AF screening boosts diagnosis rate

BY MITCHEL L. ZOLER
MDedge News

People at increased risk for atrial fibrillation who wore a screening ECG patch for about 2 weeks had their arrhythmia diagnosis rate boosted by 200%-800% during 4 months of follow-up, compared with conventionally followed adults in a randomized, novel-design trial with more than 2,600 randomized participants.

The patients who wore an ECG patch had a 3.9% rate of atrial fibrillation (AF) diagnosis in the study's intention-to-treat analysis, and a 5.1% rate in the per protocol analysis that were the co-primary endpoints for the study, compared with rates of 0.9% and 0.6%, respectively, among people followed with usual care and diagnosed with AF based only on clinical findings.

Mitchel L. Zoler/MDedge News

Dr. Steven R. Steinhubl is a cardiologist and director of digital medicine at the Scripps Translational Science Institute in La Jolla, Calif.

Patients who underwent ECG screening for AF using a patch, compared with those followed with usual care, had more AF diagnoses, greater treatment with anticoagulation over the following year, and increased use of health care resources after 1 year, Steven R. Steinhubl, MD, and his associates reported in JAMA.

The mSToPS (mHealth Screening to Prevent Strokes) trial enrolled adults covered by an Aetna commercial or Medicare health plan who fell into a high-risk group for AF onset: those aged 75 years or older or with at least one of several specified comorbidities. This identified more than 359,000 eligible insured patients. Dr. Steinhubl and his associates invited more than 100,000 people to participate, of whom 2,659 consented and met further eligibility screens. They randomized these people to either undergo immediate ECG patch screening, or have their screening delayed for 4 months while undergoing clinical follow-up.

The researchers sent two commercially available patches to the 1,366 people randomized to immediate screening, with instructions that they wear one patch for 2 weeks immediately, and wear the second patch for 2 weeks starting 3 months after they removed the first patch. Participants mailed their patches to a central site for analysis. Diagnosis of AF was based on an adjudicated episode of at least 30 seconds, and the researchers alerted participants and their individual physicians about diagnostic positives.

Among the 1,366 immediate patch recipients, a third never wore a patch for at least 30 minutes and were excluded from the per protocol analysis. The 908 patch users from the immediate screening subgroup as well as the patch users from the delayed subgroup wore each patch for an average of nearly 12 days, and about two-thirds wore both assigned patches. People diagnosed with AF had, on average, nearly 10 discrete episodes during screening, with a median episode duration of 186 minutes. The median AF burden among those who screened positive was 0.9%, reported Dr. Steinhubl, a cardiologist and director of digital medicine at the Scripps Translational Science Institute in La Jolla, Calif.

The researchers also compared medical interventions during the year following entry among all 1,738 screened patients (from both the immediate and delayed screening subgroups) and a matched group of 3,476 unscreened people who had consented to participate in the study. This showed that AF screening was linked to a doubled rate of anticoagulant treatment initiation. The ECG patch screening also identified 70 additional people with various other potentially actionable cardiac arrhythmias.

Of the 1,738 people who wore at least one patch for more than 30 minutes, 40 (2%) had skin irritation, 32 stopped using the patch prematurely because of irritation, and 2 people sought medical treatment for their irritation, which involved topical treatment.

mSToPS was funded by Janssen. Dr. Steinhubl has received research funding from Janssen, DynoSense, EasyG, Spry Health, and Striiv.

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G. Hossein Almassi, MD, FCCP, comments: This large randomized study is a new step in taking a research trial directly to patients at home remotely rather than having a face-to-face interaction between researchers and patient enrollees. The wearable Mobile Health patch (mHealth) resulted in a higher rate of atrial fibrillation diagnosis, compared with the control group, which in turn led to a greater rate of anticoagulant therapy initiation and increased resource utilization and costs. This study, however, lacks information on whether earlier detection and treatment of AF had any impact on stroke prevention, compared with standard detection of AF in the control group.

SOURCE: Steinhubl SR et al. JAMA. 2018 July 10;320(2):149-55.

24-hour ambulatory BP strongly predicts mortality

BY ANDREW D. BOWSER
MDedge News

Ambulatory measurements of blood pressure more strongly predicted all-cause and cardiovascular mortality than did BP measured in the clinic, according to analysis of a large patient registry in Spain.

The results also showed an increased risk of death associated with white coat hypertension and an even stronger association between death and masked hypertension. They were published in the New England Journal of Medicine.

Previous investigations had found that 24-hour ambulatory BP measurements were better predictors of patient outcomes than those obtained in the clinic or at home, but those investigations were small or population based.

"In these studies, the number of clinical outcomes was limited, which reduced the ability to assess the predictive value of clinic blood pressure data as compared with ambulatory data," reported José R. Banegas, MD, of the department of preventive medicine and public health at the Autonomous University of Madrid and his colleagues. "Moreover, the implications of hypertension phenotypes, such as 'whitecoat' hypertension and masked hypertension, with regard to mortality have remained ill-defined."

To better define the prognostic value of 24-hour ambulatory blood pressure measurement, Dr. Banegas and his colleagues looked at data on a large cohort of primary care patients in the Spanish Ambulatory Blood Pressure Registry. Their analysis included 63,910 adults recruited to the registry during 2004-2014.

Patients had blood pressure measurements taken in the clinic according to standard procedures. Afterward, they had ambulatory blood pressure monitoring that used an automated device programmed to record BP every 20 minutes during the day and every 30 minutes at night.

They found that overall clinic and ambulatory blood pressure measurements had a relatively similar magnitude of association with all-cause and cardiovascular mortality.

However, clinic systolic pressure lost its predictive power for all-cause mortality after adjustment for 24-hour ambulatory systolic pressure. The hazard ratio for all-cause mortality dropped from 1.54 before the adjustment to 1.02 after the adjustment, Dr. Banegas and his colleagues reported.

Continued on following page

ODYSSEY Outcomes trial: Alirocumab confers greater cardiac benefits for higher-risk diabetes patients

BY RANDY DOTINGA
MDedge News

ORLANDO – Higher risk translates to higher benefits. That's the message of a new analysis of the ODYSSEY Outcomes trial in the PCSK9-inhibitor alirocumab that finds people with diabetes gained about twice the reduction in risk of major adverse cardiac events as their nondiabetic counterparts.

"Patients with diabetes and a recent heart attack are at double the risk of a cardiovascular event in the next 3 years as are nondiabetics,

Courtesy American Diabetes Association

Dr. Kausik Ray: "The drug works in the same way and as effectively in everyone: LDL came down by 64% at 16 weeks in everyone. But absolute risk depends upon absolute risk to start with. So, in higher-risk patients, the absolute benefit is greater."

despite guideline-based care," said study presenting author Kausik Ray, MD, ChB, of the School of Public Health of Imperial College London, in an interview. "These patients in our study had LDL of around 89 mg/dL despite high-intensity statins. Current guidelines recommend a goal of LDL of 55 mg/dL in this group. We brought LDL down to around 38 mg/dL, and showed that by doing this, diabetics derived a greater reduction in the risk of major cardiovascular events. A greater absolute benefit was observed, and a smaller number needed to treat."

Dr. Ray presented the study findings, a prespecified analysis of results of ODYSSEY Outcomes, at the annual scientific sessions of the American Diabetes Association.

The trial randomly assigned 18,924 patients with recent acute coronary syndrome and LDL cholesterol of at least 70 mg/dL, despite maximum statin therapy, to 75 mg of alirocumab every 2 weeks or placebo. Doses of alirocumab were increased blindly, to 150 mg, to reach LDL cholesterol levels of 25-50 mg/dL.

During a median 2.8 years of follow-up, the overall cumulative rate of major cardiac adverse events (coronary heart disease death, nonfatal MI, ischemic stroke, or hospitalization for unstable angina) occurred in 9.5% of the overall population randomized to alirocumab and 11.1% of those on placebo, for an absolute risk reduction of 1.6% and a statistically significant and clinically meaningful 15% reduction in relative risk. The results were presented at the annual scientific sessions of the American College of Cardiology in March.

In the current analysis, in patients with diabetes, the cumulative rate of incidents was 14.1% (380 of 2,693) with alirocumab and 16.4% (452 of 2,751) with placebo, for an ARR of 2.3%.

The ARRs for the prediabetes and normoglycemia groups were both 1.2%.

Dr. Ray noted that there's no sign that the drug works differently in patients with diabetes. "The drug works in the same way and as effectively in everyone: LDL came down by 64% at 16 weeks in everyone. But absolute risk depends upon absolute risk to start with. So, in higher-risk patients, the absolute benefit is greater."

According to Dr. Ray, the number needed to treat is 43 over 30 months for people with diabetes and 73 over 30 months for people without diabetes.

Prediman K. Shah, MD, director of the Oppenheimer Atherosclerosis Research Center at Cedars-Sinai Medical Center and professor of medicine at the University of California, Los Angeles, questioned the cost-effectiveness of the medication in an interview.

"Even among the diabetics, the absolute risk reduction is about 2%, which is underwhelming considering the high cost," he said. "If the cost were to drop to levels closer to cost of statins, such a small risk reduction may be worth the expense."

Insurers have been skeptical of covering alirocumab because of its $14,000/year cost. However, Sanofi and Regeneron, which jointly market alirocumab, announced in March 2018 that they "will offer U.S. payers that agree to reduce burdensome access barriers for high-risk patients a further reduced net price for Praluent Injection (alirocumab) in alignment with a new value assessment for high-risk patients from the [United States]."

In response, Dr. Ray said "the benefits quoted are time-to-first-event, and these are modest. But if you look at recurrent events, which represent the natural course of disease, then the benefits and absolute benefits are greater. These are add-on therapies and will never be used in every single patient at current cost."

Glen J. Pearson, PharmD, of the University of Alberta, Edmonton, said in an interview that, "while these absolute numbers do seem relatively small, it must be remembered that these patients are already receiving very effective therapies to reduce their risk of future cardiovascular outcomes."

ODYSSEY Outcomes was funded by Sanofi and Regeneron. The presenter reports various disclosures including consulting and research support relationships with Sanofi and Regeneron. The other study authors report various disclosures. Dr. Pearson reports no relevant disclosures. Dr. Shah reports receiving grant support from Sanofi Regeneron.

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SOURCE: Ray K et al. ADA 2018, Abstract 6-LB.

Continued from previous page

By contrast, ambulatory systolic pressure kept its predictive value after accounting for clinical systolic pressure, with a hazard ratio for all-cause mortality of 1.58 before and after the adjustment, they said in the report.

The strongest association with all-cause mortality was found in patients with masked hypertension – normal clinic readings but elevated ambulatory readings. The hazard ratio for all-cause mortality in that group was 2.83 when adjusted for clinic blood pressure, with similar findings reported for cardiovascular mortality.

White coat hypertension was also associated with increased risk of mortality. The finding of elevated clinic BP and normal 24-hour ambulatory BP had a hazard ratio of 1.79 for all-cause mortality after adjustment for clinic BP, results showed.

"In our study, white coat hypertension was not benign, which may be due in part to the higher mean blood pressure over 24 hours in these patients (119.9/71.9 mm Hg vs. 116.6/70.6 mm Hg in normotensive patients; P less than .001) or to their metabolic phenotype," the investigators wrote.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This an interesting study on the use of ambulatory blood pressure monitoring as compared to clinic BP effect on long-term mortality. The findings that ambulatory BP is a more sensitive predictor of mortality and, that "white coat" hypertension is not a benign condition are worth noting. The authors also found that systolic blood pressure was a better predictor of mortality than diastolic blood pressure. I concur with the accompanying editorial by Dr. Raymond Townsend's recommendation in the NEJM (2018;378:1555; doi: 10.1056/NEJMe1802369) that researchers "initiate a registry" of ambulatory BP monitoring in the United States.

Lacer Laboratories, the Spanish Society of Hypertension, and some European government agencies supported the study. Dr. Banegas reported grants from Fondo de Investigación Sanitaria and personal fees from Lacer. Coauthors reported disclosures related to Vascular Dynamics USA, Relypsa USA, Novartis Pharma USA, Daiichi Sankyo, Boehringer Ingelheim, Pfizer, Lacer Laboratories Spain, and others.

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SOURCE: Banegas JR et al. N Engl J Med. 2018;378:1509-20.

Valsartan recalls: FDA, manufacturers issue advisories

BY MARY JO M. DALES
MDedge News

To address concerns regarding the voluntary recall of some valsartan products, affected drugmakers and the Food and Drug Administration have issued advisories for recognizing the recalled products and prescribing replacement products.

The affected products containing the active ingredient valsartan were voluntarily recalled because of the detection of *N*-nitrosodimethylamine (NDMA), an impurity that is classified as a probable carcinogen. The presence of NDMA was unexpected and is thought to be related to changes in the manufacturing process, the FDA announced in a press release.

The voluntary recall affects all lots of nonexpired products that contain the ingredient valsartan supplied to companies by Zhejiang Huahai Pharmaceuticals, Linhai, China.

The voluntary recall affects all lots of nonexpired products that contain the ingredient valsartan supplied to companies by Zhejiang Huahai Pharmaceuticals, Linhai, China. This company has stopped distributing valsartan. The FDA is working with the affected manufacturers – Major Pharmaceuticals, Solco Healthcare, and Teva Pharmaceuticals – to reduce or eliminate impure valsartan from future products. The voluntary recall also applies to Solco and Teva valsartan/hydrochlorothiazide (HCTZ) combination products.

The agency said its review is ongoing and includes investigating the levels of NDMA in the recalled products, assessing the possible effect on patients who have been taking them, and what measures can be taken to reduce or eliminate the impurity from future batches.

"Our drug shortages team is also working hard to ensure patients' therapeutic needs are met in the United States with an adequate supply of unaffected medications," FDA Commissioner Scott Gottlieb, MD, said.

In the interim, patients taking the recalled valsartan-containing medicines should continue taking their medicine until they have a replacement product, the statement said. To determine whether a specific product has been recalled, patients should be instructed to look at the drug name and company name on the label of their prescription bottle. If the information is not on the bottle, patients should contact the pharmacy that dispensed the medicine.

If a patient is taking one of the recalled medicines, they should follow the recall instructions provided by the company. Contact information for each manufacturer can be found as follows:

Major Pharmaceuticals: www.fda.gov/Safety/Recalls/ucm613625.htm.

Solco Healthcare: www.fda.gov/Safety/Recalls/ucm613504.htm.

Teva Pharmaceuticals: www.fda.gov/Safety/Recalls/ucm613729.htm.

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ED key to reducing pediatric asthma x-rays

BY M. ALEXANDER OTTO
MDedge News

ATLANTA – It's possible to reduce chest x-rays for routine pediatric asthma exacerbations in the ED, but accomplishing this goal takes more than a new clinical practice guideline, according to a quality improvement team at the Monroe Carell Jr. Children's Hospital at Vanderbilt University, Nashville, Tenn.

The team eventually reduced the chest x-ray rate for pediatric asthma exacerbations from 30% to 15% without increasing 3-day all-cause readmissions, but it took some sleuthing in the ED and good relations with staff. "We were way out in left field when we started this. Working in silos is never ideal," said senior project member David Johnson, MD, a pediatric hospitalist and assistant professor of pediatrics at Vanderbilt.

Dr. David Johnson

It's been known for a while that chest x-rays are almost always a waste of time and money for asthma exacerbations, and national guidelines recommend against them. X-rays don't improve outcomes and needlessly expose children to radiation.

In 2014, some of the providers at Vanderbilt, which has about 1,700 asthma encounters a year, realized that the institution's 30% x-ray rate was a problem. The quality improvement team hoped a new guideline would address the issue, but that didn't happen. "We roll out clinical practice guidelines" from on high, "and think people will magically change their behavior," but they don't, Dr. Johnson said at the annual Pediatric Hospital Medicine meeting.

The guideline was not being fully implemented. So the team asked the ED what was the standard procedure for a child presenting with asthma exacerbation. It turned out that the ED had a dyspnea order set that the team "had no idea existed." Chest x-rays were at the top of the

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list; next came blood gases, ventilation-perfusion scans, and leg Dopplers, he said.

The next conversation was to figure out why x-rays were being ordered in the first place. ED staff said they were worried about missing something, especially pneumonia. They also thought they were helping hospitalists by getting x-rays before sending kids to the ward even though, in reality, it didn't matter whether x-rays were done a few hours later on the floor. ED providers also said that ill-appearing children often got better after a few hours but were kept back from discharge because x-ray results were still pending and that sometimes these results revealed problems at 3 a.m. that had nothing to do with why the patients were in the ED but still required a work-up.

This discussion opened a door. The ED staff didn't want to order unnecessary x-rays, either. That led to talks about letting kids declare themselves a bit before x-rays were ordered. ED staff liked the idea, so the guidelines were updated in early 2016 to say that chest x-rays should be ordered only if there is persistent severe respiratory distress with hypoxia, there are focal findings that don't improve after 12 hours of treatment, or there were concerns for pneumomediastinum or collapsed lung. The updated guidelines were posted in work areas

and brought home by resident education.

It worked. Chest x-ray rates in asthma fell to 15%, and have remained there since.

"We gave them permission to take their foot off the throttle and wait a little bit, and we don't have more kids bouncing back from reduced x-rays." The approach is "probably generalizable everywhere," Dr. Johnson said.

There was no industry funding, and Dr. Johnson didn't have any disclosures.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is an excellent report about how a pediatric program evaluated and problem-solved a problem. Choosing Wisely® is an initiative of the ABIM Foundation and the Society of Hospital Medicine has a recommendation regarding not ordering chest radiographs in children with uncomplicated asthma or bronchiolitis. My only caveat is that first time "wheezers" should be considered for a chest x-ray before starting an oral steroid because of the rare risk that a steroid burst would mask initial symptoms of a T-cell lymphoma in the chest, for example.

Asthma medication ratio identifies high-risk patients

BY M. ALEXANDER OTTO
Frontline Medical News

ATLANTA – An asthma medication ratio below 0.5 nearly doubles the risk of children ending up in the hospital with an acute asthma exacerbation, according to researchers from the Medical University of South Carolina (MUSC), Charleston.

The asthma medication ratio (AMR) – the number of prescriptions for controller medications divided by the number of prescriptions for both controller and rescue medications – has been around for a while, but it's mostly been used as a quality metric. The new study shows that it's also useful in the clinic to identify children who could benefit from extra attention.

A perfect ratio of 1 means that control is good without rescue inhalers. The ratio falls as the number of rescue inhalers goes up, signaling poorer control. Children with a ratio below 0.5 are considered high risk; they'd hit that mark if, for instance, they were prescribed one control medication such as fluticasone propionate (Flovent) and two albuterol rescue inhalers in a month.


DR. ANDREWS

If control is good, "you should only need a rescue inhaler very, very sporadically;" high-risk children probably need a higher dose of their controller, or help with compliance, explained lead investigator Annie L. Andrews, MD, associate professor of pediatrics at MUSC.

The university uses the EPIC records system, which incorporates prescription data from Surescripts, so the number of asthma medication fills is already available. The system just needs to be adjusted to calculate and report AMRs monthly, something Dr. Andrews and her team are working on. "The information is right there, but it's an untapped resource," she said. "We just need to crunch the numbers, and operationalize it. Why are we waiting until kids are in the hospital" to intervene?

Dr. Andrews presented a proof-of-concept study at the Pediatric Hospital Medicine meeting. Her team identified 214,452 asthma patients aged 2-17 years with at least one claim for an inhaled corticosteroid in the Truven MarketScan Medicaid database from 2013-14.

They calculated AMRs for each child every 3 months over a 15-month period. About 9% of children at any given time had AMRs below 0.5.

The first AMR was at or above 0.5 in 93,512 children; 18.1% had a subsequent asthma-related event, meaning an ED visit or hospitalization, during the course of the study. Among the 17,635 children with an initial AMR below 0.5, 25% had asthma-related events. The initial AMR couldn't be calculated in 103,305 children, which likely meant they had less-active disease. Those children had the lowest pro-

portion of asthma events, at 13.9%.

An AMR below 0.5 nearly doubled the risk of an asthma-related hospitalization or ED visit in the subsequent 3 months, with an odds ratios ranging from 1.7 to 1.9, compared with other children. The findings were statistically significant.

In short, serial AMRs helped predict exacerbations among Medicaid children. The team showed the same trend among commercially insured children in a recently published study. The only difference was that Medicaid children had a higher proportion of high-risk AMRs, and a higher number of asthma events (Am J Manag Care. 2018 Jun;24[6]:294-300). Together, the studies validate "the rolling 3-month AMR as an appropriate method for identifying children at high risk for imminent exacerbation," the investigators concluded.

With automatic AMR reporting already in the works at MUSC, "we are now trying to figure out how to intervene. Do we just tell providers who their high-risk kids are and let them figure out how to contact families, or do we use this information to contact families directly? That's kind of what I favor: 'Hey, your kid just popped up as high risk, so let's figure out what you need. Do you need a new prescription or a reminder to see your doctor?'" Dr. Andrews said.

Her team is developing a mobile app to communicate with families.

The mean age in the study was 7.9 years; 59% of the children were boys, and 41% were black.

The work was funded by the National Institutes of Health, among others. Dr. Andrews 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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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This study reveals another way to determine asthma control or lack thereof by looking at the Asthma Medication Ratio. But I am not sure how HIPAA compliant an intervention would be that is outside of the primary care provider or subspecialist purview when caring for a patient.

Sleep may mediate healthy behavior in children

BY RICHARD MARK KIRKNER

BALTIMORE – Children who get up to 10 hours of sleep nightly may be more likely to develop healthy behaviors that reduce their chances of being overweight or obese, a 6-year follow-up of children in the Infant Feeding Practices Study II determined.

However, improving health in these children is more than a matter of simply seeing that they get more sleep, said lead investigator Jill Landsbaugh Kaar, PhD, of Children's Hospital Colorado, Aurora, in presenting the results at the annual meeting of the Associated Professional Sleep Societies. Her research indicates that three factors – sleep, diet, and activity – are more interrelated than one being causative of the others (JAMA. 2014 Feb 26;311[8]:806-14).

Dr. Kaar's research used data collected by the Centers for Disease Control and Prevention as part of a 6-year follow-up study of women from the Infant Feeding Practices Study II. Some 1,542 women completed mailed questionnaires about their 6-year-olds' diet, activity, screen time, sleep duration, height, and weight. The analysis characterized children into three health behavior pattern groups: poorest eaters (22%), healthy children (37%), and active supereaters with the highest screen time (41%). The poorest eaters were more likely to be female (58%) and obese (18%) than the other groups, but even 10% of the healthy children group were obese.

In the first model, the poorest eaters had the highest risk of obesity. In the second model, both the poorest eaters and active supereaters had shorter sleep duration than healthy children – 9.46 and 9.59 hours a night, respectively, versus 9.97 hours for healthy children – "thus telling me that sleep was really driving that relationship," Dr. Kaar said.

Dr. Kaar reported having no financial relationships. An American Heart Association Scientist Development Award provided funding for the study.

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Docs push back on step therapy in Medicare Advantage

BY GREGORY TWACHTMAN
MDedge News

A new policy that allows Medicare Advantage plans to use step therapy to control spending on prescription drugs administered in the office is not going over well with doctors.

The Centers for Medicare & Medicaid Services announced the policy change Aug. 7, which will give Medicare Advantage plan sponsors the "choice of implementing step therapy to manage Part B drugs, beginning Jan. 1, 2019," the agency said in a statement. Step therapy, as described by the announcement "is a type of prior authorization for drugs that begins medication for a medical condition with the most preferred drug therapy and progresses to other therapies only if necessary, promoting better clinical decisions."


DR. DAIKH


DR. McANENY

Doctors aren't having it.

"Put simply, this policy change is a gross affront to America's sickest Medicare patients – individuals living with diseases like inflammatory arthritis and cancer – who depend on timely access to safe, affordable, and high-quality treatments," American College of Rheumatology President David Daikh, MD, PhD, said in a statement.

"Utilization management techniques like step therapy prevent and delay important treatments for rheumatic disease patients, which can result in irreversible joint or organ damage," Dr. Daikh continued. "The action is part of the broader Trump administration initiative to lower the prices and out-of-pocket costs of prescription drugs as outlined in the American Patients First blueprint.

By "implementing step therapy along with care coordination and drug adherence programs in [Medicare Advantage], it will lower costs and improve the quality of care for Medicare beneficiaries," CMS officials said in a statement. The move to allow step therapy will give Medicare Advantage plan sponsors the ability to negotiate the designation of a preferred drug, something the agency believes could result in lower prices for these drugs, which in turn will lower the copays for Medicare beneficiaries.

Plan sponsors will be required to pass savings onto beneficiaries through some sort of rewards program, according to a memo detailing the policy change, but rewards "cannot be offered in the form of cash or monetary rebate, but may be offered as gift cards or other items value to all eligible enrollees."

The value of the rewards must be more than half of the savings generated from implementing the step therapy program, according to the memo.

CMS officials said there will be a process that beneficiaries can follow if they believe they need direct access to a drug that would otherwise be available only after failing on another drug.

The American Society of Clinical Oncology also voiced its objection. ASCO strongly opposes the Centers for Medicare & Medicaid Services decision to allow Medicare Advantage plans to employ step therapy," ASCO President Monica Bertagnolli, MD, said in a statement. "Step therapy requires patients to try and fail to have a desired clinical outcome on a lower-cost medications before they can access the medication prescribed by their health care provider. This not only delays patient access to proper treatments, [but it also] potentially leads to irreversible disease progression and other significant patient health risks."

Barbara L. McAneny, MD, president of the American Medical Association, said that physicians "are concerned with patients getting the most effective treatment, and step therapy requirements frequently get in the way. ... Physicians have no easy access to patient benefit and formulary information at the point of prescribing, so they will not be able to readily determine which drugs are preferred by their patients' [Medicare Advantage] plans. This results in treatment delays and unnecessary red tape for physicians and patients."

The new policy applies to only new prescriptions or administrations of Part B drugs. Patients will not have current treatments disrupted if that drug is not the first drug on the step therapy ladder.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: This is not a new idea, as private payers have been using this technique for many years to guide patients to preferred therapy ... not ideal therapy. That should be determined by the physician and the patient. As noted by many in the article, step therapy may delay appropriate patient care and adds administrative burdens to physician who must justify their clinical decisions. Perhaps a better solution would be to allow CMS to negotiate pricing directly with pharmaceutical companies, as is done in many other countries, where pharmaceutical prices are much lower than in the United States.

PhRMA spending leads health-sector lobbying efforts

BY RICHARD FRANKI
MDedge News

The Pharmaceutical Research and Manufacturers of America (PhRMA) led the way on health-sector lobbying in the first half of 2018 with spending that's on pace to top its previous 1-year high, according to the Center for Responsive Politics.

PhRMA spent over $15.7 million on lobbying through the end of June, and equaling that amount over the second half of the year would eclipse the $27.4 million the organization spent in 2009. PhRMA's total for the year so far puts it third among all entities: The U.S. Chamber of Commerce was first with $43.7 million and the National Association of Realtors was second at $27.3 million, the center reported on OpenSecrets.org. The Chamber has been first every year since 2001.

The health sector's 3 other representatives in the lobbying Top 10 for the first half of this year are Blue Cross/Blue Shield in fifth with $11.8 million in spending, the American Hospital Association in sixth ($11.4 million), and the American Medical Association in eighth ($11.2 million), based on the center's analysis of data from the Senate Office of Public Records. The four current health sector representatives have all been in the top 10 every year since 2013.

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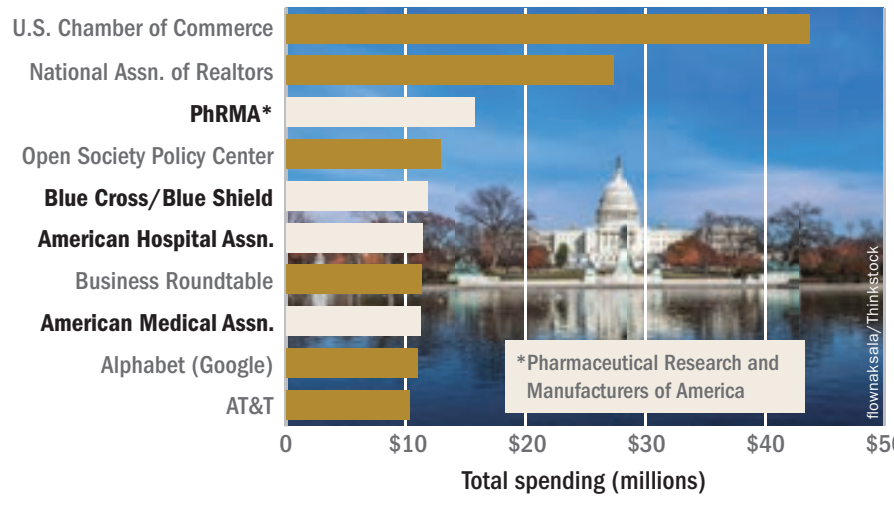
Ten highest-spending lobbyers in 2018



Note: Based on data from the Senate Office of Public Records for Jan. 1 to June 30.
Source: Center for Responsive Politics

MDedge News

TYPE 2 INFLAMMATION OCCURS IN ~50%[a] TO 70%[b] OF ADULT PATIENTS WITH ASTHMA[1,2]

Type 2 inflammation may be driving much of the **difficult-to-control asthma** in your practice—including allergic and eosinophilic asthma, or characteristics of both. Look for the signs of Type 2 inflammation to find patients who are at risk for declining lung function and severe exacerbations.[3-5]

Find at-risk patients at UnderstandingType2Asthma.com/missing

[a] N=205.
[b] N=37.

References: 1. Seys SF, Scheers H, Van den Brande P, et al. Cluster analysis of sputum cytokine-high profiles reveals diversity in T(h)2-high asthma patients. *Respir Res.* 2017;18(1):39. doi:10.1186/s12931-017-0524-y **2.** Peters MC, Mekonnen ZK, Yuan S, Bhakta NR, Woodruff PG, Fahy JV. Measures of gene expression in sputum cells can identify T_H2-high and T_H2-low subtypes of asthma. *J Allergy Clin Immunol.* 2014;133(2):388-394. **3.** Wenzel SE. Emergence of biomolecular pathways to define novel asthma phenotypes: type-2 immunity and beyond. *Am J Respir Cell Mol Biol.* 2016;55(1):1-4. **4.** Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy.* 2017;47(2):161-175. **5.** Patel M, Pilcher J, Reddel HK, et al. Predictors of severe exacerbations, poor asthma control, and β-agonist overuse for patients with asthma. *J Allergy Clin Immunol Pract.* 2014;2(6):751-758.

SANOFI GENZYME

REGENERON

US-AST-1150

CHEST 2018 KEYNOTE

Reflections on a lifetime practicing chest medicine

BY KRISTIN CROWE AND PAM GOORSKY

Richard Irwin, MD, Master FCCP, the Editor in Chief for the journal *CHEST*®, and Chair of UMass Memorial Medical Center's Department of Critical Care, has observed the way patient-focused care has evolved through the years. He will be speaking on this topic at the CHEST 2018 opening session on Sunday, October 7.

During Dr. Irwin's early years at UMass Memorial, the then chairman of Medicine, Dr. James Dalen, a longtime CHEST member who was about to begin his term as CHEST President, strongly encouraged Dr. Irwin to join the American College of Chest Physicians. By joining the college, Dr. Irwin was able to form strong connections with other influential chest medicine professionals, such as Dr. Jack Weg, a former CHEST President, and Dr. Alfred Soffer – who was the Editor in Chief of the journal *CHEST*.

While Dr. Irwin was not yet a member of the CHEST community, the college became instrumental in focusing Dr. Irwin's academic career because of a manuscript that he and colleagues had been working on, titled "Cough. A Comprehensive Review." After submitting the early version of his manuscript to ten different journals and being rejected by each one, Dr. Irwin

Dr. Richard Irwin

contacted Dr. Soffer and asked him, if he had the time, could he please read it and offer advice. Dr. Soffer, who had a reputation of being a mentor with endless generosity of his time, reviewed the manuscript and worked with Dr. Irwin on the article, leading to its publication in the *Archives of Internal Medicine* in 1977. Dr. Soffer's kindness would lead to the start of Dr. Irwin's 40-year career of studying cough.

Dr. Irwin has been very influential within the CHEST organization throughout his career. In addition to his years as the Editor in Chief of the CHEST journal, he also served on every major CHEST committee and held the office of CHEST President in 2003-2004. "If you want to join a society that has a family-feel to it and focuses on clinical care and education, then CHEST is the place to be."

Throughout his years as a physician, Dr. Irwin has been interested in the way physicians learn. During his formative years, he says the way he learned was to "see one, do one, teach one." He gives the example of the flexible fiber-optic bronchoscope, which was developed in Japan in the late 1960s, arriving in the US in 1970. It was a new way of performing bronchoscopy, which led to physicians reading about it, and then putting what they read into action. Now, there are high-fidelity simulation instruments and models and a lot of experiential learning prefacing the use of new technologies for patients.

We have CHEST to thank for being a leader in experiential learning and an international resource for simulation training.

CHEST NETWORKS

Palliative care, respiratory care, and sleep medicine

Palliative and End-of-Life Care

Patient-tailored goals-of-care discussions: Is this the new standard?

Goals-of-care discussions can be challenging conversations for even the most seasoned physicians. The challenge often is not just the timing but also knowing how to stitch together the content of the discussion. In most cases, physicians have minimal prior knowledge of patient and family preferences, and this adds to the complexity. In addition, the majority of these discussions happen in the inpatient setting (Mack et al. *Ann Intern Med.* 2012;156[3]:204) where the acuity of the illness adds to the barriers of effective communication (Fulmer et al. *J Am Geriatr Soc.* 2018;May 23. doi: 10.1111/jgs.15374. [Epub ahead of print]). Can these discussions be tailored to suit individual patient needs and can such attempts better goals-of-care communication? A recent publication by Curtis et al in *JAMA Internal Medicine* (2018;178[7]:930) attempts to shed light on these unanswered questions and provide physician guidance to better engage in these critical discussions. The cluster-randomized trial included both clinicians and patients. Patients were sent a survey assessing their individual preferences, and physicians were given a summary and communication tips based on these preferences (Jumpstart-Tips). This simple, cost-effective yet scalable intervention was able to improve the frequency, documentation, and patient-assessed quality of goals-of-care discussions in an outpatient setting. In addition, the delivery of goal-concordant care was increased at 3 months in the subgroup of patients with stable goals.

One irrefutable point is that interventions to improve communication hold the key to better end-of-life care delivery for our patients with serious illnesses.

A notable limitation of this study was the low participation among physicians. Further studies will be needed to further dissect the characteristics of participating and nonparticipating physicians. Research will also be needed to ascertain how to seamlessly integrate this into health-care delivery. But one irrefutable point is that interventions to improve communication hold the key to better end-of-life care delivery for our patients with serious illnesses. Drs. Paladino and Bernacki have aptly noted in their commentary *(JAMA Intern Med*. 2018;178[7]:940): "In the age of precision medicine, one can imagine a future of precision communication, where we…. provide customized direction for clinicians to begin these discussions based on patient-specific needs." One question remains. Will this be the new standard? The answer lies with us, the clinicians. My answer to this is a resounding "Yes," and I hope early adopters will lead the way and prove me right.

Shine Raju, MD, MBBS
Steering Committee Member

Respiratory Care

Prevention of health-care professional errors in use of inhalers

Asthma affects approximately 300 million people worldwide. The 2018 Global Initiative for Asthma (GINA) guidelines recommend assessing the patient's inhaler technique on a regular basis (*www.ginasthma.org. Updated 2018. Accessed August 1, 2018*).

The pressurized metered-dose inhaler (pMDI) and dry powder inhaler (DPI) are the most common aerosolized medication delivery devices.

DR. GARDNER

Proper inhaler technique optimizes delivery of medication, and patients rely on a variety of their health-care providers (HCP) to teach them to use the devices. Unfortunately, evidence demonstrates patients are unable to use their inhalers properly (Sanchis et al. *Chest*. 2016;150[2]:394). Improper and inadequate inhaler technique is commonly associated with poor disease control, exacerbations, hospitalization stays, and need for systemic corticosteroids and antibiotic therapy (Capanoglu et al. *J Asthma*. 2015;52[8]:838; Levy et al. *Prim Care Respir J.* 2013;22:406; Westerik et al. *J Asthma*. 2015;53[3]:1).

Incorrect inhaler use is attributed to the design of the device, poor patient understanding, and HCPs having insufficient knowledge of the inhalers and performed the correct inhaled technique 15.5% of the time (Plaza et al. *J Allergy Clin Immunol Prac.* 2018;6[3]:987).

Health-care providers who are directly responsible for managing patients with pulmonary disease must have knowledge of correct inhaler techniques to effectively teach patients and properly assess their use of these devices. The quality of the HCP instruction to the patient is key to reducing poor inhaler technique (Klijn et al. *NPJ Prim Care Respir Med*. 2017;;27[1]:24. doi: 10.1038/s41533-017-0022-1). Targeted inhaler technique educational programs for HCPs have been shown to improve clinical outcomes of patients with asthma (*Myers. Respir Care*. 2015;60[8]:1190). The Respiratory Care NetWork is developing HCP and patient handouts for each aerosol delivery device, which may be available in early 2019.

De De Gardner, DrPH, RRT-NPS, FCCP
Steering Committee Member

Sleep Medicine

Pediatric sleep disorders

The Sleep Medicine NetWork has worked hard to contribute to the CHEST 2018 exciting program of events by highlighting hot topics, discussing clinical controversies, and presenting challenging cases in sleep medicine. The goal of the Sleep Medicine NetWork has been to design content relevant to the diverse audience attending CHEST in San Antonio this year.

DR. BAUGHN

This goal includes topics relevant to pediatric sleep medicine. Why is this important to the larger audience at CHEST? Demand for pediatric sleep physicians significantly out paces access in many areas of this country (Phillips et al. *Am J Respir Crit Care Med.* 2015;192[8]:915). Adult sleep physicians may treat older children or adolescents in their practice, they may care for medically complex children when they transition to adulthood, and they may be asked for advice regarding the sleep concerns of children of their friends and colleagues. Sleep problems in children are common and may affect up to a quarter of children at some point during their lifetime (Owens. *Prim Care.* 2008;35[3]:533). The entire household is affected when children are not receiving adequate sleep; the sleep of their caregivers and family members is impacted. While many similarities exist between adult and pediatric sleep medicine, physicians who regularly care for children need to be aware of the important differences in the evaluation and treatment of pediatric sleep disorders.

How else can we connect with your practice? If you have an important topic you would like considered for CHEST 2019, please seek out the Sleep Medicine NetWork meeting in San Antonio, so we can continue to generate relevant content for your practice.

Julie Baughn, MD
Steering Committee Member

INDEX OF ADVERTISERS

To achieve your treatment goals for better breathing in symptomatic patients with COPD...

An ICS/LABA isn't the only way

Hannah, age 58, is a symptomatic patient with moderate COPD presenting with:

- **Wheezing**
- **Cough**
- **Shortness of breath**
- **No exacerbations in the last 12 months**

Hypothetical patient case.

THE **GOLD 2018** REPORT

- Continues to place a greater emphasis on the role of LAMA/LABA for patients with COPD[1]*
- Does not include ICS/LABA as preferred initial treatment in most patients[1]

*Compared with GOLD 2016 Report.

GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist.

ANORO is for the once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA.

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

CONTRAINDICATIONS

- ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or with hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- 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, including Boxed Warning, for ANORO ELLIPTA following this ad.

ANORO delivers superior lung function vs the leading† ICS/LABA for COPD[2]

†Based on IMS US Rx data as of May 2018.

Nearly 2x the lung function improvement vs FP/SAL 250/50[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 ELLIPTA **165 mL (n=353)**
FP/SAL 250/50 **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101 mL Difference (*P*<0.001)
ANORO ELLIPTA **213 mL (n=349)**
FP/SAL 250/50 **112 mL (n=348)**

ANORO ELLIPTA is a combination anticholinergic/LABA for the once-daily, maintenance treatment of airflow obstruction in patients with COPD.

FP/SAL 250/50 mcg, an ICS/LABA, is for the maintenance treatment of airflow obstruction in patients with COPD and for reducing exacerbations in patients with a history of exacerbations.

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

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

See more clinical data 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 FP/SAL 250 mcg/50 mcg (administered via the DISKUS inhaler) 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.

FEV_1=forced expiratory volume in 1 second; FP/SAL=fluticasone propionate/salmeterol; LS=least squares.

Important Safety Information for ANORO ELLIPTA (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 long-term 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.

#1 PRESCRIBED LAMA/LABA IN THE US†

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

†Based on IMS US Rx data as of May 2018.

Important Safety Information for ANORO ELLIPTA (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, including Boxed Warning, 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* 2018 report. www.goldcopd.org. Accessed February 5, 2018. **2.** Donohue JF, Worsley S, Zu CQ, 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 was developed in collaboration with INNOVIVA
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Printed in USA. 1005415R0 June 2018

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

ANORO ELLIPTA **BRIEF SUMMARY**

(umeclidinium and vilanterol inhalation powder), for oral inhalation

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA *[see Warnings and Precautions (5.1)]*.

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.

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

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]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

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. 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.

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 long-term 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 products 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.

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 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.

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 develops.

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

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

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

- 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 the one 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 (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; 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 less than 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 Trial

In a long-term safety trial, 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 that occurred with a frequency of greater than or equal to 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.

(continued on next page)

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

Teratogenic Effects

Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. Women should be advised to contact their heathcare providers if they become pregnant while taking ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (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.

Nonteratogenic Effects

Umeclidinium: There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA

It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium

It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol

It is not known whether vilanterol is excreted in human breast milk. However, other $beta_2$-agonists have been detected in human 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 less than 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 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 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 1 time 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 reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death

Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

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 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.

ANORO ELLIPTA was developed in collaboration with INNOVIVA

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NAMDRC news

BY PHIL PORTE
Executive Director, NAMDRC

NAMDRC will host its 42nd Annual Educational Conference March 14-16, 2019, in Sonoma, California, with a blue chip program featuring nationally recognized speakers. Keynote speakers include Bartolome Celli, MD, FCCP; E. Wesley Ely Jr., MD, FCCP; and a special "Conversation on Health Care Strategies" with Troyen Brennan, MD, Executive Vice President and Chief Medical Officer of CVS Health.

The NAMDRC conference format is unlike other pulmonary focused conferences. All sessions are plenary, and speakers are encouraged to take advantage of our wireless audience response system by simply texting their responses to questions. Sessions begin by 8:00 AM each day and conclude by 12:30 PM to provide ample time for all attendees to enjoy the Napa Sonoma region.

Details regarding registration, lodging, and more specifics regarding the program, social events, and related matters are available at the NAMDRC website at www.namdrc.org.

A few highlights:

• **Thursday, March 14**

Wesley Ely, MD – ICU Liberation and the ABCDEF Bundle – New Data; and ICU Delirium in Ventilated Patients – New Data

Neil MacIntyre, MD – Managing Severe Hypoxemic Respiratory Failure: The Ever Expanding Evidence Base

Samuel Hammerman, MD – Role of Long Term Acute Care

A Panel with Drs. Ely and MacIntyre – Challenges in Critical Care: Spontaneous Ventilation in Lung Injury, ECMO and Other.

Troyen Brennan, MD – A Conversation on Health Care Strategies

• **Friday, March 15**

Peter Gay, MD, FCCP – Heart Failure in Central Sleep Apnea

Susan Jacobs, RN, Christine Garvey, FNP, MSN, Phil Porte – Optimizing Oxygen Therapy

Bartolome Celli, MD, FCCP – Changing the Natural Course of COPD

Alan Plummer, MD, FCCP – Coding Update, 2019

Steve Peters, MD, FCCP – Practice Management Update

Phillip Porte – Legislative and Regulatory Updates

• **Saturday, March 16**

Bartolome Celli, MD, FCCP -- Pharmacological Therapy of COPD: Reasons for Optimism

Richard Channick, MD – Management of Acute Pulmonary Embolism: New Approaches

Colleen Channick, MD – The Role of Interventional Pulmonology in the Management of Cancer: From Diagnosis to Palliation

Stanley Yung-Chuan Lui, MD – Surgical Approach to OSA

Daniel Culver, DO, FCCP – Sarcoidosis

Regulatory proposals from CMS trigger NAMDRC responses

CMS has released several proposed rules to take effect January 1 that, if implemented, will impact patients and physicians. The first regulation recommends important changes in the durable medical equipment competitive bidding program in general, with specific recommendations related to improving availability of liquid oxygen. CMS acknowledges that access to liquid oxygen has become problematic and is seeking comment on a proposal that would bump payment for liquid oxygen, including high flow, approximately 50%.

While the acknowledgement is important, the proposed solution falls far short of what virtually everyone in the industry believes is workable. For perspective, allowable charges for 2016 for liquid portable systems was just over $2 million, less than 2% of all outlays for portable equipment. Statutory language would require "budget neutrality," thereby reducing payment for all other oxygen systems to bump liquid payment. Experts agree that the proposed 50% bump is nowhere near the bump necessary to address the costs to suppliers to provide oxygen. Just as most oxygen modalities fit into the "nondelivery business model" that has reduced direct contact with patients, liquid fits into a "delivery business model" that necessitates constant refills by the supplier. That added cost needs to be reflected in any payment, and competitive bidding has eviscerated that payment.

NAMDRC and other societies recommend a "carve out" for liquid oxygen, removing it entirely from competitive bidding. While this approach would revert to a 1986 payment methodology, adjusted over time, it could be enough incentive for some suppliers to re-enter the liquid arena.

The second proposal espoused by CMS reduces payment for Level 4 and Level 5 office visits, with extra dollars going to lower intensity visits. Depending on a physician's particular practice, the impact could be minimal or, at the other end of the spectrum, quite damaging. The proposal has its origins with the family practice community, long frustrated by the relatively low payment for Level 1 and level 2 visits. CMS ostensibly refers to reduced paperwork, but most physician groups see the real impact affecting their memberships.

CMS will publish final rules, reflecting public comment, around November 1, with an implementation date of January 1, 2019.

This month in the journal *CHEST*®

BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief

Giants in Chest Medicine

Douglas J. Mathisen, MD
By Douglas E. Wood

Original Research

Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial.
By Dr. G. A. Silvestri, et al.

Predictive Variables for Failure in Administration of Intrapleural Tissue Plasminogen Activator/ Deoxyribonuclease in Patients With Complicated Parapneumonic Effusions/ Empyema.
By Dr. D. Khemasuwan, et al.

How Fragile Are Clinical Trial Outcomes That Support the CHEST Clinical Practice Guidelines for VTE?
By Dr. E. Edwards, et al.

Special Features

Marijuana and Lung Disease.
By Dr. D. Tashkin

Impact factor news for the journal *CHEST*®

The journal *CHEST*® was recently awarded a 2-year impact factor of 7.652, the highest in its history, which equates to a 24% increase over last year's score. In addition, our 5-year impact factor is 7.854, a 7% increase over last year. With respect to the 2-year factor, *CHEST*® is ranked 4th out of 33 journals in the Critical Care category and 7th out of 59 journals in the Respiratory System category.

Our recent Eigenfactor places us as the second-highest ranked journal in both respiratory and critical care categories. The Eigenfactor metric adjusts the impact factor by eliminating self-citations and factoring in citations in the top-tier journals.

Congratulations to our journal *CHEST*®!

NetWorks Challenge recap

The CHEST Foundation is proud to announce the completion of the 2018 NetWorks Challenge Giving Month! Through your generous contributions, we reached our ambitious fundraising goal of $60,000 over the course of just 1 month.

CHEST® FOUNDATION

This year, every NetWork was eligible to win travel grants to CHEST 2018 by donating in their NetWorks name during the month of June.

The highest contributing NetWork, Pulmonary and Vascular Disease NetWork, and the NetWork with highest percentage of participation, the Practice Operations NetWork, each receive additional travel grants and session time at CHEST 2018! Additionally, the Transplant NetWork raised over $5,000 through their efforts and will be receiving a travel grant to CHEST 2018 for their strong support of our clinical research grants, patient education initiatives, and community service events.

Thank you to all who contributed during the NetWorks Challenge Giving Month!

CHEST 2018 keynote to bridge the gap between generations

BY KRISTIN CROWE


Scott Zimmer

Scott Zimmer, a product of generation X, went through college with a passion for public speaking, as well as a deep interest in the generational divide. In 2013, he began working for a company called BridgeWorks and so began his career as one of three speakers at this firm of "generational junkies and trend spotters."

Founded in 1998, Bridgeworks strives to bridge the generational gaps that are found in all workplaces through research, keynote speakers, workshops, blogs, training, trivia, and more. Bridgeworks is a team of 13 people coming from the baby boomer generation down to millennials on the cusp of being classified with generation Z (gen edgers, as Zimmer calls them). Each team member has their own interesting and diverse background with a passion for the topic of generations, and everyone engages this passion by conducting research with the BridgeWorks team.

There are generational clashes in every single industry, according to Zimmer. Just at BridgeWorks, he even notices when simply sending a text he perceives as "normal" to one of his millennial coworkers, that it is sometimes received as curt and leaves the recipient concerned that they have done something to offend him. This topic is not foreign to anyone— everyone has had a moment of saying "kids these days," or "ugh, old people." Because of this, Zimmer starts every session knowing that each person will leave with relevant insights and actionable takeaways.

Zimmer also loves to integrate nostalgia into his presentations, and working with generational theory at BridgeWorks allows him to do just that in a way that helps drive home points and makes ideas more relatable. "Some people like to say we are all just people and we grow out of certain things. But we develop specific traits and values at an impressionable age, and I love looking at what was happening in our lives during those formative years. What are these shared experiences that will form who we are?" This love of nostalgia set Zimmer up for a great opportunity to develop his own trivia gameshow at BridgeWorks. GenPOP! is an interactive trivia gameshow that pairs members of different generations up and quizzes them on all things pop culture from different decades, while also teaching audience members new things about the people they interact with every day.

"So much goes into who we are and who shows up to the workplace, what effects our behavior, and our motivation," says Zimmer when asked where his passion for this topic stems. "It could be our gender, the region we grew up in, or birth order, and I personally like looking at it through the lens of these different generations."

So, what will Zimmer bring to CHEST 2018? During his keynote presentation on Monday, October 8 ,in San Antonio, Zimmer will examine the generational gaps that are existent in the medical community. "You don't want your young medical professionals to feel like they are sitting at the 'kids table' or being talked down to when they have something to share because they do not have equal experience."

Each generation and each member of a medical team communicates differently, and understanding those differences and feeling like an equal part of the team is very important. How information is conveyed to patients and medical team members of any age affects how they perceive given information and the level of comfort that is felt by each party. Finding ways to bridge the obvious gaps between the generations is a key component to making any team work efficiently.

SLEEP STRATEGIES

Value-based sleep: understanding and maximizing value

BY EMERSON M. WICKWIRE, PHD

In addition to well-documented health consequences, obstructive sleep apnea (OSA) is associated with substantial economic costs borne by patients, payers, employers, and society at large. For example, in a recent white paper commissioned by the American Academy of Sleep Medicine, the total societal-level costs of OSA were estimated to exceed $150 billion per year in the United States alone. In addition to direct costs associated with OSA diagnosis and treatment, indirect costs were estimated at $86.9 billion for lost workplace productivity; $30 billion for increased health-care utilization (HCU); $26.2 billion for motor vehicle crashes (MVC); and $6.5 billion for workplace accidents and injuries.[1]

More important, evidence suggests that OSA treatments provide positive economic impact, for example reducing health-care utilization and reducing days missed from work. Our group at the University of Maryland is currently heavily involved in related research examining the health economic impact of sleep disorders and their treatments.

Value-based sleep is a concept that I created several years ago to guide a greater emphasis on health economic outcomes in order to advance our field. In addition to working with payers, industry partners, employers, and forward-thinking startups, much effort has been invested into provider education regarding the health economic aspects of sleep. This article examines what value-based sleep is, how to increase the value of sleep in your practice setting, and steps to prepare for payment models of the future.

Value is in the eye of the beholder

Unlike sleep medicine providers (and some patients), the majority of society views sleep as means to an end and not as an end-in-itself. That is, people only value sleep insofar as sleep will help them achieve their primary objectives, whatever they might be. In health economic terms, these distinct viewpoints are referred to as perspectives. For example, from the patient perspective, sleep is valued to the extent that it helps to increase quality of life.

Table 1. Stakeholders and perspectives in sleep medicine

Stakeholder perspective	Value-based outcome
Patient	Quality of life, ease of experience
Payer	Cost savings
Employer	Workplace productivity, accident risk
Health system	Revenue (margin)
Society	Aggregated costs and outcomes

From the payer perspective, sleep is valued to the extent that it reduces health-care utilization. From the employer perspective, sleep is valued to the extent that it increases workplace productivity and reduces health-care expenses. Table 1 summarizes common stakeholders and perspectives in sleep medicine.

Speaking the language of value

In order to define, demonstrate, and maximize the perceived value of sleep medicine services, sleep physicians must understand and clearly articulate the values of these multiple constituents. Most important, this means that sleep physicians must move beyond discussing the apnea-hypopnea index (AHI). To be clear, no one other than sleep medicine insiders care about the AHI! Of course, the AHI is an important (albeit imperfect) measure of OSA disease severity and treatment outcomes. However, when was the last time that a patient told you they woke up one morning dreaming about a lower AHI? It simply does not happen. Instead, stakeholders care about outcomes that matter to them, from their own unique perspectives. To speak directly to these interests and frame the value of sleep, sleep medicine providers must methodically develop value propositions with each unique target constituency in mind. Speak the language of your audience, and use terms that matter to them.

Adopting value-based payments

Much has been spoken about a transition from fee-for-service to value-based care in medicine. New health-care business models will soon impact patients, providers, payers, and health systems. To guide and ensure sustainable change, multi-stakeholder organizations, such as the Health Care Payment & Learning Action Network, are heavily engaged in the development and implementation of alternate payment models (APMs) to facilitate the transition from fee-for-service to population health. As depicted in Figure 1, sequential steps toward value-based care include increased fees corresponding to improved outcomes. A reimbursement model that is fully value-based centers on shared financial risks. Although private practitioners may be ill-equipped to provide population-level services or negotiate fully value-based models, sleep medicine providers should do well to increase familiarity with APMs and their impact on primary and specialty care services.

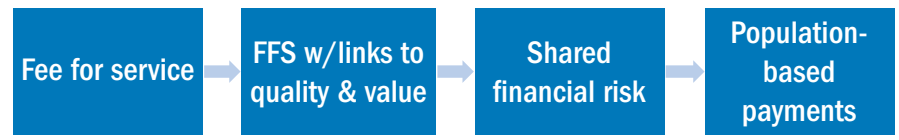

Figure 1. The transition from volume to value. Alternate payment models (APMs) seek to increase value by moving from volume-based fee-for-service (FFS) payments to value-based care. Beginning with the status quo, sequential steps first link FFS payments to indicators of quality and value, then share financial risk, and finally provide fixed payments for managing population health. For more detail, readers are referred to the excellent white paper published by the Health Care Payment & Learning Action Network at www.hcp-lan.org.

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Five steps to a value-based approach

In the modern health-care climate of increasing costs on the one hand and limited resources on the other, sleep medicine providers must embrace a value-based perspective to survive, thrive, and grow in a new world of value-based care. This will require sleep medicine providers to learn, adapt, and adjust. The good news is that regardless of your practice or organizational setting, these strategies and tactics will help guide you:

1. *Know thyself.* What are your personal and organization objectives? Where are you, career-wise? Where do you want to be in 2, 3, and 5 years?
2. *Know your customer.* Whom do you serve? More broadly, whom does sleep serve? Listen carefully and identify the outcomes that matter to your constituents. Make these your endpoints.
3. *Develop customer-centric language.* Develop scripts. Rehearse them.
4. *Understand trends in payments and technology.* Is your region adopting bundled payments or paying more for improved outcomes? How might telemedicine or preauthorization for PAP impact your practice?
5. *Know your numbers.* To negotiate with confidence, you need to know your numbers. What are your costs per patient, per test, per outcome, and lifetime value of the patient?

Summary and next steps

To survive and thrive in a value-based future, you need to define, demonstrate, and maximize your perceived value. This will require greater attention to the language that you use, the results that you emphasize, and the data that you use to make decisions, all while attending to the perspectives of diverse stakeholders. The need for sleep medicine services has never been greater. Adopt a value-based sleep approach to ensure your bright future.

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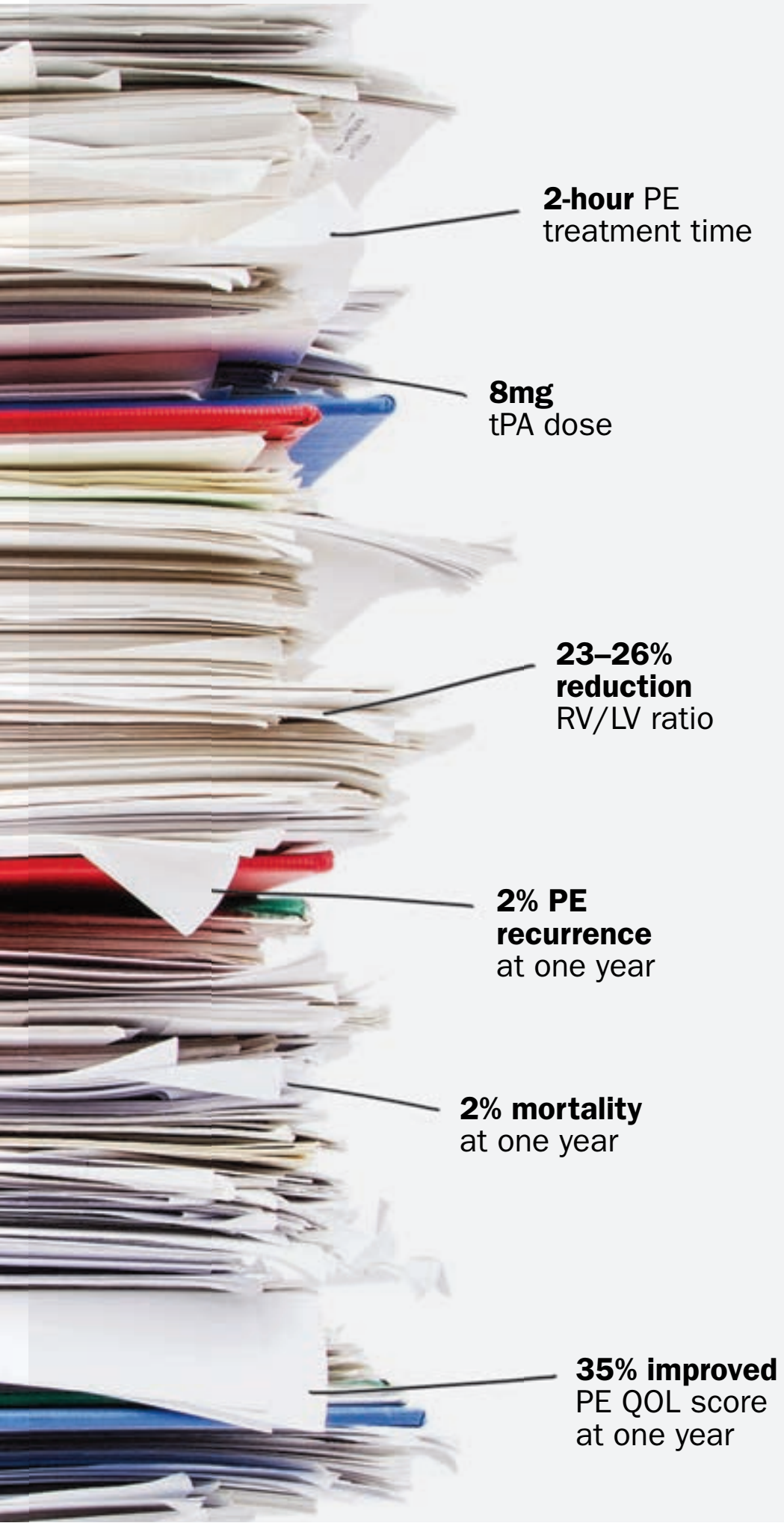

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*Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL. Feb 2018.

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