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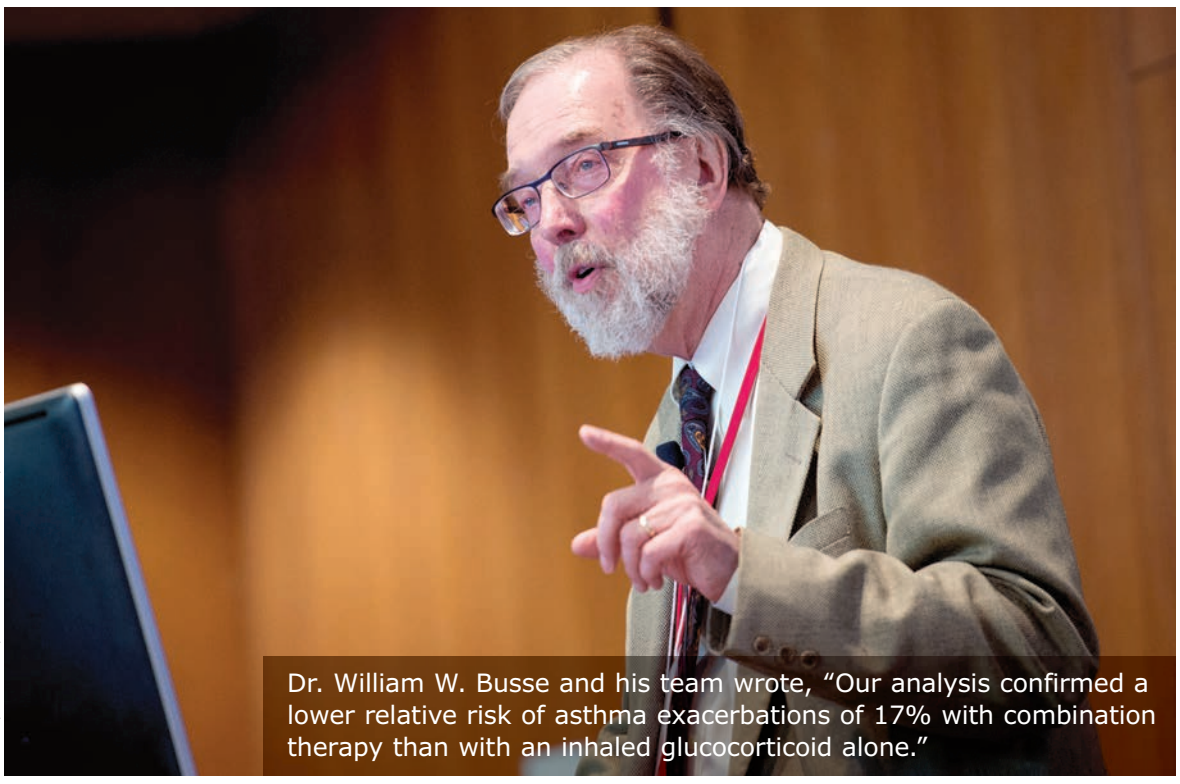

Courtesy University of Wisconsin Health System

Dr. William W. Busse and his team wrote, "Our analysis confirmed a lower relative risk of asthma exacerbations of 17% with combination therapy than with an inhaled glucocorticoid alone."

FDA walks back warning on LABA-containing asthma medications

BY MICHELE G. SULLIVAN
MDedge News

The combination a long-acting beta agonist (LABA) and an inhaled glucocorticoid decreases the risk of an asthma exacerbation by 17%, without increasing the risk of asthma-related intubation or death.

An independent analysis of four large, drug company–sponsored trials supports the Food and Drug Administration's recent decision to remove the black box warning on LABA/inhaled glucocorticoid products, wrote William W. Busse, MD, and his colleagues. The report was published in the New England Journal of Medicine.

"Our analysis confirmed a lower relative risk of asthma exacerbations of 17% with combination therapy than with an inhaled glucocorticoid alone. This finding corresponds to the lower relative rates of asthma exacerbations that were reported in the sponsored individual trials: by 21% in the GlaxoSmithKline trial [hazard ratio 0.79], by 16% in the AstraZeneca trial [HR. 0.84], and by 11% in the Merck trial [HR 0.89]," wrote Dr. Busse of the University of Wisconsin, Madison, and his coauthors.

The FDA based its December 2017 reversal on an initial review of the studies, which were reviewed by an independent committee and are now public. Dr. Busse led the expert analysis of

LABA // *continued on page 7*

Fluoroquinolones linked to fatal hypoglycemia, safety review finds

BY MICHELE G. SULLIVAN
MDedge News

Fluoroquinolones have caused at least 67 cases of life-threatening hypoglycemic coma, including 13 deaths and 9 permanent and disabling injuries, according to an internal safety review by the Food and Drug Administration. Most cases (44) were associated with levofloxacin.

The review also found new neuropsychiatric side effects associated with fluoroquinolones, including disturbances in attention, memory impairment, and delirium.

Considering these findings, the agency will strengthen warning labels on all fluoroquinolones, which already warn that the antibiotics may cause hypoglycemia and mental health issues, especially in older people, the FDA said in a press statement.

"Health care professionals should be aware of the potential risk of hypoglycemia, sometimes resulting in coma, occurring more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin," the statement said. "Alert patients of the symptoms

FLUOROQUINOLONE // *continued on page 13*

INSIDE HIGHLIGHT

CRITICAL CARE COMMENTARY

Balanced crystalloids vs saline for critically ill patients

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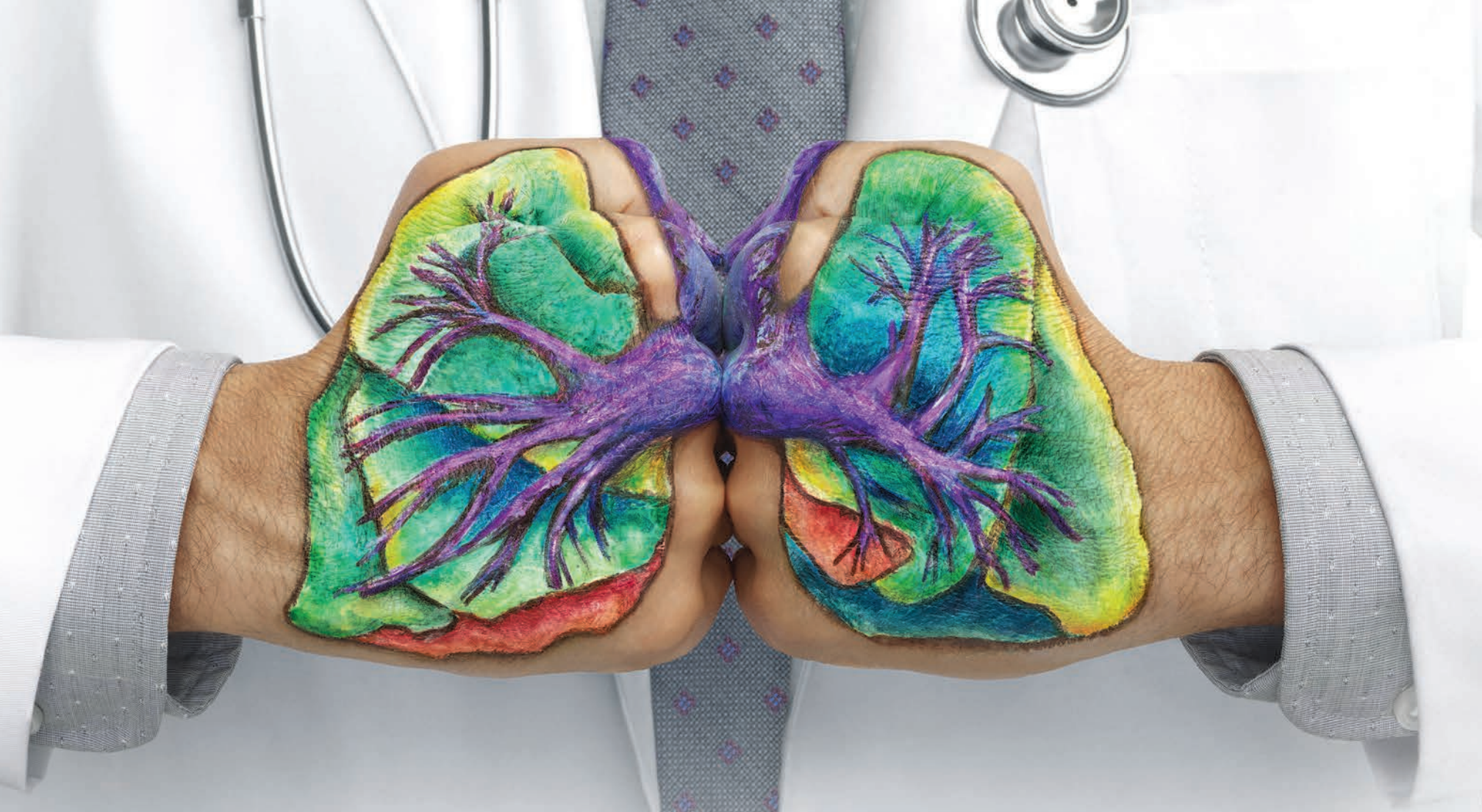

Indication

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

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) 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 patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

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

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and

Genentech

A Member of the Roche Group

WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.[1–4]

STUDIED IN A RANGE OF PATIENTS

Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[1]

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[2†]

COMMITTED TO PATIENTS

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

WORLDWIDE PATIENT EXPERIENCE

More than 31,000 patients have taken pirfenidone worldwide[1§]

pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal diseases requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet 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. You may also report side effects to Genentech at 1-888-835-2555.

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

References: 1. Data on file. Genentech, Inc. 2016. **2.** Esbriet Prescribing Information. Genentech, Inc. January 2017. **3.** 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. **4.** 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.

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).[2] 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.[3] 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.[4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[2,3] 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).[1,2,4] **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.[2,4]**

†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).[2]

‡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.[2]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

Medicare bundles didn't deliver expected cost savings

BY ANDREW D. BOWSER
MDedge News

Participation in Medicare's bundled payments initiative didn't significantly change payments per episode or care outcomes for the top five medical conditions selected under the program, a new analysis shows.

Payments for the common conditions (congestive heart failure, pneumonia, chronic obstructive pulmonary disease, sepsis, and acute myocardial infarction) remained around $24,000 per episode before and during participation in the Bundled Payments for Care Improvement (BPCI) initiative for the 125 participating hospitals evaluated in this study, conducted by Karen E. Joynt Maddox, MD, of Washington University, St. Louis, and her coauthors.

The finding contrasts with a pre-

vious study showing that hospitals in BPCI successfully lowered overall Medicare payments for patients who underwent joint replacement.

"Bundling of services to encourage more efficient care has great face validity and enjoys bipartisan support," Dr. Joynt Maddox and her colleagues wrote. "For such bundling to work for medical conditions, however, more time, new care strategies and partnerships, or additional incentives may be required."

The Center for Medicare & Medicaid Innovation initiated the voluntary BPCI demonstration project in 2013. The program targets 48 conditions that account for about 70% of Medicare spending. Hospitals that achieve cost targets for a specific condition get to keep a portion of the savings, and they reimburse Medicare for part of the difference when costs are exceeded.

The present study focused on 2013-2015 Medicare claims for the five medical conditions that account for two-thirds of patients enrolled in medical bundles: congestive heart failure, pneumonia, chronic obstructive pulmonary disease, sepsis, and acute myocardial infarction.

Mean baseline payments per episode for those conditions were $24,280 before participation in the BPCI. After hospitals joined, their average payments per episode were $23,993 ($P$ = .41). For a set of matched control hospitals, payments were a mean of $23,901 at baseline and $23,503 in the corresponding follow-up period (P = .08).

That amounted to a $286 payment reduction for BPCI hospitals and a $398 reduction for controls, a difference of $112 ($P$ = .79), the study investigators reported.

Changes in length of stay, readmissions, emergency department use, and clinical complexity of cases from baseline to follow-up periods were not significantly different between BPCI and control hospitals. For example, 90-day mortality increases were seen in both groups, and the degree of increase was not statistically different between the groups. "Despite the importance of episode-based payment, there has been little research examining its efficacy or determining whether it has unintended consequences, such as hospitals' selecting patients with relatively less complex conditions to reduce costs and improve outcomes," Dr. Joynt Maddox and her colleagues cautioned.

It's unclear why the previous joint replacement study showed a successful reduction in costs under BPCI, while the new study did not. However, patients in the new analysis of the most common bundled conditions were older and had higher rates of poverty and disability.

"As a result of these complexities, patients admitted for medical conditions may have had post–acute care needs that were less amenable to intervention," Dr. Joynt Maddox said.

The investigators added that hospitals' lack of effective influence on post–acute care services may blunt their ability to achieve greater savings under BPCI. Better relationships with skilled nursing facilities, long-term care hospitals, home health agencies, and inpatient rehabilitation facilities could make a difference.

The Commonwealth Fund supported the study. One study author reported personal fees from the Department of Health & Human Services outside the submitted work, and another reported that he is an associate editor for the New England Journal of Medicine. No other disclosures were reported.

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SOURCE: Joynt Maddox KE et al. N Engl J Med. 2018 Jul 19;379(3):260-9.

New hypertension guidelines add 15.6 million diagnoses

BY ANDREW D. BOWSER

A new analysis estimates that adopting the 2017 American College of Cardiology/American Heart Association hypertension guidelines would add 15.6 million Americans to the ranks of the hypertensive patients, and half of those would be candidates for treatment.

Similar increases would occur in other countries, according to study authors, who analyzed two large datasets from the United States and China.

DR. KRUMHOLZ

That happened by resetting the definition of adult hypertension from the long-standing threshold of 140/90 mm Hg to a blood pressure at or above 130/80 mm Hg, meaning more than half of people aged 45-75 years in both countries would be classified as having hypertension, according to the researchers, led by Harlan M. Krumholz, MD, of the Center for Outcomes Research and Evaluation at Yale–New Haven (Conn.) Hospital and the section of cardiovascular medicine at Yale.

An additional 7.5 million Americans would be recommended for treatment under the new lower treatment thresholds, with a correspondingly large increase in the Chinese population, according to results published in the BMJ.

The guideline changes are "not firmly rooted in evidence" and could have health policy implications that include strain on public health programs, Dr. Krumholz and his colleagues wrote in their report on the study.

"The change occurs at a time when both countries have substantial numbers of people who are not aware of having hypertension, and who have hypertension that is not controlled, even according to the previous standards," they wrote.

The analysis by Dr. Krumholz and his colleagues was based on the two most recent cycles of the U.S. National Health and Nutrition Examination Survey (NHANES), representing 2013-2014 and 2015-2016 periods, as well as the China Health and Retirement Longitudinal Study (CHARLS) in 2011-2012.

Under the new ACC/AHA guidelines, they found, 70.1 million Americans aged 45-65 years would be classified as hypertensive, representing 63% of that age group. That's a 27% relative increase over the 55.3 million individuals, or 49.7%, with hypertension as defined in the JNC-8 guidelines. In addition, 15.6 million persons would be classified as eligible for treatment but not receiving it, up from 8.1 million under the JNC-8 guidance.

Previous estimates projected a far greater jump in new hypertension classifications, including one that used data from the National Health and Nutrition Examination Survey, antihypertensive clinical trials, and population-based cohort studies. That study estimated that 31 million people would newly carry the label (JAMA Cardiol. 2018 May 23. doi: 10.1001/jamacardio.2018.1240).

Dr. Krumholz noted that the ACC/AHA guideline changes were prompted by results from SPRINT. However, the improvements in outcomes seen in SPRINT, which included patients at high risk for cardiovascular events but without diabetes, have not been observed in individuals at low or intermediate risk, or in those with diabetes, they said.

"Expanding the pool of patients who merit treatment to include those at low risk could potentially render public health programs less efficient and viable," they wrote in a discussion of health policy implications.

Dr. Krumholz reported research agreements from Medtronic and from Johnson and Johnson (Janssen) through Yale University, and a grant from the Food and Drug Administration and Medtronic. He reported other disclosures related to UnitedHealth, the IBM Watson Health Life Sciences Board, Element Science, Aetna, and Hugo, a personal health information platform he founded. First author Rohan Khera, MD, reported support from the National Institutes of Health.

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SOURCE: Khera R et al. BMJ. 2018 Jul 11;362:k2357.

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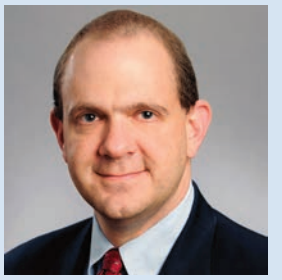

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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FDA expedited approvals can lack top-notch evidence

BY MICHELE G. SULLIVAN
MDedge News

About half of the drugs approved under the Food and Drug Administrations's Breakthrough Therapy designation have lacked the gold-standard evidence of a double-blind, randomized, placebo-controlled trial, according to a new JAMA report.

"This study of all FDA approvals granted Breakthrough Therapy designation from 2012 through 2017 suggests that pivotal trials supporting these approvals commonly lacked randomization, double-blinding, and control groups, used surrogate markers as primary end points, and enrolled small numbers of patients," wrote Jeremy Puthumana and his coauthors. "Furthermore, more than half were based on a single, pivotal trial."

The average premarket development time was about 5 years, but regulatory review of these agents took less than 7 months on average, the report found.

Mr. Puthumana, of Yale University, New Haven, Conn., and his coauthors, reviewed all 46 of the drugs and biologics approved by the FDA from 2012 to 2017 under the designation. The Breakthrough Therapy designation allows for the rapid review of drugs and biologics for serious or life-threatening conditions where there is preliminary evidence demonstrating a substantial improvement over existing therapies. The researchers identified all pivotal trials supporting approval, looking at randomization, blinding, comparator group, primary endpoint, and patient numbers.

Of these drugs, most (25) were oncologic agents; other indications were infectious disease (8), genetic or metabolic disorders (5), and other unspecified purposes (8). The median number of patients enrolled among all pivotal trials supporting an indication approval was 222.

Most of the approvals (27) were based on randomized trials, 21 (45.7%) were based on double-blind randomization, 25 (54.3%) employed an active or placebo comparator group, and 10 (21.7%) used a clinical primary endpoint.

Compared with drugs without accelerated approval, drugs with accelerated approval status were less likely to be examined in randomized or double-blinded trials (24 vs. 3 and 20 vs. 1, respectively), and were less likely to include a control group (32 vs. 3).

All drugs with Accelerated Approval status underwent at least one clinical safety or efficacy-focused postmarketing requirement, as did 64.3% of those without that status.

Mr. Puthumana reported having no financial disclosures.

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SOURCE: Puthumana J et al. JAMA. 2018;320(3):301-3.

VIEW ON THE NEWS

Some approvals are worth the risks

"The idea that doing something more quickly means it is not done as well has considerable face validity," Austin B. Frakt, PhD, wrote in an accompanying editorial. Nevertheless, at least one study suggests that expedited FDA approvals do confer substantial gains in quality of life. "However, drugs subject to less FDA scrutiny are more likely to exhibit safety problems, be withdrawn from the market, or carry black box warnings. ...Because expedited review programs are intended for drugs that treat serious conditions and address unmet medical needs, accepting greater risk may be reasonable and more consistent with patients' preferences," he said.

Dr. Frakt is director of the Partnered Evidence-Based Policy Resource Center at the Boston Veterans Affairs Healthcare System. His remarks are adapted from an accompanying editorial (JAMA. 2018;320[3]:225-6).

Independent analysis confirms industry trial findings

// *continued from page 1*

the studies, which the FDA required after it put the black box warning on the combination products.

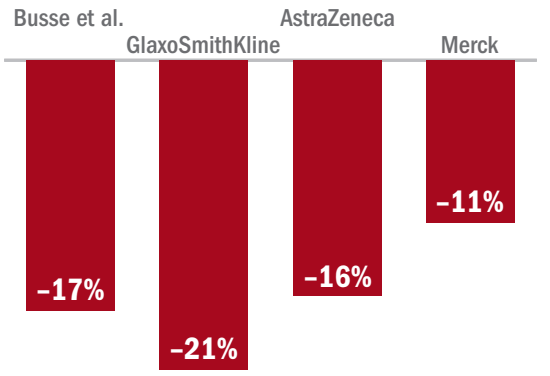
In 2010, the FDA advised that LABAs shouldn't be used as first-line therapy for asthma and required a black box warning on all LABA-containing products. Despite an FDA-conducted meta-analysis that found no increase in serious asthma-related incidents, the agency said there wasn't enough subgroup evidence to support the safety of LABAs when combined with an inhaled glucocorticoid.

"FDA stated that the small numbers of patients who were enrolled in these studies prevented a definitive conclusion regarding mitigation of serious asthma-related events with the addition of inhaled glucocorticoids," the investigators stated.

The agency required the four companies marketing a LABA for asthma to conduct prospective randomized trials comparing the safety of LABA/inhaled glucocorticoid to inhaled glucocorticoid alone. The trials by AstraZeneca, GlaxoSmithKline, Merck, and Novartis were identical. Three had complete, 26-week data; Novartis submitted partial data, as it withdrew its product from the American market in 2015. The committee reviewed all of the studies, which comprised a total of 36,010 teens and adults (aged 12-91 years). The primary endpoint was a composite of asthma-related intubation or death; secondary endpoints were a composite of hospitalization, intubation, or death, and individual assessments of each of those events.

Decreased risk of asthma exacerbation

LABA/inhaled glucocorticoid vs. glucocorticoid alone



MDedge News

Note: Busse et al. based on data for 36,010 teens and adults from the three studies shown plus a Novartis trial.

Source: N Engl J Med. 2018;78:2497-505

Among the four studies, there were three asthma-related intubations: two in the inhaled-glucocorticoid group and one in the combination-therapy group. There were also two asthma-related deaths, both in the combination group.

Serious asthma-related events occurred in 108 of the inhaled glucocorticoid group (0.60%) and in 119 of the combination-therapy group (0.66%), a nonsignificant difference.

However, the combination therapy did confer a significant 17% reduction in asthma exacerbations. Exacerbations occurred in 11.7% of the inhaled glucocorticoid group and in 9.8% of the combination therapy group (relative risk 0.83; *P* less than 0.001). All four trials showed a similarly decreased risk of exacerbation.

The committee looked at several subgroups, dividing the cohort by age, race/ethnicity/ obesity, and smoking history. The advantage associated with combination therapy remained significant in all these analyses.

"… Our data provide support for the treatment guidelines of both the Global Initiative for Asthma and the Expert Panel Report 3 of the National Asthma Education and Prevention Program, which recommend the use of a low-dose glucocorticoid (step 3) and a medium-dose glucocorticoid (step 4), plus a LABA, with the caution that LABAs should not be used as monotherapy in asthma; the convenience and safety of a combination inhaler is a likely plus," the committee wrote. "Finally, our combined analysis provides strong evidence to support the recent FDA decision to remove the boxed safety warning for combination therapy with a LABA plus an inhaled glucocorticoid for asthma treatment."

Dr. Busse disclosed financial relationships with a number of pharmaceutical companies, including Novartis, but noted that none of them were relevant to this work.

msullivan@mdedge.com

SOURCE: Busse WW et al. N Engl J Med. 2018;78:2497-505.

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.

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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

GlaxoSmithKline
Research Triangle Park, NC 27709

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Project aims to identify and categorize pulmonary hypertension phenotypes

BY DOUG BRUNK
MDedge News

SAN DIEGO – A massive effort to better understand and treat patients with pulmonary hypertension and right heart dysfunction is underway.

The endeavor, funded by the National Heart, Lung, and Blood Institute and the Pulmonary Hypertension Association and known as Redefining Pulmonary Hypertension Through Pulmonary Vascular Disease Phenomics (PVDOMICS), began recruiting participants in 2017, with a goal of 1,500 by 2019. The aim is to perform comprehensive phenotyping and endophenotyping across the World Health Organization–classified pulmonary hypertension (PH) clinical groups 1 through 5 in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with pulmonary vascular disease.

At an international conference of the American Thoracic Society, one of the study's investigators, Robert P. Frantz, MD, discussed the role of echocardiography and MRI in the overall PVDOMICS program, which he characterized as a work in progress. "Imaging is critically important as we try to integrate severity of pulmonary vascular disease along with how well the ventricle functions as way to try and understand why some patients have a failing RV [right ventricle] at a given pulmonary resistance and others don't," said Dr. Frantz, who directs the Mayo Pulmonary Hypertension Clinic in Rochester, Minn. The goals are to be able to integrate cardiac morphology and function with contemporaneous hemodynamics, he said. This will allow for validation of noninvasive hemodynamics versus right heart catheterization across all the phenotypes.

"In addition, we'll have imaging parameters as predictors of hemodynamics at rest and with exercise, particularly in conditions like heart failure with preserved ejection fraction or concerns about left atrial stiffness," he said. "In these cases, our ability on the basis of echocardiography or MRI to guess what the wedge pressure is at rest or exercise, or to think about other more recently described phenotypes like left atrial stiffness in patients who have left atrial ablation procedures, will be enabled by looking at parameters such as left atrial strain."

Ultimately, he continued, a key goal of PVDOMICS is to be able to correlate the "-omics" with markers of RV compensation in an effort to understand what the determinants of RV compensation are across the varying types of pulmonary vascular disease.

To illustrate how this research might lead to new therapies, Dr. Frantz cited findings from researchers who set out to identify and characterize homogeneous phenotypes by a cluster analysis in scleroderma patients with pulmonary hypertension, who were identified from two prospective cohorts in the United States and France (PLoS ONE. 2018 May 15;13[5]:e0197112).

The researchers identified four different clusters of scleroderma patients: those with mild to moderate PH with no or minimal interstitial lung disease and low diffusing capacity for carbon monoxide; those with precapillary PH with severe ILD and worse survival; those with severe PH, who trended toward worse survival, and those similar to the first cluster but with higher DLCO.

Other parameters that can be analyzed include ventricular fractional area change, tricuspid annular plane systolic excursion, and RV free wall strain. "That strain of the right ventricle is one of the most important ways of looking at how the right ventricle works," Dr. Frantz said. "With this, we can integrate the concept of severity of RV dysfunction with severity of pulmonary vascular disease. This is where the rubber hits the road. It's going to be very complicated and time consuming, but I think critically important. Ultimately, we can make proteomic heat maps that track these correlates, and ultimately identify pathways that may be driving RV compensation in pulmonary vascular disease."

Dr. Frantz reported having no relevant financial disclosures.

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Alert highlights potential neuropsychiatric side effects

// *continued from page 1*

of hypoglycemia and carefully monitor blood glucose levels in these patients and discuss with them how to treat themselves if they have symptoms of hypoglycemia. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose. Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances and switch to a non–fluoroquinolone antibiotic if possible. Stop fluoroquinolone treatment immediately if a patient reports serious side effects involving the tendons, muscles, joints, or nerves, and switch to a non–fluoroquinolone antibiotic to complete the patient's treatment course."

The statement also warned not to prescribe fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections because the risks outweigh the benefits in these patients.

The FDA conducted the postmarketing review on all five of the fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin). The newest fluoroquinolone, delafloxacin, approved a year ago, was not included in the class review. However, the agency expects that similar adverse events will be associated with delafloxacin and labeling on that drug will include the new warnings.

The agency reviewed cases in the FDA Adverse Event Reporting System, and in published medical literature, during 1987-2017. Most of the incidents (56) were in the system; 11 additional cases were published. Levofloxacin caused most of the incidents (44), followed by ciprofloxacin (12), moxifloxacin (9), and ofloxacin (2). Four of the fluoroquinolones have a labeled drug interaction with sulfonylurea agents, which can cause hypoglycemia.

Some of those who died were getting the antibiotics for complicated infections, including urinary tract and upper respiratory tract infections, and postoperative antibiotic prophylaxis. Others had renal insufficiency – a risk factor for hypoglycemia.

Of the 54 patients who survived, 9 never fully recovered and had permanent disabilities. Four patients remained in a coma for at least 1 month, despite blood sugar normalization. Five experienced some type of neurologic injury.

The new label changes will also fortify the existing warning about mental health side effects, after the review found new reactions that are not listed in the current warning, including the new reports of disturbance in attention, memory impairment, and delirium.

The statement warned physicians not to prescribe fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

"In an effort to harmonize the psychiatric adverse reactions described in the drug labels across the class of fluoroquinolones, we are requiring that all fluoroquinolones include six psychiatric adverse reactions (disturbance in attention, memory impairment, delirium, nervousness, agitation, and disorientation) in the Central Nervous System Effects of the Warnings and Precautions section of the labels. Disturbance in attention, memory impairment, and delirium are new adverse reactions to be added to the labels of the entire class of fluoroquinolones. Nervousness, agitation, and disorientation had been previously listed in the fluoroquinolone drug labels and will now be added to the Warnings and Precautions section of each drug label to harmonize labels across the fluoroquinolone drug class."

The FDA has previously warned about other adverse events associated with fluoroquinolones in May 2016, restricting use for certain uncomplicated infections; July 2016, for disabling side effects; August 2013, for peripheral neuropathy; and July 2008, for tendinitis and tendon rupture.

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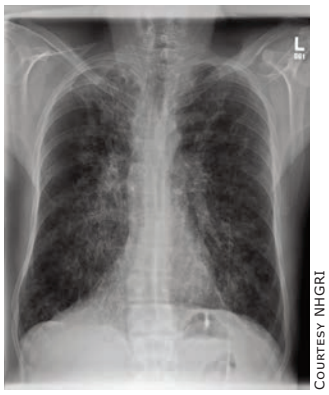
Delayed CF diagnosis portends worse prognosis

BY BIANCA NOGRADY
MDedge News

Older age at diagnosis, diabetes, and poorer lung function are all predictors of reduced survival among adults diagnosed with cystic fibrosis (CF), new research suggests.

A growing number of people with cystic fibrosis are diagnosed in adulthood, partly because of increased awareness among physicians of variations in disease presentation, more accessible genotyping, and easier diagnostic criteria.


COURTESY NHGRI

Adult-diagnosed cystic fibrosis patients generally have a milder form of the disease than that of those diagnosed in childhood; however, less is known about their prognosis and life expectancy.

Researchers reported the outcomes of a retrospective cohort study of 362 adults diagnosed with cystic fibrosis at age 18 years or older. The median age at diagnosis was 34.3 years, and 71% of patients presented with pulmonary and/or gastrointestinal symptoms. The study was published in Annals of the American Thoracic Society.

The patients were followed for a median of 7.7 years, during which time there were 15 lung transplants and 33 deaths without transplant. Overall, 10-year lung transplant–free survival was 87.7%, and 15-year survival was 86.1%.

Those who were diagnosed young and who had higher lung function had the best median survival times. For each 5-year increase in age at diagnosis, the risk of death or transplant increased by 24%, and for each 5% decrease in forced expiratory volume in 1 second (FEV_1), the risk was 35% higher.

Individuals who had diabetes at baseline had a more than fourfold higher risk of death or transplant than did those without diabetes.

"While newborn screening programs will reduce the rate of missed diagnoses in the future, clinicians still need to consider CF as a possible diagnosis if individuals are presenting with suspicious CF symptoms (e.g., GI or pulmonary symptoms) during adulthood, particularly if born prior to the introduction of newborn screening in their jurisdiction," wrote Sameer Desai, of the University of British Columbia, Vancouver, and his coauthors.

Commenting on the association with diabetes, the authors noted that this finding had some uncertainty but suggested the additional inflammatory burden could increase the risk of death in individuals with cystic fibrosis.

The authors highlighted that fewer than 5% of people with adult-diagnosed cystic fibrosis had two copies of the F508del mutation, which is associated with severe, early-onset disease. However, those who were homozygous for that mutation tended to be diagnosed at a younger adult age, had worse nutritional status and a lower FEV_1 percent predicted, compared with the overall adult-diagnosed population.

"This finding suggests potential delays in CF diagnosis for these people leading to worse outcomes," the authors wrote.

The researchers also identified 25 individuals who had a possible unconfirmed diagnosis based on the most recent cystic fibrosis diagnostic guidelines. These individuals were either asymptomatic or had unknown symptoms, had sweat chlorides at or below 60 mmol/L (where available), and either unknown or two non–cystic fibrosis–causing mutations. They were also more likely to be male, to be nonwhite, to have increased unknown mutations, and to be pancreatic sufficient, compared with individuals with a confirmed diagnosis.

The study looked at whether *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex increased the risk of transplant or death, but found these did not significantly predict survival.

"Adult CF clinicians can use this information to educate newly diagnosed adults with CF about their prognosis and to guide treatment decisions, specifically those at high-risk for a worse prognosis," the authors wrote.

The study was partly funded by the Rare Disease Foundation. Two authors declared support from Cystic Fibrosis Canada, but no other conflicts of interest were declared.

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SOURCE: Desai S et al. Ann Am Thorac Soc. 2018 Jun 26. doi: 10.1513/AnnalsATS.201801-037OC.

For smokers, the ends may not justify the ENDS

BY RICHARD FRANKI
MDedge News

Smokers who used e-cigarettes and other electronic nicotine delivery systems (ENDS) were less likely to quit than were those who did not use such products, according to a 2015 survey and a follow-up conducted a year later.

"Under 'real world' use and conditions [ENDS] may have suppressed or delayed quitting among some adult smokers," Scott R. Weaver, PhD, and his associates at Georgia State University, Atlanta, wrote in PLoS ONE. The original survey, conducted in August and September of 2015, involved 1,284 U.S. adult smokers from the GfK KnowledgePanel, of whom 858 completed the follow-up survey in September 2016.

Smokers who used ENDS at baseline were slightly more likely to attempt to quit (53.7%) than were those who did not (48.6%) but were much less likely to have quit (defined as no smoking for at least 30 days at the time of follow-up): 9.4% vs. 18.9%, for an adjusted odds ratio of 0.30. Those who used ENDS at any time during the study were much more likely than were non-ENDS users to make an attempt (58.5% vs. 44.4%), but they were, again, much less likely to succeed (7.7% vs. 22.2%; AOR, 0.25), the investigators reported.

The results were similar for the subset of respondents who smoked every day: ENDS users were more likely to attempt to quit but less likely to succeed. Odds ratios for quitting were 0.37 for those using ENDS at baseline and 0.36 for those who used ENDS at any time since the first survey, Dr. Weaver and his associates said.

"Use of current ENDS products in real world conditions [does] not seem to improve the chances of quitting for smokers, and, under the current landscape, may not be the disruptive technology that increases the population quit rate and reduces the harm of combustibles," they wrote.

The study was supported by the National Institute of Drug Abuse and the Food and Drug Administration's Center for Tobacco Products. One of the investigators has received funding in the form of grant funding from Pfizer and the National Institutes of Health and another has served as a paid consultant to the Centers for Disease Control and Prevention.

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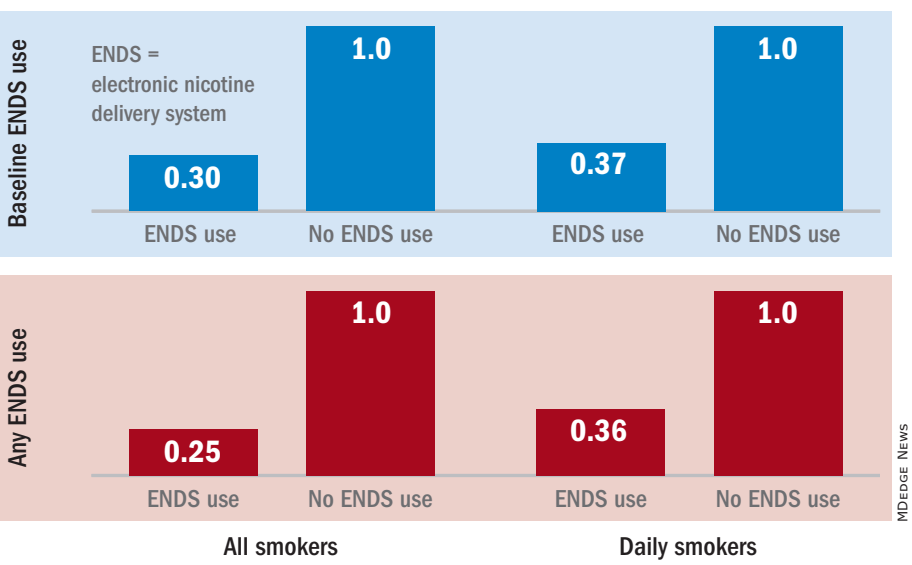
SOURCE: Weaver SR et al. PLoS ONE. 2018 Jul 9;13(7): e0198047. doi: 10.1371/journal.pone.0198047.

Odds ratios of not smoking for ≥30 days at follow-up



Note: 858 respondents to the original survey in 2015 completed the follow-up a year later.
Source: PLoS ONE. 2018 Jul 9:13(7): e0198047

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

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[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.

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REM sleep disorder linked to synucleinopathies

BY M. ALEXANDER OTTO
MDedge News

LOS ANGELES – At least 70% of patients with idiopathic REM sleep behavior disorder will develop a neurodegenerative disease within about a decade, according to a years-long, multicenter investigation of 1,280 patients – the largest study of the issue to date.

REM sleep behavior disorder (RBD) has been known for years to increase the risk for synucleinopathies, namely Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. However, previous studies have mostly been conducted at single institutions, so the exact extent to which RBD increases the risk wasn't clear.

The new investigation lays the issue to rest. It nailed "down a precise and generalizable" estimate, according to lead investigator Ronald Postuma, MD, a movement disorder specialist at McGill University, Montreal. "What we found overall is that the risk is 6.3% per year; 50% of patients phenoconvert at 7.5 years, and at 12 years, we are up to 73%. This is quite striking. The bottom line is, if you have a patient with polysomnographic-proven RBD in front of you, you are talking to [someone] destined to develop a neurodegenerative disease in the next 10-12 years," he said.

These findings have important implications for the field. Now that it's known who's at risk, "we have a chance to do neuroprotective therapy. It's time to move forward and start preventing disease," Dr. Postuma said at the American Academy of Neurology annual meeting. He estimated that it would take only a few hundred patients to do a 2-year trial of neuroprotective therapy.

The 1,280 study subjects were selected from 24 sleep centers on four continents, all of them participants in the international RBD study group. The patients needed for a trial "are sitting right now" in the study group, "so maybe we can get on with this," he said.


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Dr. Ronald Postuma declared, "It's time to move forward and start preventing disease."

REM sleep – the dream state – normally paralyzes people, but something breaks down in RBD, and people act out their dreams, sometimes to disturbing effects. It occurs in about 1% of the population, usually in older people and in slightly more men than in women.

The risk of neurodegenerative disease in RBD increases even more if patients test positive at baseline for movement declines, cognitive issues, olfactory problems, constipation, color vision loss, erectile dysfunction, or abnormal dopamine transporter scans. Dr. Postuma and his team found no predictive value for somnolence, insomnia, urinary problems, depression, or anxiety. These negative findings were surprising, he said, because mood disorders and sleep troubles are known to increase the risk in the general population.

The subjects all had polysomnographic-proven RBD at baseline without neurodegenerative disease. Most of them were men and were about 70 years old, on average. Subjects were tested for synucleinopathies and risk variables annually. The mean disease-free follow-up was about 4 years but ranged out to 19 years. Risks were adjusted for age, sex, and study center.

Cognition deficits were the only thing that distinguished future dementia patients from those destined for movement disorders. "Everything [else] is really the same between who gets dementia and who gets Parkinsonism," Dr. Postuma said.

The study was funded by the Canadian Institute of Health Research and the Fonds de la Recherche Sante Quebec. Dr. Postuma disclosed consulting, speaking for, and receiving other fees from Biotie, Roche/Prothena, Teva Neurosciences, Novartis Canada, Theranexus, Jazz Pharmaceuticals, and GE HealthCare.

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SOURCE: Postuma R et al. AAN 2018, Plenary session.

Reduced waking theta activity found in depressed patients

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Disruption of slow-wave activity may potentially explain the positive influence that sleep deprivation may have on major depressive disorder, according to results of a study presented at the annual meeting of the Associated Professional Sleep Societies.

Jennifer Goldschmied, PhD, of the University of Pennsylvania, Philadelphia, reported preliminary results of a study of disruption of slow-wave activity (SWA) in 26 subjects – 12 healthy controls and 14 people diagnosed with major depressive disorder (MDD) – that found a significant decrease of about 20% in waking theta activity, as measured with EEG, in the MDD group. In the 3-night sleep study, conducted at the University of Michigan, Ann Arbor, an adaptation night was followed by baseline and SWA disruption nights with EEGs performed each night. After the baseline night, patients also had a morning and afternoon EEG.

Across the baseline day, patients with depression showed "no modulation of theta activity whatsoever," Dr. Goldschmied said. "And then we see, following slow-wave disruption, a significant decrease in theta activity," whereas healthy controls showed no change in waking theta following slow-wave disruption. "So what this means is that the presence of SWA may actually be facilitating the reduction of theta or sleep propensity during typical sleep in healthy individuals," she added. In MDD patients, the decline in theta power following slow-wave disruption was from about 5.4 to 4.3.

Dr. Goldschmied noted that this finding somewhat supports what is known as the synaptic homeostasis hypothesis that University of Wisconsin researchers Giulio Tononi, MD, PhD, and Chiara Cirelli, MD, PhD, reported (Brain Res Bull. 2003;62:143-50). This hypothesis holds that SWA is a marker of synaptic strength and promotes the downscaling of synaptic strength during sleep. No method for measuring synaptic strength in humans exists, Dr. Goldschmied added, but waking theta can be considered a proxy for net synaptic strength across the cortex.

Dr. Goldschmied noted other research that has found SWA disruption improves mood (Psychiatry Res. 2015;228:715-8; J Psychiatr Res. 2011;45:1019-26), but the study she reported on found no role of decreased theta activity in that change. "To go even further," she said, "we looked at the entire data set and found no relationship between the decrease in theta and any of the measures of sleep architecture – so there's really no way to predict this decrease in our sample of people with depression."

SWA plays a significant role in depression and merits more study, Dr. Goldschmied said. She noted that future research should examine the effects of SWA disruption in a larger sample, investigate theta findings with other proxy measures of synaptic strength such as brain-derived neurotrophic factor and transcranial magnetic stimulation, explore differences in SWA between sexes, and explore how SWA enhancement influences mood and theta activity.

Dr. Goldschmied reported having no financial relationships.

SOURCE: Goldschmied J et al. Sleep 2018, Abstract 0245.

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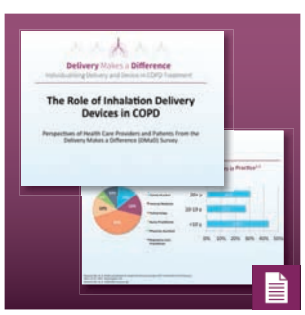

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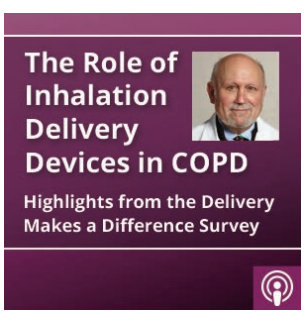

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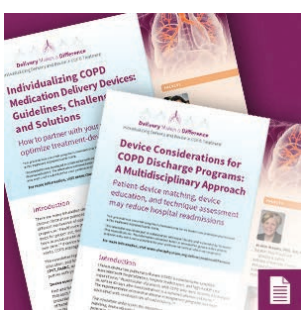

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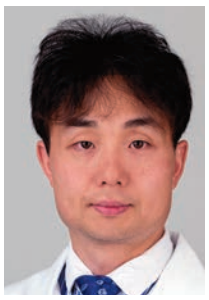
Trial finds OSA associated with larger aortic diameter

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Individuals with moderate to severe obstructive sleep apnea were found to have slightly larger ascending aortic diameters and thus may be at a heightened risk of cardiovascular events, according to an analysis of a national, multisite research study presented at the annual meeting of the Associated Professional Sleep Societies.


DR. KWON

"Sleep apnea severity is associated with increased thoracic aortic size, particularly in women," Younghoon Kwon, MD, assistant professor of cardiovascular medicine at the University of Virginia Health System, Charlottesville, said in presenting the results. "However, obstructive sleep apnea severity was not associated aortic pulse-wave velocity or aortic distensibility."

The study evaluated a subgroup of 708 patients with no history of cardiovascular disease (CVD) from the Multi-Ethnic Study of Atherosclerosis (MESA).

Dr. Kwon noted that previous studies have shown that patients with thoracic aortopathy have a high rate of obstructive sleep apnea (OSA) (Am J Respir Crit Care Med. 2003;168:1528-31) and that those with OSA tend to have higher thoracic aortic size (J Am Coll Cardiol. 2008;52:885-6).

"There's also a degree of evidence suggesting that OSA is associated with high arterial stiffness, which is a marker of primary organ damage and a major cardiovascular risk that is predictive of cardiovascular disease," Dr. Kwon said (J Intl Med Res. 2011;39:228-38).

However, he also noted that some studies have found no relationship between OSA and aortic disease (Respiration. 2006;73:741-50). "The question can be raised as to whether sleep apnea may have implications" in thoracic aortic disease, he said.

Dr. Kwon's study evaluated three groups: patients with no OSA (apnea hypopnea index [AHI] less than 5, n = 87), mild OSA (AHI 5-15, n = 215), and severe OSA (AHI greater than 15, n = 406). All patients had polysomnography as part of an ancillary study. Cardiac MRI measured these three features of aortic function and physiology (unadjusted results):

- Diameter at the pulmonary artery bifurcation, which ranged from 3.13 cm in patients with no OSA to 3.37 cm in those with severe OSA (P = .0017).
- Pulse wave velocity, which averaged 8.07 m/s in the no-OSA group and 9.11 m/s in the severe group (P less than .0001).
- Distensibility, or aortic stiffness, which was 1.73% per mm Hg in the no-OSA group, 1.54% per mm Hg in the mild group, and 1.68% per mm Hg in the severe group (P = .0141).

"There was maybe some higher pulse wave velocity across the significant OSA group," Dr. Kwon said. "However, with aortic distensibility, there did not seem to be any significant trend."

In the adjusted analysis of aortic diameter, "there did appear to be a small but significant difference in the significant OSA group, compared with the reference group," Dr. Kwon said. He also noted that women with OSA typically had significantly larger aortic diameters than did non-OSA counterparts, whereas that trend was not as pronounced in men.

"Thoracic aorta size does seem to increase with OSA severity, but this has a sex-interaction component; it's more pronounced in women," Dr. Kwon said. He also noted a discrepancy in the results: "The functional properties of the aorta did not seem to bear a significant association with OSA severity."


monkeybusinessimages/Getty Images

In explaining why these results differed from previous studies, Dr. Kwon said that the study populations or their characteristics may be the cause or that MRI-based measures of aortic properties have not been extensively studied before.

"This is probably the first study to look at an unselected population, use a large sample size that was ethnically diverse, and use cardiac MRI technology," he said.

Limitations he noted were the study's cross-sectional nature and its small population of patients with enlarged thoracic aorta size, which left it underpowered to evaluate that population.

Dr. Kwon reported having no financial relationships.

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SOURCE: Kwon Y et al. SLEEP 2018, Abstract 0465.

Phase 3 trial: Tasimelteon effective for jet lag disorder

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Tasimelteon, a drug approved for non–24-hour sleep-wake disorder, has been shown to increase sleep times in travelers with jet lag, according to results from a phase 3 trial.

"Tasimelteon demonstrated an increase in total sleep time of 85 minutes versus placebo and also demonstrated improvement in next-day alertness versus placebo," Christos Polymeropoulos, MD, medical director of Vanda Pharmaceuticals, said in presenting results of the JET8 trial during the late-breaking abstracts session at the annual meeting of the Associated Professional Sleep Societies.

Tasimelteon, sold under the trade name Hetlioz, is a melatonin receptor agonist that is Food and Drug Administration–approved for non–24-hour sleep-wake disorder – but not for treatment of jet lag disorder (JLD). Dr. Polymeropoulos noted there is no FDA-approved treatment for JLD.

JET8 induced the circadian challenge equivalent to crossing eight time zones. The study involved 318 individuals randomized evenly to 20 mg tasimelteon or placebo 30 minutes before bedtime. The primary endpoint of the study was total sleep time in the first two-thirds of night measured by polysomnography.

Those on tasimelteon averaged 216.4 minutes of total sleep time in the first two-thirds of night versus 156.1 for those on placebo (P less than .0001), Dr. Polymeropoulos said. Full total sleep times were 315.8 minutes versus 230.3 minutes (P less than .0001), respectively.

"For total sleep time, the tasimelteon subjects gained about an hour and a half, as measured by PSG [polysomnography]," Dr. Polymeropoulos said.

Other key markers the trial measured were latency to persistent sleep and wakefulness after sleep onset. They measured 15 minutes less and 74.6 minutes less, respectively, in the tasimelteon arm.

Dr. Polymeropoulos also disclosed early results of a second trial of tasimelteon in JLD: the JET Study, a two-phase transatlantic travel study of 25 patients. The subjects were flown from four U.S. cities to London and then received tasimelteon or placebo for 3 nights.

The study was terminated before reaching its enrollment goal of 90 patients because of its complexity, Vanda said in a separate press release. Over 3 nights of study, the tasimelteon arm gained a total of about 130 minutes of sleep, Dr. Polymeropoulos said.

Vanda has said it plans to file a supplemental new drug application for tasimelteon for treatment of JLD in the second half of this year.

Dr. Polymeropoulos is an employee of Vanda Pharmaceuticals.

chestphysiciannews@chestnet.org

SOURCE: Polymeropoulos C et al. SLEEP 2018, LBA 2.

New insights into sleep, pregnancy weight gain

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Pregnant women who are overweight and obese are like the general population in that the less they sleep, the more weight they gain, particularly in the first half of pregnancy. Prolonged daily total eating time was not associated with gestational weight gain in these women, particularly early in pregnancy, according to findings from a small study presented at the Associated Professional Sleep Societies annual meeting.

Those findings point to a need to further study the early gestational period to better understand the relationship between sleep, metabolic function, and pregnancy, said Rachel P. Kolko, PhD, a postdoctoral scholar at the Western Psychiatric Institute and Clinic of the University of Pittsburgh.

DR. KOLKO

"The association with total sleep time was found to be significant, such that if you had less sleep, you had higher amounts of weight gain; we did not find a significant relation with our eating window variable," Dr. Kolko said.

She reported on research involving 62 pregnant women, 53% of whom were overweight with a body mass index of 25-29.9 kg/m^2 and 47% of whom were obese with BMI greater than 30. Nearly half of the study population were nonwhite.

The research grew out of a need to identify potentially modifiable factors to curtail excessive gestational weight gain during pregnancy, she said. The study hypotheses were that both shorter total sleep time and longer total eating time would lead to higher gestational weight gain, but the study confirmed only the former as a contributing factor.

The women in the study were at 12-20 weeks of pregnancy. Gestational weight gain was calculated as the difference between self-reported pre-pregnancy weight and current weight. Total sleep time was based on the Pittsburgh Sleep Quality Index, and total eating time was calculated as the time difference between the day's first meal or snack of more than 50 calories and the last, as self-reported.

Average total sleep time was 7.8 hours, with total eating time spanning 10.8 hours. On average, study participants gained 9.7 pounds through the first half of pregnancy, Dr. Kolko said. She noted that the Institute of Medicine, now known as the National Academy of Medicine, recommends that women who are overweight gain 15-25 pounds during pregnancy and women who are obese gain 11-20 pounds (JAMA. 2017;317:2207-25).

Dr. Kolko reported having no financial relationships to disclose.

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New generation sequencing for NSCLC cuts costs

BY SUSAN LONDON
MDedge News

Comprehensive testing of newly diagnosed metastatic non–small cell lung cancer (NSCLC) with next-generation sequencing (NGS) for known lung cancer–related genomic alterations is cost-saving relative to single-gene testing strategies and often faster, a new study finds.

"We know now that genomic testing for all patients with advanced NSCLC is the standard of care to help detect oncogenic drivers, to inform treatment decisions," lead study author Nathan A. Pennell, MD, PhD, codirector of the Cleveland Clinic lung cancer program, said in a press briefing leading up to the ASCO annual meeting. But the optimal strategy for this testing is unclear.

He and his colleagues conducted a decision analytic modeling study among hypothetical insurance plans having 1 million enrollees. Outcomes were compared between NGS testing and three single-gene testing strategies.

Data indicated that, compared with exclusionary, sequential, or hot-spot panel testing approaches, NGS testing simultaneously for eight genomic alterations having Food and Drug Administration–approved or investigational targeted therapies could save up to $2.1 million among Medicare beneficiaries and up to $250,842 among patients covered by commercial insurance. The costs to payers decreased as the percentage of patients receiving NGS testing increased. Moreover, the wait time for results was similar or roughly half as long with NGS.

In the CMS population, NGS testing would save about $1.4 million compared with exclusionary testing, more than $1.5 million compared with sequential testing, and about $2.1 million compared with panel testing.

"Our results showed that there were substantial cost savings associated with upfront NGS testing compared to all other strategies," Dr. Pennell said. "In addition, NGS had a faster turnaround time than either sequential or exclusionary testing, which is critically important for sick lung cancer patients, to make sure they get their treatment as quickly as possible. Waiting a month or longer is simply no longer viable for patients because they get sick very quickly and these treatments work very well."

Of note, the model indicated that some patients undergoing initial single-gene testing strategies never had their genomic alterations detected because tissue for testing ran out and they were too sick to undergo another biopsy.

"The bottom line is, ultimately, using the best single test upfront results in the fastest turnaround time, the highest percentage of patients with targetable alterations identified, and overall the lowest cost to payers," he summarized.

A major challenge in this population is going back and retesting for known or new genomic alterations, agreed ASCO President Bruce E. Johnson, MD, FASCO. "At our upcoming meeting, we are going to hear about *RET*, which may end up as a target and may therefore need to be tested for."

Recently, oncologists have a new attractive option of billing for NGS panels rather than for single gene tests, he noted.

"This study really shows that by doing all the testing at the same time, you can both get results back more quickly as well as get information," said Dr. Johnson, professor of medicine at the Dana-Farber Cancer Institute and a leader of the Dana-Farber/Harvard Cancer Center Lung Cancer Program, Boston. "This study looked at an NGS panel of 8 genes, but most of the NGS panels contain somewhere between 50 and 400 genes, so you get a lot more information with this at a cost that's competitive or less. So this will be welcome news to people who are ordering these gene panels."

Study details

For NSCLC, there are currently approved treatments that target alterations in *EGFR, ALK, ROS1*, and *BRAF*, and investigational treat-

Continued on following page

Cell-free DNA assays successfully detect lung cancer

BY SUSAN LONDON
MDedge News

CHICAGO – A set of blood-based assays that search for abnormalities in cell-free DNA shows moderately good sensitivity for detecting lung cancer in its early stages, according to the first interim report from a substudy of the large, ongoing Circulating Cell-Free Genome Atlas (CCGA).


DR. OXNARD


DR. GRAHAM

"Lung cancer screening with low-dose CT is known to improve outcomes. And yet, CT-based lung cancer screening is not widely adopted," said lead study author Geoffrey R. Oxnard, MD, associate professor of medicine at Dana-Farber Cancer Institute and Harvard Medical School, Boston, in a press briefing at the annual meeting of the American Society of Clinical Oncology, where the study was reported. "Criticisms of low-dose CT include the risk of false positives and overdiagnosis. We proposed to investigate an untapped opportunity for cancer detection, which is using cell-free DNA."

Main substudy results among 164 patients with lung cancer and 923 comparable individuals without known cancer showed that, at a specificity of 98%, the three assays evaluated detected up to 51% of early-stage (stage I-IIIA) lung cancers and up to 91% of late-stage (stage IIIB-IV) lung cancers. And among the healthy participants with false-positive results for lung cancer, several were ultimately found to have cancers of other types.

"This first interim analysis of the CCGA study demonstrates that comprehensive sequencing of the plasma cell–free DNA can generate high-quality data across the entire genome, and it permits noninvasive cancer detection. The assays can detect lung cancer across stages, across histologies, across populations," Dr. Oxnard said.

"Together, these results support the promise of using cell-free, DNA-based assays to develop an early cancer detection test with high specificity. Further assay and clinical development is ongoing: There is a separate prospective trial enrolling, the STRIVE study, and there remain thousands of patients still on this CCGA study to be analyzed for further optimization and focusing of this assay toward an eventual cancer diagnostic."

The cohort studied was not a screening population, so the assays' performance cannot be compared with that of low-dose CT at this point, he said. But the hypothesis going forward is that the assays will have comparatively higher specificity, sparing some patients an unnecessary diagnostic work-up.

The population in which the final blood test might be used will depend on its diagnostic performance once the assays are fully refined and clinic ready, which will take some time, according to Dr. Oxnard. However, "2 years ago, this was a pipe dream. Two years ago, it was completely just a brainstorm that had no data to support it, and I didn't believe that this could be done. Today, we actually have data to show that this is really feasible to find early-stage cancer in the blood. So this is a huge step forward and actually means that this is going to be a reality."

"This is an important first step toward an easier way to detect lung cancer at earlier and hopefully more curable stages," agreed ASCO Expert David Graham, MD, who is also medical director at the Levine Cancer Institute in Charlotte, N.C. "If the promise of this report holds, we could easily see a day when a person could be screened for lung cancer and possibly other cancers simply by going into their regular doctor's office for a blood draw."

Study details

The CCGA study has enrolled more than 12,000 of its planned 15,000 participants (70% with cancer, 30% without) across 142 U.S. and Canadian sites.

The substudy reported had a development cohort (118 patients with lung cancer, 561 individuals without cancer) and a validation cohort (46 patients with lung cancer, 362 individuals without cancer), with the lung cancer and noncancer groups matched on age, race, and body mass index. "Having a comparable control cohort is very important in developing such a diagnostic for accurate analysis of the potential false-positive rate," Dr. Oxnard noted.

Three prototype assays were tested: A targeted sequencing assay entailing very deep sequencing across 507 genes for somatic mutations such as single-nucleotide variants and small insertions and/or deletions; a novel, whole-genome sequencing assay to detect somatic gene copy number changes; and a novel, whole-genome methylation sequencing assay to detect abnormal epigenetic changes.

Sequencing was also performed on DNA from white blood cells. "That's very important. The white blood cells are rich with mutations that can pollute the DNA and make you think that there is cancer present in the cell-free DNA," Dr. Oxnard explained. "You screen out this interference from the white blood cells and other biologic noise, and you are left with the final features: mutations, copy number variations, and methylation signatures that then go into the final assays being studied."

Results showed that when assay specificity was 98%, sensitivity for early-stage (stage I-IIIA) lung cancer ranged from 38% to 51%, and sensitivity for late-stage (stage IIIB-IV) lung cancer ranged from 87% to 91%.

Among five presumed cancer-free individuals having positive results on all three assays, two subsequently received a cancer diagnosis (one with stage III ovarian cancer, one with stage II endometrial cancer).

An additional 19 cancer types across all stages were tested in the CCGA substudy. Early results for breast, gastrointestinal, gynecologic, blood, and other cancers were also reported at the meeting (abstracts 536, 12021, and 12003).

Dr. Oxnard disclosed that he has a consulting or advisory role with AstraZeneca, Inivata, Boehringer Ingelheim, Takeda, Genentech/Roche, Novartis, Loxo Oncology, Ignyta, DropWorks, and GRAIL, and that he has patents, royalties, and/or other intellectual property with Chugai Pharmaceutical, Bio-Rad, Sysmex, and Guardant Health. The study was funded by GRAIL.

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SOURCE: Oxnard GR et al. ASCO 2018, Abstract LBA8501.

Continued from previous page

ments in clinical trials that target alterations in *MET, HER2, RET*, and *NTRK1*.

In the model Dr. Pennell and his colleagues developed, patients with newly diagnosed metastatic NSCLC received testing for programmed death ligand 1 (PD-L1) plus testing for the above known lung cancer–related genes using one of four strategies:

- NGS testing (testing of all eight genes plus *KRAS* simultaneously).
- Sequential testing (testing one gene at a time starting with *EGFR*).
- Exclusionary testing (testing for *KRAS* mutation, the most common genomic alteration, followed by sequential testing for changes in other genes only if *KRAS* was not mutated).
- Hot-spot panel testing (combined testing for *EGFR, ALK, ROS1*, and *BRAF*), followed by either single-gene or NGS testing for alterations in other genes.

Model results indicated that among 1 million hypothetical plan enrollees, 2,066 patients covered by the Centers for Medicare & Medicaid Services and 156 covered by U.S. commercial insurers would have newly diagnosed metastatic NSCLC and therefore be eligible for testing.

Estimated time to receive test results was 2 weeks for NGS testing and for panel testing, compared with 4.7 weeks for exclusionary testing and 4.8 weeks for sequential testing.

In the CMS population, NGS testing would save about $1.4 million compared with exclusionary testing, more than $1.5 million compared with sequential testing, and about $2.1 million compared with panel testing. In the commercial health plan cohort, NGS would save $3,809 compared with exclusionary testing, $127,402 compared with sequential testing, and $250,842 compared with panel testing.

Dr. Pennell disclosed that he has a consulting or advisory role with AstraZeneca, Lilly, and Regeneron, and that his institution receives research funding from Genentech, NewLink Genetics, Clovis Oncology, Astex Pharmaceuticals, Celgene, AstraZeneca, Pfizer, and Merck. The study received funding from Novartis.

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SOURCE: Pennell NA et al. ASCO Annual Meeting, Abstract 9031.

FDA approves minimally invasive endobronchial valve to treat severe emphysema

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved the Zephyr endobronchial valve system for those with severe emphysema who are experiencing difficulty breathing. The valve is the first minimally invasive device approved in the United States for treating such patients, according to Pulmonx, the device manufacturer.

The FDA previously granted the novel device expedited review, as patients who did not respond to drug treatment had only limited alternative options, including lung volume reduction and lung transplant, Tina Kiang, PhD, of the FDA's Center for Devices and Radiological Health, said in a press release. "This novel device is a less invasive treatment that expands the options available to patients," said Dr. Kiang, acting director of the center's Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices.

The device, which is the size of a pencil eraser, is designed to prevent air from entering the damaged parts of the lung but to allow trapped air and fluids to escape. It is placed into the damaged areas of the lung using a flexible bronchoscope.

The valve is contraindicated in patients with active lung infections; those allergic to nitinol, nickel, titanium, or silicone; and active smokers.

The approval is based on a multicenter study of 190 patients with severe emphysema. A total of 128 received Zephyr valves and medical management, while 62 received medical management only. The primary measure was the number of patients who achieved at least a 15% improvement in their pulmonary function score: At 1 year, 47.7% of the Zephyr valve patients had achieved such improvement versus 16.8% of the control group, according to the FDA.

Adverse events included death, pneumothorax, pneumonia, worsening of emphysema, coughing up blood, shortness of breath, and chest pain. The valve is contraindicated in patients with active lung infections; those allergic to nitinol, nickel, titanium, or silicone; and active smokers.

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Tools needed to triage ED sepsis patients for discharge

BY DOUG BRUNK
MDedge News

SAN DIEGO – More than 16% of emergency department sepsis patients are not admitted to the hospital, preliminary results from a large, retrospective cohort study found.

"Nothing is really known about this topic," lead study author Ithan D. Peltan, MD, said in an interview at an international conference of the American Thoracic Society. "In previous research, we've been focused on patients with sepsis who are admitted to the hospital. We have never thoroughly recognized that a fair number of patients who meet clinical criteria for sepsis in the emergency department are actually triaged to outpatient management. We don't really know anything about these patients. What are their clinical characteristics and what are the factors that are leading them to be discharged from the ED rather than be admitted to the hospital?"

To find out, he and his associates retrospectively reviewed the medical records of 12,002 adult ED patients who met criteria for sepsis at two tertiary hospitals and two community hospitals in Utah between July 2013 and December 2016. They excluded trauma patients, those who left the ED against medical advice, those who were discharged to hospice or who died in the ED, and eligible patients' repeat ED encounters. Patients transferred to another acute care facility were considered admitted, while transfers to nonacute care such as skilled nursing or psychiatric facilities were classified as discharges. Next, Dr. Peltan and his associates employed inverse probability weights using a propensity score for ED discharge based on age, sex, Charlson score, ED acuity score, initial ED vital signs, white blood cell count, lactate, sequential organ failure assessment (SOFA) score, busyness of the ED, and study hospital to compare 30-day mortality between patients admitted to the hospital versus those discharged from the ED.

Doug Brunk/MDedge News

Dr. Ithan D. Peltan

Of the 12,002 patients included in the analysis, 10,032 (83.6%) were admitted, while 1,970 (16.4%) were discharged. Compared with admitted patients, discharged patients were younger (a mean of 53 vs. 60 years, respectively; *P* less than .001); more likely to be female (65% vs. 55%; *P* less than .001); more likely to be nonwhite or Hispanic (21% vs 17%; *P* less than .001), and had fewer comorbidities and physiologic derangements. In addition, crude mortality at 30 days was lower in discharged versus admitted patients (1.0% vs. 6.2%, respectively; *P* less than .001). After the propensity-adjusted analysis, there was no significant difference in 30-day mortality for discharged versus admitted sepsis patients (adjusted odds ratio 1.0).

"We were worried that discharged ED sepsis patients were being mismanaged and weren't going to do well as similar patients who were admitted to the hospital," Dr. Peltan said. "This analysis is still a work in progress, but with that caveat, our findings so far suggest that physicians are making pretty good decisions overall."

The researchers also found that, among 89 ED physicians who cared for 20 or more eligible patients, some did not discharge any of their sepsis patients, while others discharged 39% of their sepsis patients. "That was surprising," Dr. Peltan said. "This could mean that some hospital sepsis admissions depend on physician practice style more than the patient's condition or treatment needs."

Researchers emphasized that they do not recommend routine outpatient management for individual sepsis patients. "Almost certainly, some of the discharged patients should have been admitted to the hospital." Dr. Peltan said. "I think there's still a lot of opportunity to understand who these patients are, understand why there is so much physician variation, and to develop tools to further optimize triage decisions."

The study was funded in part by the Intermountain Research and Medical Foundation in Salt Lake City. Dr. Peltan reported having no financial disclosures.

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SOURCE: Peltan ID et al. ATS 2018, Abstract A5994/702.

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]*

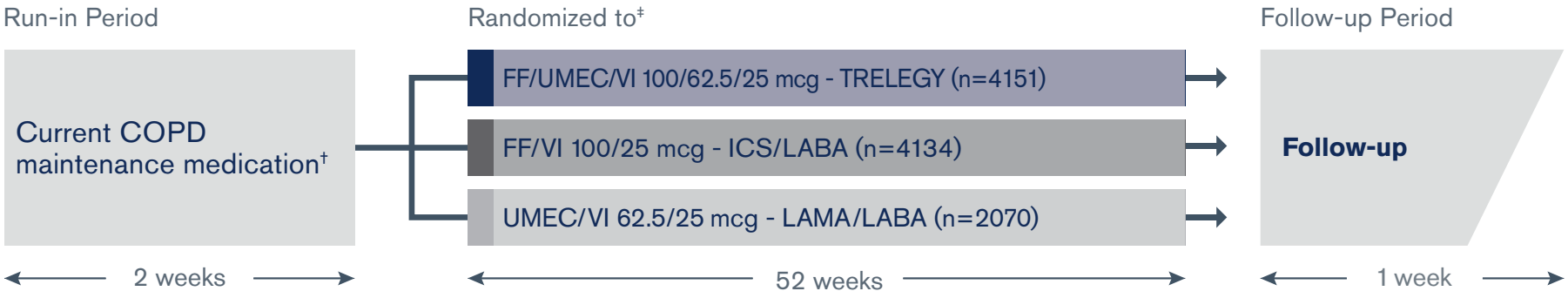
52-WEEK STUDY

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)

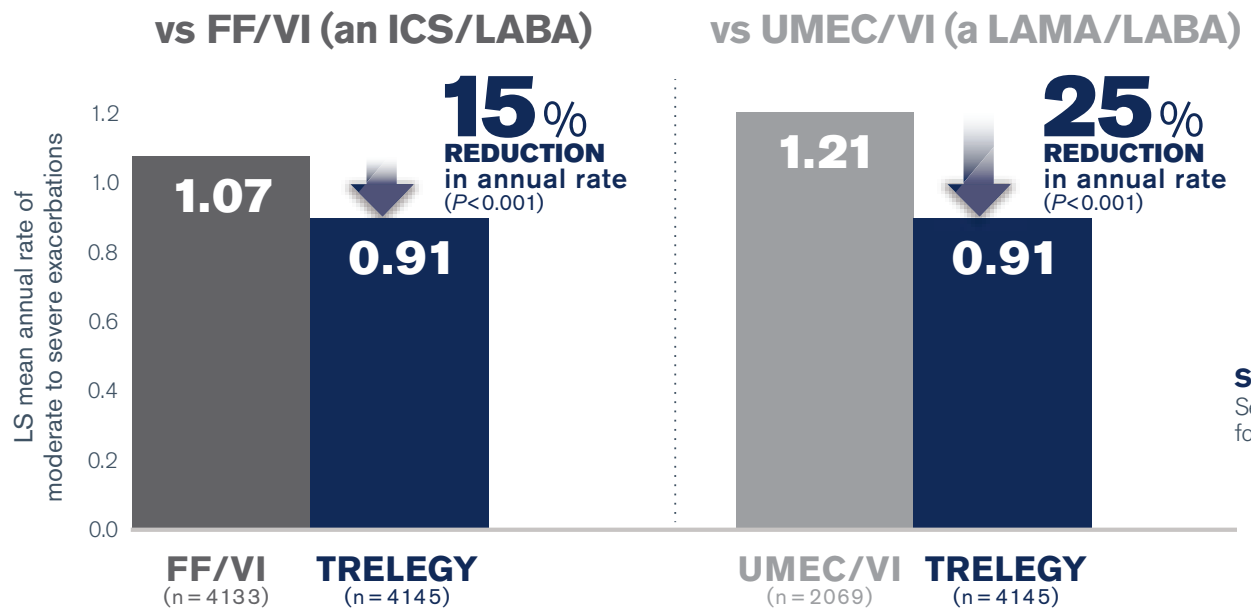
WARNINGS AND PRECAUTIONS (cont'd)

- 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

Printed in USA. 1004815R0 May 2018

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

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TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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

Protocol helped identify inpatient children at VTE risk

BY DOUG BRUNK
MDedge News

SAN DIEGO – Following simple institutional care guidelines helped clinicians identify pediatric patients at moderate-to severe risk of venous thromboembolism (VTE), results from a single-center study showed.

"Hospital-acquired VTE is on the rise in the pediatric population," lead study author Emily Southard, MD, said at the biennial summit of the Thrombosis & Hemostasis Societies of North America. "This consists of a DVT [deep vein thrombosis] or [pulmonary embolism] 48 hours or more after admission, or any time at the site of a central venous catheter."

One published study found a 70% increased incidence in the pediatric population for 2001-2007 (Pediatrics. 2009;124[4]:1001-8). More than half of the children in that study (63%) had at least one coexisting complex medical condition.

Hospital-acquired VTE cases tend to harbor a number of complications, said Dr. Southard, who is a pediatric hematology/oncology fellow at Children's Hospital Colorado, Aurora. Risk factors in pediatric trauma patients include ICU admission (odds ratio, 6.25), transfusion of blood products (OR, 2.1), lower extremity fracture (OR, 1.8), and neurosurgery (OR, 2.13). She and her associates hypothesized that understanding the relative contributions of clinical, biological, and genetic risk factors for pediatric VTE would help appropriately risk stratify patients and allow better prophylactic approaches.

In 2012, Children's Hospital Colorado implemented a VTE risk assessment tool as part of a hospitalwide patient safety initiative. The assessment is triggered via an Epic Best Practice Advisory to complete in certain higher-risk patients, including ICU patients, hematology/oncology floor patients, any patients with a central-line catheter, and those who are over age 12 and obese.

Risk factors in pediatric trauma patients include ICU admission, blood transfusion, and lower extremity fracture.

Clinicians also assess for risk factors such as significant infection, recent surgery, and personal or family history of thrombophilia. Next, they classify each patient's risk of hospital-acquired VTE as high, moderate, or low risk.

In a pilot study, Dr. Southard and her associates set out to validate the accuracy of the institution's VTE risk assessment tool since it was implemented in 2012. She presented findings from 215 hospital-acquired VTE cases in patients younger than age 18, compared with age-matched inpatient controls. Data from patients under 6 months of age are available after October 2016, coinciding with a change in definition of pediatric hospital-acquired VTE.

Most hospital-acquired VTE patients (77.2%) ranged in age from 1 to 17 years. The number of patients admitted for a trauma diagnosis was similar between VTE cases and controls (7.4% vs. 7.9%, respectively). However, compared with controls, a significantly greater number of VTE cases were immobile (41.8% vs. 10.3%, respectively), required ICU admission (86.4% vs. 26.5%), had a central venous catheter (80.4% vs. 10.9%), had a positive blood culture (16.7% vs. 1.9%), required surgery or a medical procedure (57.7% vs. 36.7%), and had a longer procedure time (a mean of 151 vs. 133 minutes).

Dr. Southard had no financial disclosures.

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SOURCE: Southard E et al. THSNA 2018.

Respiratory distress common in ED ambulatory setting

BY MADHU RAJARAMAN
MDedge News

Respiratory illness was the most common pediatric emergency in ambulatory settings, followed by psychiatric and behavioral illness, seizures, and syncope, according to results published July 20 in Pediatrics.

Investigators conducted a retrospective observational study of data from the Indianapolis emergency medical services (EMS) system between Jan. 1, 2012, and Dec. 31, 2014. All patients younger than 18 years were eligible.

Of 38,841 pediatric EMS transports in the Indianapolis metropolitan area during the 3-year period, fewer than 1% (322) were verified as originating from an ambulatory practice, reported Matthew L. Yuknis, MD, and his coauthors at Indiana University, Indianapolis. Respiratory distress was the most common emergency (58%), followed by psychiatric and behavioral illness (6%), seizure (6%), and syncope (5%).

The most common interventions were use of supplemental oxygen (27%), albuterol (26%), and intravascular access (11%). The most common critical care interventions were administration of fluid bolus (2%), benzodiazepine (2%), or racemic or intramuscular epinephrine (1%). None required use of an artificial airway, cardiopulmonary resuscitation, intraosseous access, or bag mask ventilation, Dr. Yuknis and his colleagues said.

The average time from call to on-scene arrival was 6 minutes (ranging from less than 1 to 15 minutes). The average patient transport time was 13 minutes (ranging from less than 1 to 38 minutes). The average annual frequency of pediatric outpatient emergencies was 42 emergencies per 100,000 people under 18 years of age. Lower socioeconomic status was correlated with increased frequency of emergencies in ambulatory settings, the authors reported.

"These findings update and clarify existing literature with regard to the frequency of pediatric emergencies in the ambulatory setting, the conditions these patients present with, and the use of EMS data to define these events," the authors wrote. Additionally, the findings can be used to "inform future decisions regarding necessary equipment and procedures."

No relevant financial disclosures were reported. There was no external funding.

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SOURCE: Yuknis ML et al. Pediatrics. 2018. doi: 10.1542/peds.2017-3082.

Two-thirds of pediatric asthma exacerbations triggered by one or more respiratory viruses

BY JILL D. PIVOVAROV
MDedge News

NATA_ZHEKOVA/THINKSTOCK

Children with asthma who present to emergency departments for treatment are significantly more likely to test positive for one or more respiratory pathogens, reported Joanna Merckx, MD, of the Montreal Children's Hospital at the McGill University Health Centre, and her associates.

Nearly two-thirds of patients tested positive for one or more respiratory viruses in a study conducted by Dr. Merckx and her associates. "Given the documented safety of influenza immunization in children with asthma and its expected protective effect," such cases should be among those prioritized to receive influenza immunization.

Multicenter, prospective study

Dr. Merckx and her associates conducted an ancillary multicenter, prospective, ethics-approved cohort study to identify a possible connection between diagnosed respiratory pathogens, severity of illness, and the overall risk of ED treatment failure using data from the DOORWAY (Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth) study.

Dr. Merckx and her colleagues sought to determine whether closely evaluating the effects of specific respiratory pathogens could be useful in further developing appropriate preventive treatments for children with asthma; improving efforts to diagnose pathogens at the time of ED treatment; and identifying patients at higher risk of treatment failure who could be candidates for more intensive treatment protocols.

Children aged 1-17 years presenting to one of five EDs in the Pediatric Emergency Research Canada network during 2011-2013 with moderate or severe asthma flares were considered for the study. All eligible DOORWAY study participants with a valid respiratory specimen were included in the study and received a standardized dose of oral and bronchodilator treatment with salbutamol; those with severe exacerbations also received ipratropium bromide (Atrovent).

Within 1 hour of study inclusion, patients were tested by way of nasopharyngeal aspirate or swab. Patients identified with coinfection presented with two or more pathogens. Failure of ED management was defined as patients admitted to the hospital for asthma; ED treatment lasting 8 or more hours after corticosteroid treatment; or returns to the ED within 72 hours after discharge that led to hospital admission or prolonged ED stay.

Study findings

Of 1,012 children enrolled in the study, 958 were assessed for worsening of asthma symptoms. Of the 958 respiratory specimens tested, 62% tested positive for one or more pathogens, 8.5% were found to have coinfection, of which respiratory syncytial virus (RSV) and coronavirus were the most frequent copathogens. Rhinovirus was the most prevalent pathogen, occurring in 29%, and of these, rhinovirus C was the most frequent species (18.2%), followed by RSV (17.9%); only two patients tested positive for *Mycoplasma pneumoniae*.

Children with a laboratory-confirmed pathogen were younger, had higher tobacco exposure, and were slightly more likely to present with fever (29% vs. 24%), compared with children without a laboratory-confirmed pathogen. Children with rhinovirus were less often febrile (16% vs 41%) and less frequently diagnosed with pneumonia (5% vs. 16%.) than those without a rhinovirus infection The proportion of children presenting with a severe exacerbation of asthma was 33%.

Overall, 17% of patients experienced treatment failure. Those with current respiratory infection were at increased risk of treatment failure, for a risk difference of 8% (95% confidence interval, 3.3%-13.1%). RSV, influenza, and parainfluenza virus (PIV) were associated with 21%, 38%, and 47% higher risks of treatment failure, respectively, noted Dr. Merckx and her associates. These resulted in absolute risks of 9%, 25%, and 34%, respectively, the authors reported in Pediatrics.

Coronavirus, adenovirus, enterovirus D68, and the presence of a coinfection, however, were not found to increase the risk of treatment failure, they noted.

Although rhinovirus may play a role in triggering reactions that require medical attention, such cases still appear to respond favorably to treatment, they said.

Confirmation of findings

A separate study cited by Dr. Merckx and her associates observed the same outcome for rhinovirus patients but more patients diagnosed with nonrhinovirus pathogens, especially human metapneumovirus (hMPV) and PIV, had moderate, rather than severe, symptoms and were much more likely to experience higher treatment failure, particularly those infected with RSV, influenza, and PIV.

"It appears reasonable to pursue strategies to improve immunization coverage for influenza and invest in efforts for the development of vaccines for RSV and rhinovirus," they said.

In cases in which respiratory pathogens were present (especially nonrhinovirus pathogens), greater treatment failure occurred, despite use of inhaler and corticosteroids. The researchers noted that severity of condition at time of treatment and patient response to treatment should be considered as two separate, distinct dimensions of viral infection impact in children with acute asthma. "The high prevalence of rhinovirus C in children presenting with asthma exacerbation, its presumed association with asthma-related hospitalization, and its peak in the fall," also should be considered as a leading cause for more potential severe disease.

Clinical implications

Dr. Merckx and her associates did point to several possibly significant implications with their findings. Intensifying treatment using inhaled anticholinergics or magnesium sulfate could block the vagally mediated reflex bronchoconstriction typically seen in cases of asthma exacerbation worsened by viral infection. Although these therapies currently only are used only in severe reactions, it may be useful to examine their efficacy in any cases triggered by RSV, influenza, and PIV because these have been associated with a poor treatment response.

While it still is necessary to clarify its mechanism of action, azithromycin's demonstrated benefit in preschoolers with severe reactions suggests it could be a possible alternative pathogen–nonspecific therapy to address antineutrophilic inflammation, they said.

Dr. Merckx had no relevant disclosures; two of her associates reported receiving grants, salary rewards, and/or unrestricted donations from various pharmaceutical companies or foundations.

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SOURCE: Merckx J et al. Pediatrics. 2018 Jun;142(1):e20174105.

Asthma prescriptions up

BY ANDREW D. BOWSER
MDedge News

Use of prescription medication overall decreased in children and adolescents over the past 15 years, but certain medication classes saw increases over that time period, according to a comprehensive analysis of cross-sectional, nationally representative survey data.

Reported use of any prescription medication in the past 30 days decreased from 25% during 1999-2002 to 22% during 2011-2014 ($P = .04$), according to the analysis based on data from 38,277 children and adolescents aged 0-19 years in the National Health and Nutrition Examination Survey (NHANES).

That decrease in part reflected less prescribing of antibiotics, antihistamines, and upper respiratory drugs, according to a report on the study in JAMA.

However, the study showed increases over time in prescribing of medications for asthma, ADHD, and contraception, according to Craig M. Hales, MD, of the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md., and his coinvestigators.

"Monitoring trends in use of prescription medications among children and adolescents provides insights on several important public health concerns, such as shifting disease burden, changes in access to health care and medicines, increases in the adoption of appropriate therapies, and decreases in use of inappropriate or ineffective treatments," Dr. Hales and his coauthors said.

Of note, antibiotic usage decreased significantly from 8% during 1999-2002 to 5% during 2011-2014, including decreases in amoxicillin, amoxicillin/clavulanate, and cephalosporins. Likewise, antihistamine use was down over time, from 4% to 2%, as was use of upper respiratory combination medications, which decreased from 2% to 0.5%.

Conversely, they found prevalence of ADHD medication usage increased significantly from 3% during 1999-2002 to 4% during 2011-2014, including significant increases for both amphetamines and centrally acting adrenergic agents.

Asthma medication also increased, from 4% to 6%, including significant increases in inhaled corticosteroids and montelukast. Taken together, these findings suggest an overall decrease in medication prescribing among children and adolescents, despite significantly increased prevalence of prescribing for certain drug classes, the investigators said.

They noted that the study had limitations. For example, NHANES does not include data on most over-the-counter medications, and for the drugs it does include, there are no data on dosages, frequency of use, or specific formulations, they said.

Dr. Hales and his coauthors had no conflicts of interest.

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SOURCE: Hales CM et al. JAMA. 2018;319(19):2009-20.

VIEW ON THE NEWS

Implications uncertain for practice

"Some of these trends likely signal potential improvements in the care of children, others may suggest little progress has been made, and yet others are difficult to interpret with certainty," Gary L. Freed, MD, wrote.

One finding that seems clear in the data, according to Dr. Freed, is a decrease in antibiotic use among children and adolescents, from 8% to 5% from the 1999-2002 to 2011-2014 time period. That likely reflects the success of efforts to decrease overuse of these agents in community settings.

On the other hand, the decreased use of antihistamines documented in this study may reflect the success of efforts to reduce overuse, or the fact that several prescription medications became approved for OTC use over the course of the study. NHANES does not include OTC drug data in its survey.

Dr. Freed is a pediatrician with the Child Health Evaluation and Research Center, University of Michigan, Ann Arbor. These comments are derived from his editorial accompanying the study by Hales et al. (JAMA. 2018;319[19]:1988-9). Dr. Freed had no conflicts of interest.

Implantable monitor best at detecting subclinical AF

BY BRUCE JANCIN
MDedge News

ORLANDO – An insertable continuous ECG monitor detected previously unidentified atrial fibrillation that would otherwise have gone unnoted with other intermittent ambulatory monitoring strategies, in a secondary analysis from the REVEAL AF study.

"If you really want to look for atrial fibrillation because your concern is that the patient has a high-risk profile, and if you saw it you would anticoagulate it and maybe prophylactically use rate control, nothing beats the implanted monitor," James A. Reiffel, MD, said at the annual meeting of the American College of Cardiology.

He was principal investigator for REVEAL AF, a multicenter prospective single-center study in which 385 patients without previously known atrial fibrillation (AF) received an insertable cardiac monitor and were followed for 30 months. Of note, this was a population at high risk for AF and for stroke as well, as demonstrated by the requirement that they either had to have a CHADS2 score of 3 or more, or a score of 2 plus either known coronary artery disease, renal impairment, chronic obstructive pulmonary disease, or sleep apnea.

As previously reported (JAMA Cardiol. 2017 Oct 1;2[10]:1120-7), the primary outcome – an AF episode lasting for at least 6 minutes – occurred during the first 18 months of the study in 29% of participants. By 30 months, it was 40%. At ACC 2018, Dr. Reiffel presented a new analysis looking at how the insertable cardiac monitor (ICM) would have stacked up against other device-based strategies aimed at detecting silent AF, including a 30-day implantable memory loop, daily transtelephonic ECG monitoring, and one-time or periodic 24- or 48-hour Holter monitoring.

Dr. Reiffel and his coinvestigators conducted modeling studies harnessing the REVEAL AF continuous monitoring data. They looked at how many of the real-world patients found to have AF in the study would have been identified had they instead undergone a one-time recording period lasting 1, 2, 7, 14, or 30 days beginning at the time they would have received their ICM. They also looked at the yield of repeated monitoring strategies, including monthly or quarterly 24- or 48-hour Holter monitoring sessions. They repeated the various simulated monitoring strategies 10,000 times each in order to beef up the sample size and stability of the results.

It was no contest, according to Dr. Reiffel, professor of clinical medicine at Columbia University in New York.

That's because the median time to AF detection in REVEAL AF was 123 days. Thus, any monitoring strategy of 30 days duration or less was doomed to be of comparatively low yield. Indeed, the 12-month AF incidence rate as detected by ICM in REVEAL AF was 27.1%, compared with 1.1%-13.5% for the various modeled monitoring strategies.

Among patients who met the primary endpoint in REVEAL AF, 10.2% had one or more AF episodes lasting 24 hours or more. So a significant proportion of the asymptomatic episodes of AF were not brief.

The take-home lesson of this analysis is straightforward, he said. "While the incidence of screen-detected atrial fibrillation is dependent upon the population screened, it is also strongly dependent upon the duration and intensity of monitoring."

Session cochair Jeanne E. Poole, MD, observed that, while the new REVEAL AF analysis is informative, it leaves unanswered the big questions regarding the clinical importance of these silent episodes of subclinical device-detected AF. That is, are these episodes associated with significantly increased stroke risk, and if so are they just another nonmodifiable risk marker, or are they a risk factor that can be dampened via oral anticoagulation, like symptomatic AF? said Dr. Poole, professor of medicine and director of the clinical cardiac electrophysiology program at the University of Washington, Seattle.

"My own belief is that they are both a risk marker and a risk factor that contributes to stroke," Dr. Reiffel replied.

He noted that there are two major ongoing clinical trials evaluating the impact of oral anticoagulation in patients with ICM-detected AF. The 3,400-patient German multicenter Non–vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH–AFNET 6) trial is testing whether oral anticoagulation with edoxaban (Savaysa) is superior to aspirin or no antithrombotic therapy for prevention of stroke or cardiovascular death. And the 4,000-patient Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) trial is randomizing patients to apixaban (Eliquis) or aspirin.

"We'll know within the next 3-4 years whether patients with high-risk profiles for atrial fibrillation but no clinically manifest atrial fibrillation should in fact be detected and should in fact be anticoagulated if atrial fibrillation is detected. Putting on my 'Carnac The Magnificent' hat [made famous by Johnny Carson on the 'Tonight Show'], I predict the answer to both of those questions is likely to be yes," the cardiologist added.

"There's no major surgical technique involved in putting [the ICM] in," he said.

The REVEAL AF study was sponsored by Medtronic. Dr. Reiffel reported serving as a consultant to the company.

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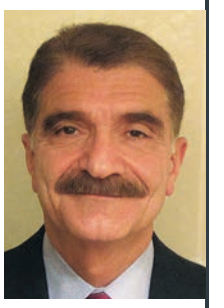
SOURCE: Reiffel JA et al. ACC 2018, Abstract 900-08.

VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: Technically speaking, the implantable Cardiac Monitor (ICM) is a continuous Holter monitor used for the detection of silent episodes of atrial fibrillation. Although subcutaneous implantation is quite quick and easy, the device is expensive. As mentioned by the chair of the session during this paper presentation at the ACC and the author's response, the clinical significance of silent AF episodes detected by ICM device, and by extension, the need for oral anticoagulation, awaits further studies currently underway.

DOACs' safety affirmed in real-world setting

BY ANDREW D. BOWSER
MDedge News

Direct oral anticoagulants (DOACs) were associated with decreased bleeding risk versus warfarin in a recent retrospective analysis of primary care databases.

Apixaban (Eliquis) was associated with decreased risk of major bleeding events versus warfarin both in patients with atrial fibrillation (AF) and those prescribed anticoagulants for other causes, according to study results.

Rivaroxaban (Xarelto) was associated with a decrease in risk of intracranial bleeding, compared with warfarin in patients without AF, as was dabigatran (Pradaxa), reported Yana Vinogradova, a research statistician in the division of primary care at the University of Nottingham (England) and her coauthors.

An increased risk of all-cause mortality was seen with both rivaroxaban and low-dose apixaban, possibly because more patients died of age-related causes while on these direct oral anticoagulants, they reported.

"This large observational study, based on a general population in a primary care setting, provides reassurance about the safety of DOACs as an alternative to warfarin across all new incident users," Ms. Vinogradova and her colleagues said in the BMJ.

Evidence establishing the noninferiority of DOACs to warfarin comes mostly from controlled trials in AF leaving "residual concerns" about the safety of these newer agents in real-world settings, where a broader range of patients may receive them.

They conducted an analysis based on patient data from two U.K. primary care databases representative of the national population, according to the researchers. A total of 196,061 patients were represented in the study, including 103,270 (53%) with AF and 92,791 (47%) who received anticoagulants for other reasons.

A total of 67% of patients received warfarin, though its use declined from 98% in 2011, the beginning of the study period, to 23% in 2016, the end of the study period. Over that same time period, use of rivaroxaban rose from 1% to 42%, and use of apixaban rose from 0% to 31%, while dabigatran use peaked in 2013 at 10%, dropping to 3% by 2016.

For patients with AF, apixaban was linked to a lower major bleeding risk, both versus warfarin (adjusted hazard ratio, 0.66; 95% confidence interval, 0.54-0.79) and versus rivaroxaban, the published data show. Apixaban was associated with a lower risk of intracranial bleed versus warfarin in patients with AF (aHR, 0.40; 95% CI, 0.25-0.64) as was dabigatran (aHR, 0.45; 95% CI, 0.26-0.77).

For patients without AF, apixaban was again associated with a lower risk of major bleeding versus warfarin and versus rivaroxaban, while rivaroxaban was associated with lower intracranial bleeding risk versus warfarin, and apixaban with lower risks for gastrointestinal bleeds.

"Our study has shown that the risk of major bleeding is lower in patients taking apixaban regardless of the reason for prescribing," they wrote. The study was supported by a grant from the National Institute for Health Research. The investigators had no relevant disclosures.

SOURCE: Vinogradova Y et al. BMJ. 2018;362:K2505.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP comments: This retrospective analysis of primary care databases in a large patient population of over 196,000 in the U.K. is a comparison of the use, safety, and risks of three DOACs vs warfarin. All three agents had a better risk profile with apixaban having the more favorable results. One notable exception was a higher all-cause mortality with rivaroxaban and lower-dose apixaban, compared with warfarin. The findings of this study are of value to the physicians caring for elderly and patients with a higher risk profile for cardiovascular events.

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CHEST 2018 postgrad courses – incredible learning opportunities

BY DAVID A. SCHULMAN, MD, FCCP
CHEST 2018 Program Chair

CHEST Annual Meeting 2018

One of the great educational opportunities that comes with each annual CHEST meeting is the slate of postgraduate courses that kicks the meeting off. I have always found them to be in-depth, clinically relevant reviews on specific aspects of pulmonary, critical care, and sleep medicine, as delivered by the best educators and clinical experts CHEST has to offer. And, this year is no exception.

We have a total of 11 courses offered this go around, including four dedicated full-day sessions on subjects as wide-ranging as lung and pleural ultrasonography, state-of-the-art practices in the diagnosis and management of interstitial lung diseases, and a year-in-review of the best of the pulmonary literature. The American Association for Bronchology and Interventional Pulmonology will hold its annual 1-day meeting at this time, as well.

If you prefer our half-day courses, we have seven: morning sessions focus on pulmonary hypertension, asthma, and sleep medicine, while our afternoon courses cover updates in lung cancer, critical care medicine, use of noninvasive ventilation, and our always-popular InPHOCUS case-based hands-on simulation course for pulmonary vascular disease.

It has been a little while since I attended my first CHEST meeting as a pulmonary and critical care medicine fellow, but I vividly remember thinking how incredibly valuable these courses were, how engaging and welcoming the faculty was, and how much knowledge CHEST was able to cram into a single day. Those opinions have not changed over the last 2 decades. While we think we've got some pretty cool stuff going on throughout the San Antonio meeting, I hope you won't miss the chance to sign up for these incredible learning opportunities.

Looking forward to seeing you all in Texas!

chestmeeting.chestnet.org

This month in the journal *CHEST*®

Editor's Picks

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

GIANTS IN CHEST MEDICINE
Professor Pamela B. Davis, MD, PhD
By Dr. Mitchell Drumm

ORIGINAL RESEARCH
Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study
By Dr. J. R. Bledsoe, et al.

Investigation of Public Perception of Brain Death Using the Internet
By Dr. A. H. Jones, et al.

EVIDENCE-BASED MEDICINE
Chronic Cough Related to Acute Viral Bronchiolitis in Children: CHEST Expert Panel Report
By Dr. A. B. Chang, et al, and the CHEST Expert Cough Panel

News from the Board – June 2018

BY JACK BUCKLEY, MD, FCCP
Regent-at-Large

The Board of Regents met at CHEST headquarters in June to review our work and progress with the 2018-2022 Strategic Plan. As President of CHEST, Dr. John Studdard leads these meetings and shared the great progress toward our goals.

• A theme emphasized by John and CHEST EVP and CEO Steve Welch is the importance of nurturing healthy relationships with other organizations. Whether these are sister societies, like ATS and SCCM, industry partners, or international organizations, CHEST's mission is furthered when we collaborate on important issues. Keep an eye out for upcoming collaborative projects on everything from position statements and clinical guidelines on medical topics, to educational materials for our patients and joint conferences with our international partners; we anticipate holding more than 20 international events over the next year, including programs in Dubai, China, Bangkok, India, Helsinki, and Athens.

DR. BUCKLEY

• The finance committee, led by Dr. Jan Mauer, reported that CHEST is on track to meet its budget for the year. In addition, greater revenue from our publishing enterprises is anticipated for next year, which will help enable enhanced offerings at CHEST courses, live-learning events, and other programs. Thanks to all of our members for making *CHEST*® journal and *CHEST*® *Physician* the top two most widely read publications in the field of Pulmonary Medicine.

• CHEST's new Governance Committee will be reviewing nominations for President and members of the Boards of Regents and Trustees, with a goal to ensure our leaders reflect our membership and bring a wide variety of skills to match organizational needs.

• Planning continues for CHEST's annual meeting October 6-10, 2018, in San Antonio, Texas. Under the leadership of the Scientific Program Chair, Dr. David Schulman, this year's theme is Learn by Doing and will offer more than ever before hands-on learning activities as requested by so many of our members. We look forward to seeing you in San Antonio.

• On a related note, there was a lengthy discussion regarding abstract and case report acceptance. CHEST is very fortunate to receive hundreds of excellent submissions for its annual meeting each year. There are always some proposals that are not accepted for presentation but likely could be with a little polishing. The Board agreed to develop a plan to mentor these submitters to help them get their content accepted for the meeting;

this will roll out for submissions to CHEST 2019.

• CHEST's Board of Regents continues to pursue its own development. Max Reed, Vice President of Leadership and Strategic Initiatives at Lake Forest Graduate School of Management, was invited to the meeting to help the board better understand unconscious bias and learn the steps to strengthen the goals of being an inclusive organization. This most worthwhile half-day educational session will help CHEST achieve one of the most important goals of its strategic plan.

Editor's Note

One of the missions of *CHEST® Physician* is to keep you—our members, colleagues, and friends—apprised of ongoing actions of your CHEST Board of Regents. Thanks to Dr. Buckley for penning this column. We plan to run quarterly updates from the Board, and hope to have regular updates from the CHEST Foundation's Board of Trustees, as well! If there are additional items that you'd like to see related to the function of the College or the Foundation, please let us know at pgoorsky@chestnet.org.

David A. Schulman, MD, FCCP

Restaurants galore at CHEST 2018

San Antonio is known for its sports teams, the River Walk, and, of course, the Alamo, but one thing that doesn't get the recognition it deserves is the food. San Antonio offers a variety of must-try food items that you simply can't find anywhere else. Ready to get your grub on? Here are just a few picks to try out while visiting the Alamo City.

Bella on the River

A 13-minute walk from the Convention Center along the River Walk will land you at this San Antonio hotspot. Bella on the River is known for its "Texas Style Italian food," which means bigger, flavor-packed portions with an Italian twist. From antipasto to paella, you're sure to find something on the menu to feast on. Be sure to take a look at their extensive wine list, as well.

Cookhouse

Who says you can't get a little taste of New Orleans while in Texas? The Cookhouse is serving up cajun favorites just a 6-minute drive from the Convention Center. Known for its New Orleans barbequed shrimp, fried boudin balls, and Po' Boys, it'll be hard to pick which one to feast on for dinner.

El Mirador

Just a 4-minute Uber from the Convention Center, you'll find El Mirador, known for its deliciously authentic Mexican food. El Mirador has been serving up chicharrones, fresh breakfast tacos, and other savory dishes to the San Antonio community since 1968. Be sure to grab a seat on their outdoor patio, and take a look at the nearby shops and bars while enjoying your delicious meal.

La Fonda on Main

Take a trip to the Alta Vista neighborhood post-CHEST and visit the oldest Mexican restaurant in San Antonio, open since 1932. La Fonda on Main is known for its lively atmosphere and its traditional Tex-Mex food options. Be sure to take your dinner outside, and sit along their tree-lined patio. As this is one of San Antonio's most recommended restaurants, we suggest making reservations.

Restaurant Gwendolyn

Tired out from the latest in medical advancements and tech? Kick it old school and grab a seat at Restaurant Gwendolyn along the River Walk and feast on local, seasonal, and handmade food from around the San Antonio area. This restaurant's mission is to serve food entirely old school, which means using what they had and creating food like it was prepared prior to the industrial revolution in 1850. If you like surprises, you're in luck, as the menu constantly changes based on what is available at that time!

Keep in mind, these are just some of the San Antonio restaurants serving up delicious dishes. If you find other restaurants we should add to our list, tag us on social media (@accpchest) with your picks!

Clinician educator opportunities at CHEST 2018

BY MATTHEW MILES, MD, MEd, FCCP
Vice-Chair, CHEST Training and Transitions Committee

Are you a clinician educator? Chances are, the answer is yes! Teaching is integral to the practice of chest medicine, whether the audience is medical students, residents, fellows, nurse practitioners, physician assistants, nurses, respiratory therapists, or patients. If you are interested in further developing this essential skill, CHEST 2018 has you covered! This year at the annual meeting, you will find more than 25 hours of content focused on enhancing your teaching.

If most of your teaching is in an academic setting, be sure to make time for the CHEST/APCCMPD Symposium on Sunday afternoon. Here you will learn from experienced program directors and faculty how to implement state-of-the art faculty development methods. You will also have the opportunity to discuss your own experience giving feedback to learners, as best practices are discussed and shared. And the Sunday content doesn't stop there; we also have sessions on ICU burnout – an important factor for all of us – and the use of new mobile technologies to enhance your teaching.

DR. MILES

Monday's sessions will cover teaching in several different settings. First up, a session covering several techniques you can use to teach one-on-one or in a small group setting – perfect for enhancing your teaching during rounds!

Next, learn practical tips to increase the impact of your teaching in a large group lecture or a small group session. The afternoon opens with the latest innovations in Pulmonary and Critical Care fellowship training, to keep you abreast of the newest opportunities for your learners, and a session at the end of the day reviews advances in the teaching of point-of-care ultrasound.

Finally, don't miss the 3:15 symposium on tips to get your CHEST Foundation Grant funded – this session will be pure gold for increasing your proposal's chance for success!

Educators will also be interested in the Tuesday sessions on implicit bias. Although educators always have clear and defined curriculum that we teach to our learners, we can all recognize when a "hidden curriculum" exists. This hidden curriculum can influence our learning and working environment in positive or negative ways. Learning more about our implicit biases can help tilt the balance in the right direction!

Above and beyond the didactics, CHEST 2018 will offer many opportunities for clinician educators beyond what I've described here. While you are planning your personal meeting schedule, be sure to make time for networking with other clinician educators from around the globe. As is the case with so many other skills, we are better teachers together!

Looking forward to seeing you at CHEST 2018!

For more on CHEST 2018—**chestmeeting.chestnet.org**

CHEST® Annual Meeting 2018

FASENRA is indicated as an add-on maintenance treatment of patients 12 years or older with severe eosinophilic asthma.

POWER TO PREVENT EXACERBATIONS

WITH BETTER BREATHING AFTER THE FIRST DOSE*[1-4]

FASENRA is proven to reduce annual exacerbation rate and improve lung function in patients with severe eosinophilic asthma. Improvements in lung function were observed as early as Week 4.*[1-4]

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

*Statistical significance for FEV_1 improvement was established at end of treatment. Week 4 results were descriptive only. FASENRA demonstrated greater improvements in change from baseline in pre-bronchodilator FEV_1 compared with placebo at Week 4 (first measured time point after administration of treatment dose) that were maintained through end of treatment.[2-4]

†The pharmacodynamic response (blood eosinophil depletion) following repeat SC dosing was evaluated in asthma patients in a 12-week phase 2 trial. Patients received 1 of 3 doses of benralizumab [25 mg (n=6), 100 mg (n=6) or 200 mg (n=6) SC] or placebo (n=6) every 4 weeks for a total of 3 doses. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of blood eosinophil levels, which was maintained throughout the dosing period.[1,5]

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

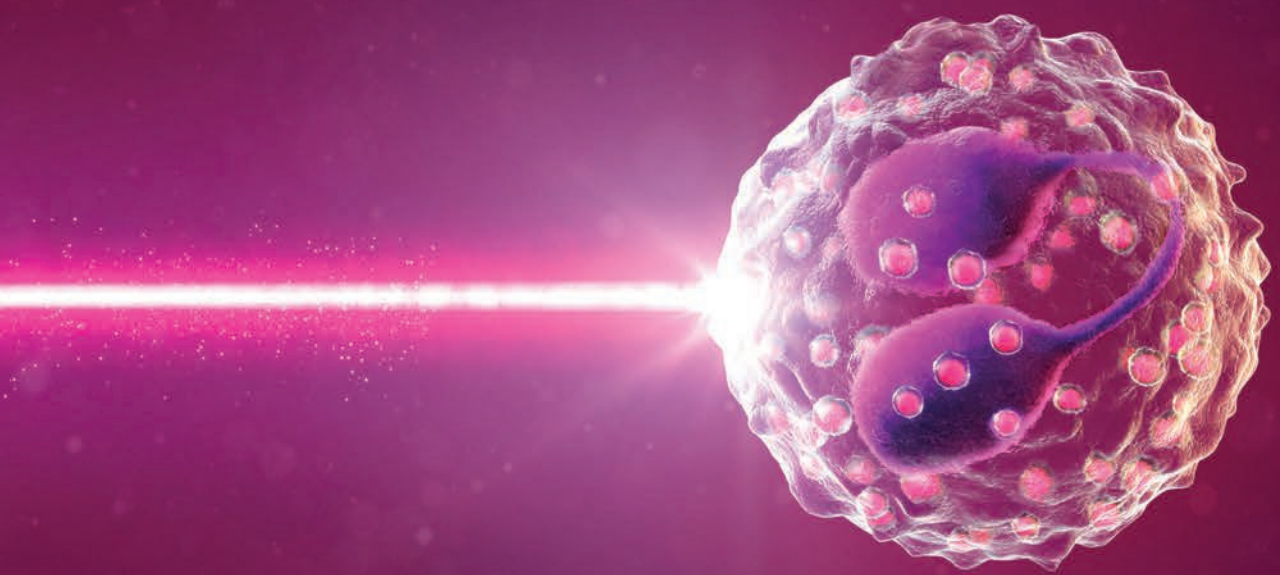
Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

- **FASENRA is the first and only biologic that provides near complete depletion of blood eosinophils in 24 hours†[1,5]**
  - **The mechanism of action of benralizumab in asthma has not been definitively established**
    - The relationship between the pharmacologic properties and clinical efficacy has not been established
- **FASENRA is the first and only biologic for severe asthma with a prefilled syringe and Q8W maintenance dosing schedule[1]**
- **The most common adverse reactions (incidence greater than or equal to 5%) include headache and pharyngitis[1]**



GET STARTED AT
FASENRAFACTS.COM

IMPORTANT SAFETY INFORMATION (cont'd)

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

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

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

Fasenra™
(benralizumab) Subcutaneous Injection 30 mg
FROM THE START

STUDY DESIGNS

TRIALS 1 AND 2

Trial 1 (48-week) and Trial 2 (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (Trial 1) and 1306 (Trial 2) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (Trial 1) and medium- to high-dose ICS (Trial 2) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. The primary endpoint was annual exacerbation rate ratio versus placebo in patients with blood eosinophil counts of ≥300 cells/μL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.[2,3]

TRIAL 3

A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of **FASENRA** (30 mg SC) Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC) Q4W, and placebo (SC) Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and chronic OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/μL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.[6]

PHASE 2 STUDY

A 12-week, phase 2, randomized, double-blind, placebo-controlled, dose-increase study of benralizumab in adults with mild to moderate asthma. Patients were randomized to receive SC administration of benralizumab 25 mg (n=6), benralizumab 100 mg (n=6), benralizumab 200 mg (n=6), or placebo (n=6) Q4W for a total of 3 doses. One objective was to assess the effect of benralizumab on blood eosinophil counts and protein biomarkers. Median blood eosinophil levels at baseline were 400, 200, 120, and 200 cells/μL in the 25, 100, and 200 mg benralizumab and placebo groups, respectively.[5]

References: 1. FASENRA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128-2141. **4.** Data on File, REF-19697, AZPLP. **5.** Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21-29. **6.** Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448-2458.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

INDICATION

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

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

Please see adjacent Brief Summary of full Prescribing Information on reverse side.

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

Fasenra™
(benralizumab) Subcutaneous Injection 30 mg

FROM THE START

FASENRA™ (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

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

Limitations of use:

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

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

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

Preparation and Administration

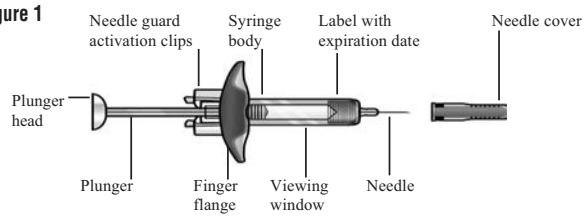
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

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

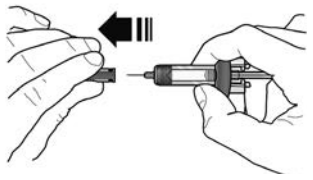
Figure 1



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

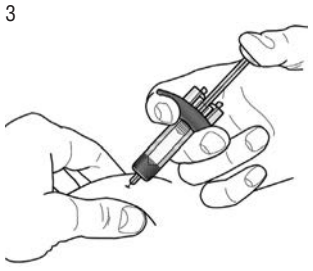
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



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

3



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

4

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

5

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

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

28-Week Trial

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

Injection site reactions

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

Immunogenicity

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

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

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

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

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CHEST NETWORKS

Ebola virus, social media, opioid crisis, gender in pulmonary disease

Disaster Response

Ebola virus outbreak preparedness

The 2014-2016 Ebola virus disease (EVD) outbreak in West Africa highlighted the global reach of emerging infectious diseases and shattered a sense of complacency in an increasingly interconnected world. Consequently, a subsequent outbreak of EVD in the Democratic Republic of the Congo (DRC) in early May 2018 triggered a swift response. International agencies and workers benefited from increased experience with the disease, new investigational vaccines, including the rVSV-ZEBOV vaccine, and novel therapies, including ZMapp, favipiravir, and remdesivir (GS-5734).


DR. MAVES


DR. MADAR

However, are health-care providers and facilities outside of outbreak areas truly more prepared to handle high-risk pathogens today than they were in 2014? The answer, at least in the United States, seems to be "yes," due to a regional concentration of funding and resources.

The US Department of Health and Human Services (HHS) has identified treatment centers for Ebola and other special pathogens nationwide.[1] The National Ebola Training and Education Center (NETEC) trains health systems' staff to implement disease management plans.[2] The Centers for Disease Control and Prevention (CDC) has prepared recommendations for public health planners.[3]

In nonreferral centers, providers should always obtain a travel history, remain cognizant of emerging diseases,[4] and optimize supportive care. Early collaboration with public health authorities and appropriate infection control precautions are necessary for rapid confirmation of a suspected high-risk pathogen and for ensuring patient and staff safety. Most centers will not need to care for a patient with EVD for an extended period, but the ability to recognize, contain, and refer is essential for good outcomes.

Ryan Maves, MD, FCCP
Cristian Madar, MD, FCCP
Steering Committee Members

References

1. www.hhs.gov/about/news/2016/06/14/hhs-selects-regional-ebola-treatment-center-southwestern-us.html. Accessed July 18, 2018.
2. www.netec.org. Accessed July 18, 2018.
3. www.cdc.gov/vhf/ebola/public-health-planners. Accessed July 18, 2018.
4. www.cdc.gov/travel/notices. Accessed July 18, 2018.

Practice Operations

Current impact of social media on health care

In an age of connectivity, social media websites pose many challenges. Not immune to this are the physicians and their health-care practices, particularly in regards to their online presence to their patients.

Many of these sites publish user-submitted patient appreciation or complaints. These postings are generally viewable to the public and often not moderated or restricted in content. With value-based care at the front lines, these posts may be detrimental to the success of the practice. Public postings exist regardless of providers' awareness or management of them.

There is limited training on social media presence, handling negative reviews, addressing patient-specific posts online, or mediating conflicts. This includes legal issues related to licensing, privacy, litigation, and fraud. Compliance to ethical requirements and protecting patient privacy online still remains crucial in the heavily regulated health-care industry.

The burden of social media remains a widely unacknowledged impediment to growing physicians' practice. While several organizations have published guidelines to help ensure success and to better inform physicians, these are not widely practiced or well known.

However, significant potential benefits to social media include marketing opportunities, education, and connection with patients. Social media has been key for support group networks amongst patients. Similar to professionals in other fields, it is recommended that providers separate their public and private social media accounts or use alternate names.


DR. SISK


DR. ANJUM

For more information about social media and answers to many legal questions, attend the Practice Operations NetWork Featured Lecture at the CHEST Annual Meeting on Monday, October 8, at 1:30 PM.

Megan Sisk, DO
Fellow-in-Training Member
Humayun Anjum, MD, FCCP
Steering Committee Member

Transplant

Implications of the opioid crisis on organ donation for lung transplantation

The opioid epidemic in the United States claims a substantial number of lives annually, with overdose-related deaths increasing five times between 2000 and 2016.[1]

In the midst of this national crisis, perhaps one solace is an increase in organ donation for thoracic transplantation. In fact, data show that patients dying of overdose have the highest donation rates,[2] and a staggering 10 times increase in the proportion of eligible donors dying of overdose has been witnessed over this period (1.2% of donors in 2000, 13.7% in 2016),[3] with a parallel increase in transplants performed.[4]

Despite this, transplant program organ utilization in overdose deaths falls well short of expected, in part due to disease transmission concerns, supported by the observation that these donors are two to five times more likely designated as "Public Health Service (PHS)-Increased-Risk" Criteria for transmission of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV.[2,5] In lung transplantation, additional concerns over donor quality often exist, including aspiration, edema, or other opioid-induced injuries.

Although a disturbing premise, as the health-care community and lawmakers attempt to curtail the opioid epidemic, it is important to recognize opportunities for improvement in organ utilization, which offers potential to help many patients with cardiopulmonary disease. In addition to community-wide organ donation campaigns, this may stem from dissemination of knowledge of the low infectious risks in PHS-increased-risk donors,[5] as well as analyses showing similar survival among recipients of allografts from overdose-death donors compared with donors from other causes.[3]


DR. KUMAR


DR. KAPNADAK

Use of HCV-positive organs, particularly in the modern era of infectious testing and therapies, offers additional potential,[6] as does fine-tuning technologies such as ex-vivo lung perfusion, which may enhance organ quality making lungs suitable for transplant.

Anupam Kumar, MD
Fellow-in-Training Member
Siddhartha G. Kapnadak, MD
Steering Committee Member

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Women's Health

Sex and gender in pulmonary disease

On September 18-19, 2017, the National Heart, Lung, and Blood Institute convened a workshop of investigators with the National Institutes of Health, the Office of Research on Women's Health, and the Office of Rare Diseases Research to discuss the role of sex and gender in pulmonary disease. The findings of this workshop, published online ahead of print (Han MK, et al. *Am J Respir Crit Care Med*. 2018 May 10. doi: 10.1164/rccm.201801-0168WS. [Epub ahead of print]), outline important future directions for research in pulmonary medicine.

DR. DESAI

The group identified several areas in which there are substantial sex-specific differences in clinical presentation and treatment outcomes in pulmonary diseases, including tobacco cessation, circadian rhythms and sleep-disordered breathing, COPD, asthma, cystic fibrosis, and interstitial lung disease.

In addition to defining the terms sex and gender, the committee called for standardization of the reporting of sex as a variable in animal and cellular models. Given the observed relationship between sex hormones and the development of lung disease, a collaboration across disciplines, including endocrinology, would be useful to understand this relationship at a basic and clinical science level.

Furthermore, in the era of big data research, sex and gender should be included as co-variates when possible to better clarify the contributions of these variables in pulmonary disease.

The workshop also highlighted the need to educate clinicians about these differences. Just as trainees are taught that women can present with atypical symptoms for a heart attack, so should they be taught about the differences in management of chronic lung disease and tobacco dependence between men and women.

Nikita Desai, MD
Fellow-in-Training Member

New opportunity for CHEST Foundation

In June 2018, the CHEST Foundation was approved to participate as a National Organization in the 2018 Combined Federal Campaign (CFC).

The CFC is the only authorized solicitation of employees in the federal workplace on behalf of charitable organizations. As an approved organization, we will be listed on the 2018 CFC Charity List and receive our own code to promote to donors. Receiving this approval to participate in the CFC is a wonderful honor for the CHEST Foundation, and we are excited to share our news with you!

CHEST Foundation President, Lisa K. Moores, MD, FCCP, shares her insight and value about this new opportunity to engage and support the foundation's mission of clinical research, community service, and patient education.

"As a long-time federal employee, I am extremely excited that I can now show my support of the CHEST Foundation through employee giving during the annual CFC campaign," Dr. Moores said. "This will also allow me to share the story of the CHEST Foundation with colleagues. When they choose who they want to give to for their work place giving, they can support the CHEST Foundation, as well. This is a great opportunity for the CHEST Foundation, as I know each year during the CFC campaign (September -January), it is highly encouraged and promoted to employees. This increased exposure is very exciting and will hopefully allow us to strengthen the philanthropic work we do with the Foundation."

Stay tuned for more information as we kick off the Combined Federal Campaign in September 2018!

CRITICAL CARE COMMENTARY

Balanced crystalloids vs saline for critically ill patients

BY MATTHEW W. SEMLER, MD, MSc

If you work in an ICU, chances are good that you frequently order IV fluids (IVF). Between resuscitation, maintenance, and medication carriers, nearly all ICU patients receive IVF. Historically, much of this IVF has been 0.9% sodium chloride ("saline" or "normal saline"). Providers in the United States alone administer more than 200 million liters of saline each year (Myburgh JA, et al. *N Engl J Med.* 2013;369[13]:1243). New evidence, however, suggests that treating your ICU patients with so-called "balanced crystalloids," rather than saline, may improve patient outcomes.

For over a century, clinicians ordering IV isotonic crystalloids have had two basic options: saline or balanced crystalloids (BC). Saline contains water and 154 mmol/L of sodium chloride (around 50% more chloride than human extracellular fluid). In contrast, BCs, like lactated Ringer's (LR), Hartman's solution, and others, contain an amount of chloride resembling human plasma (Table 1). BC substitute an organic anion such as bicarbonate, lactate, acetate, or gluconate, in place of chloride, resulting in lower chloride level and a more neutral pH.

Over the last 2 decades, evidence has slowly accumulated that the different compositions of saline and BC might translate into differences in patient physiology and outcomes. Research in the operating room and ICU found that saline administration caused hyperchloremia and metabolic acidosis. Studies of healthy volunteers found that saline decreased blood flow to the kidney (Chowdhury AH, et al. *Ann Surg.* 2012;256[1]:18). Animal sepsis models suggested that saline might cause inflammation, low blood pressure, and kidney injury (Zhou F, et al. *Crit Care Med*. 2014;42[4]:e270). Large observational studies among ICU patients found saline to be associated with increased risk of kidney injury, dialysis, or death (Raghunathan K, et al. *Crit Care Med.* 2014 Jul;42[7]:1585). These preliminary studies set the stage for a large randomized clinical trial comparing clinical outcomes between BC and saline among acutely ill adults.

Between June 2015 and April 2017, our research group conducted the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) (Semler MW, et al. *N Engl J Med.* 2018;378[9]:819). SMART was a pragmatic trial in which 15,802 adults in five ICUs were assigned to receive either saline (0.9% sodium chloride) or BC (LR or another branded BC [PlasmaLyte A]). The goal was to determine whether using BC rather than saline would decrease the rates of death, new dialysis, or renal dysfunction lasting through hospital discharge. Patients in the BC group received primarily BC (44% LR and 56% another branded BC [PlasmaLyte A]), whereas

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patients in the saline group received primarily saline. The rate of death, new dialysis, or renal dysfunction lasting through hospital discharge was lower in the BC group (14.3%) than the saline group (15.4%) (OR: 0.90; 95% CI, 0.82-0.99; *P*=.04). The difference between groups was primarily in death and new dialysis, not changes in creatinine. For every 100 patients admitted to an ICU, using BC rather than saline would spare one patient from experiencing death, dialysis, or renal dysfunction lasting to hospital discharge (number needed to treat). The benefits of BC appeared to be greater among patients who received larger volumes of IVF and patients with sepsis. In fact, among patients with sepsis, mortality was significantly lower with BC (25.2%) than with saline (29.4%) (*P*=.02).

Another trial was conducted in parallel. Saline against LR or another branded BC (PlasmaLyte) in the ED (SALT-ED) compared BC with saline among 13,347 non-critically ill adults treated with IVF in the ED (Self WH, et al. *N Engl J Med*. 2018;378[9]:829). Like the SMART trial, the SALT-ED trial found a 1% absolute reduction in the risk of death, new dialysis, or renal dysfunction lasting to hospital discharge favoring BC.

The SMART and SALT-ED trials have important limitations. They were conducted at a single academic center, and treating clinicians were not blinded to the assigned fluid. The key outcome was a composite of death, new dialysis, and renal dysfunction lasting to hospital discharge – and the trials were not powered to show differences in each of the individual components of the composite.

Despite these limitations, we now have data from two trials enrolling nearly 30,000 acutely ill patients suggesting that BC may result in better clinical outcomes than saline for acutely ill adults. For clinicians who were already using primarily BC solutions, these results will reinforce their current practice. For clinicians whose default IVF has been saline, these new findings raise challenging questions. Prior to these trials, the ICU in which I practice had always used primarily saline. Some of the questions we faced in considering how to apply the results of the SMART and SALT-ED trials to our practice included:

1. Recent data suggest BC may produce better clinical outcomes than saline for acutely ill adults. Are there any data that saline may produce better clinical outcomes than BC? Currently, there are not.

2. Cost is an important consideration in critical care, are BC more expensive than saline? The cost to produce saline and BC is similar. At our hospital, the costs for a 1L bag of saline, LR, and another branded BC (PlasmaLyte A) are exactly the same.

Table 1. Composition of common IV isotonic crystalloid solutions

	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Lactate	Gluconate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111		1–2		275–295
0.9% saline	154				154				308
Lactated Ringer's	130	4.0	2.7		109		28		273
PlasmaLyte A®	140	5.0		3.0	98	27		23	294

MDedge News

Note: All values are in mEq/L except calculated osmolarity, which is in mOsm/L. 0.9% saline is "Sodium Chloride Injection, USP"; lactated Ringer's is "lactated Ringer's Injection, USP"; and PlasmaLyte A® is "Multiple Electrolyte Injection, Type 1, USP"; all from Baxter Healthcare Corporation in Deerfield, IL, USA.

Source: Dr. Semler

These data challenge ICU providers primarily using saline to evaluate the available data, their current IVF prescribing practices, and the logistical barriers to change, to determine whether there are legitimate reasons to continue using saline, or whether the time has come to make BC the first-line fluid therapy for acutely ill adults.

3. Is there a specific population for whom BC might have important adverse effects? Because some BC are hypotonic, the safety of administration of BC to patients with elevated intracranial pressure (eg, traumatic brain injury) is unknown.

4. Are there practical considerations to using BC in the ICU? Compatibility with medications can pose a challenge. For example, the calcium in LR may be incompatible with ceftriaxone infusion. Although BC are compatible with many of the medication infusions used in the ICU for which testing has been performed, less data on compatibility exist for BC than for saline.

5. Are BC as readily available as saline? The three companies that make the majority of IVF used in the United States produce both saline and BC. Recent damage to production facilities has contributed to shortages in the supply of all of them. Over the long term, however, saline and BC are similar in their availability to hospital pharmacies.

After discussing each of these considerations with our ICU physicians and nurses, consultants, and pharmacists, our ICU collectively decided to switch from using primarily saline to BC. This involved (1) our pharmacy team stocking the medication dispensing cabinets in the ICU with 90% LR and 10% saline; and (2) making BC rather than saline the default in order sets within our electronic order entry system. Based on the results of the SMART trial, making the change from saline to BC might be expected to prevent around 100 deaths in our ICU each year.

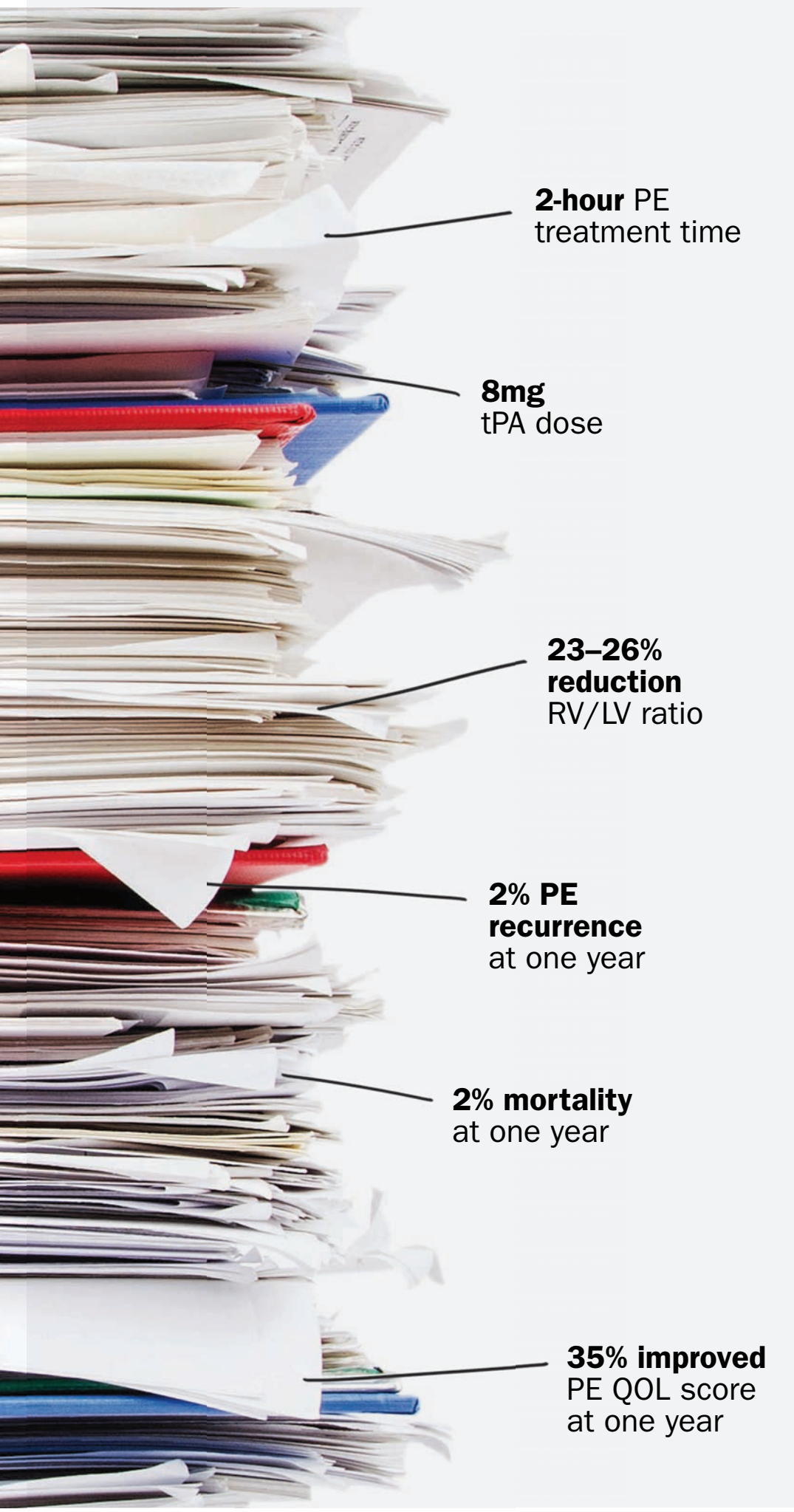
Many questions regarding the effect of IV crystalloid solutions on clinical outcomes for critically ill adults remain unanswered. The mechanism by which BC may produce better clinical outcomes than saline is uncertain. Whether acetate-containing BC (eg, PlasmaLyte) produced better outcomes than non-acetate-containing BC (eg, LR) is unknown. The safety and efficacy of BC for specific subgroups of patients (eg, those with hyperkalemia) requires further study. Two ongoing trials comparing BC to saline among critically ill adults are expected to finish in 2021 and may provide additional insights into the best approach to IVF management for critically ill adults. An ongoing pilot trial comparing LR to other branded BC (Plasmalyte/Normosol) may inform the choice between BC.

In summary, IVF administration is ubiquitous in critical care. For decades, much of that fluid has been saline. BC are similar to saline in availability and cost. Two large trials now demonstrate better patient outcomes with BC compared with saline. These data challenge ICU providers, pharmacies, and hospital systems primarily using saline to evaluate the available data, their current IVF prescribing practices, and the logistical barriers to change, to determine whether there are legitimate reasons to continue using saline, or whether the time has come to make BC the first-line fluid therapy for acutely ill adults.

Editor's Comment

For a very long time, normal saline has been the go-to crystalloid in most ICUs around the globe. In the recent past, evidence started mounting about the potential downside of this solution. The recent SMART trial, the largest to date, indicates that we could prevent adverse renal outcomes by choosing balanced crystalloids over normal saline. These results were even more marked in patients who received a large amount of crystalloids and in patients with sepsis. Dr. Matthew Semler presents solid arguments to consider in changing our practice and adopting a "balanced approach" to fluid resuscitation. We certainly should not only worry about the amount of fluids infused but also about the type of solution we give our patients. Hopefully, we will soon learn if the different balanced solutions also lead to outcome differences.

Angel Coz, MD, FCCP – Section Editor



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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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