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Doug Brunk/MDedge News

"When patients with COPD are receiving triple therapy but are not having frequent exacerbations, it's safe to 'de-escalate,'" Dr. Kenneth R. Chapman said.

Most COPD patients on triple therapy can withdraw steroids

BY DOUG BRUNK
MDedge News

SAN DIEGO – In patients on long-term triple therapy and up to one exacerbation in the previous year, the withdrawal of inhaled corticosteroids (ICS) led to a small decrease in lung function that was not clinically important, with no associated difference in the rates of chronic obstructive pulmonary disease (COPD) exacerbations, dyspnea, or as-needed bronchodilator use.

Those are key findings from the SUNSET trial, a 26-week, randomized, double-blind, parallel-group multicenter study to assess the efficacy and safety of the switch from long-term triple therapy to indacaterol/glycopyrronium (IND/GLY, 110/50 mcg once daily) or continuation of triple therapy with tiotropium 18 mcg once daily and salmeterol/fluticasone propionate fixed-dose combination 50/500 mcg b.i.d.

"When patients with COPD are receiving triple therapy but are not having frequent exacerbations, it's safe to 'de-escalate' to the bronchodilator foundation of second generation LABA/LAMA," lead study author Kenneth R. Chapman, MD, FCCP, said in an interview prior to an international conference of the American Thoracic Society. "In a minority of patients with high blood eosinophil counts, one should make the move cautiously."

Dr. Chapman, director of the asthma and

WITHDRAWING STEROIDS // *continued on page 6*

In critically ill, lower glucose target linked to lower death risk

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST® ▪ In critically ill patients, treating blood glucose with a low target of 80-110 mg/dL was associated with a lower risk of 30-day mortality compared with patients with a target of 90-140 mg/dL, according to results of a retrospective cohort analysis.

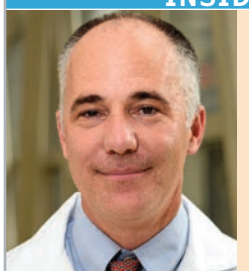
With the computerized intravenous insulin protocol used in the study, the strict target could be achieved with a low rate of hypoglycemia, the authors wrote. The analysis was published in the journal *CHEST®*.

These findings do not suggest that clinicians should practice counter to current guidelines, which recommend against intensive insulin therapy, noted Andrew M. Hersh, MD, of the division of pulmonary and critical care at San Antonio Military Medical Center, and his coauthors.

However, it does raise the possibility that earlier investigations finding an association between intensive insulin therapy and excess mortality "may have been accurate only in the setting of technologies which led to high rates of severe

REDUCING THE GLUCOSE TARGET // *continued on page 7*

INSIDE HIGHLIGHT



PULMONARY PERSPECTIVES®

Post-ICU Discharge Clinics

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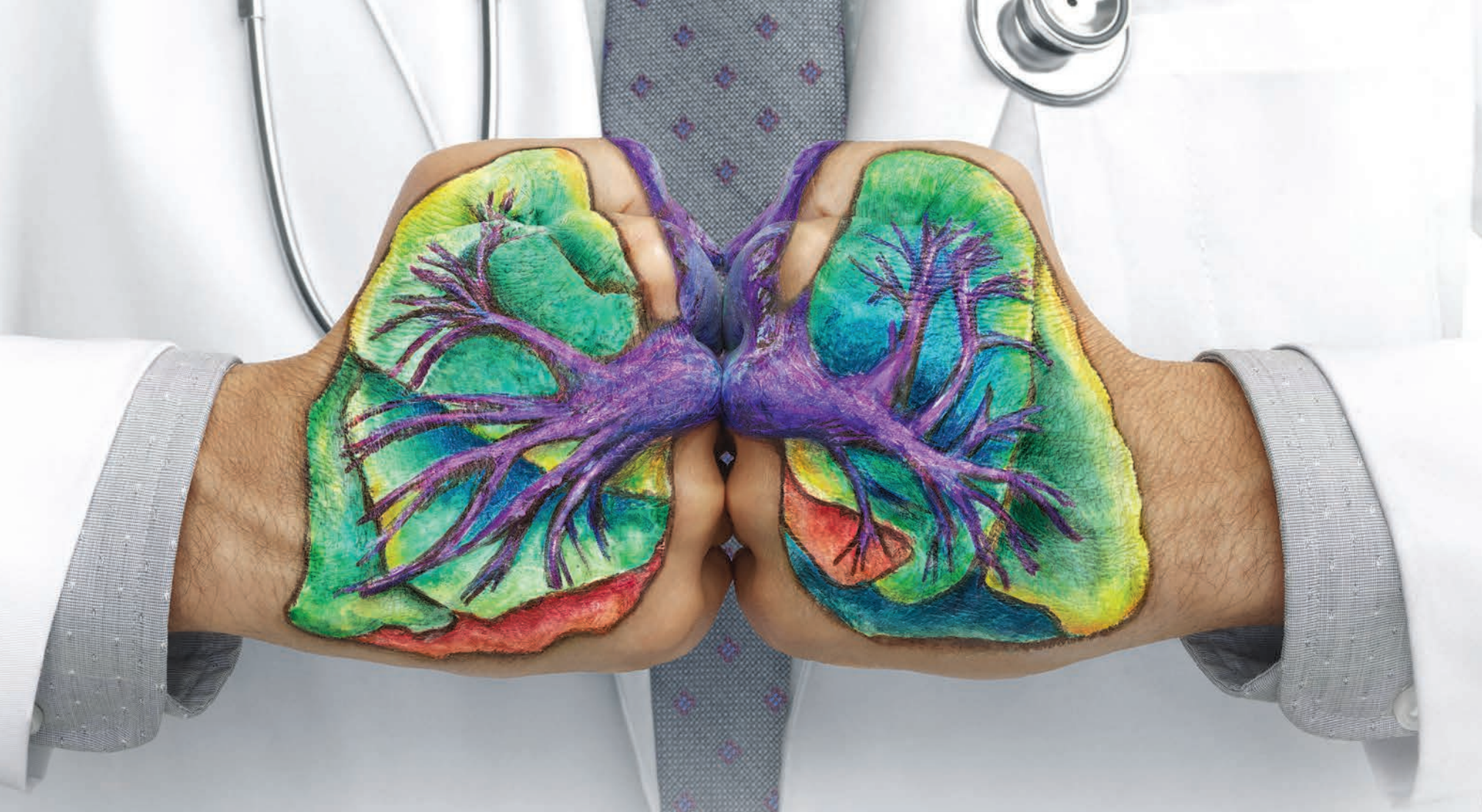

Indication

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

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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

FDA expands indication for COPD therapy

BY KATIE WAGNER LENNON
MDedge News

The Food and Drug Administration has approved a new indication for the chronic obstructive pulmonary disease therapy fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), which allows physicians to prescribe the drug to a broader class of COPD patients, according to a statement from two pharmaceutical companies.

This triple-therapy inhaler was approved for use as a long-term, once-daily maintenance treatment in some COPD patients back in September 2017. Those were defined as COPD patients who were already using the corticosteroid and long-acting beta$_2$-agonist (LABA) drug combination fluticasone furoate/vilanterol (Breo Ellipta) but required additional

bronchodilation or those who were already using the same drugs contained in Trelegy Ellipta by taking both of the following two therapies: Breo Ellipta and the long-acting muscarinic antagonist (LAMA) umeclidinium (Incruse Ellipta). Physicians can now use fluticasone Trelegy Ellipta to treat all COPD patients who have airflow limitation or have experienced an acute worsening of respiratory symptoms, according to the statement that GlaxoSmithKline and Innoviva released on April 24. In this new population of COPD patients who are now approved to use Trelegy Ellipta, the drug will continue to serve as a long-term once-daily maintenance therapy.

The results of the IMPACT trial, which was the first study to compare a single-inhaler triple therapy with two dual therapies, were published on April 18 (N Engl J Med. 2018. doi: 10.1056/NEJMoa1713901).

This study randomized 10,355 symptomatic COPD patients with a history of moderate to severe exacerbations patients to 52 weeks of either triple inhaled therapy involving a once-daily combination of the corticosteroid, 100 mcg fluticasone furoate; the LAMA, 62.5 mcg of umeclidinium; and the LABA, 25 mcg of vilanterol; or dual inhaled therapy involving either 100 mcg fluticasone furoate plus 25 mcg of vilanterol, or 62.5 mcg of umeclidinium plus 25 mcg of vilanterol.

After 1 year, the rate of moderate to severe COPD exacerbations in the triple-therapy group was 0.91 per year, compared with 1.07 in the fluticasone furoate–vilanterol group and 1.21 in the vilanterol-umeclidinium group. This translated to a 15% reduction with triple therapy compared with fluticasone furoate–vilanterol and a 25% reduction, compared with vilanterol-umeclidinium (*P* less than .001 for both).

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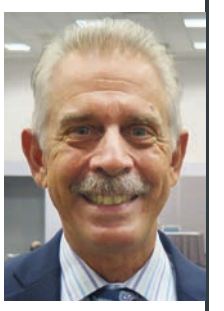
VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Mr. Brown came to my clinic this week. He has severe COPD manifested by exertional dyspnea, chronic cough, and frequent exacerbations of his disease. I have been treating him with tiotropium (LAMA), fluticasone (inhaled corticosteroid), and salmeterol (LABA). The latter two medicines are contained in a combination inhaler. He also has a rescue inhaler. He has quit smoking and completed a course of pulmonary rehabilitation, but still has daily symptoms. What else can I do?



I recently read a report about a new combination inhaler that was a "three-in-one" device: LAMA, LABA, and ICS all in the same delivery system. I was glad to see that "triple therapy" now has more robust objective, scientific support. I figured that a combination inhaler might be more convenient and may facilitate compliance. I wondered, though, whether this new device represents truly novel therapy or a re-packaging of existing therapies? Will other companies spend their research dollars to develop their own "triple threat," or will they develop truly new drugs to help my patient with his breathing?

Withdrawing steroids

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airways clinic at University Health Network, Toronto, noted that relatively few patients with COPD benefit from inhaled steroids. "Given the risk of adverse events (pneumonia, osteoporosis, etc.), we'd rather not give them when they're not needed," he said. "Inhaled steroids seem to play only one role in COPD: They tend to reduce exacerbations in the exacerbation-prone COPD patient. That's about 20% of the COPD population. Despite this, a great many patients end up on triple therapy [long-acting bronchodilators/long-acting muscarinic antagonist (LABA/LAMA) and ICS] needlessly."

For the study, Dr. Chapman and his associates enrolled 1,053 patients with moderate to severe COPD who'd had no more than one exacerbation in the previous year who had used triple therapy for at least 6 months prior to study inclusion. The primary endpoint of the study was noninferiority on change from baseline in postdose trough forced expiratory volume in 1 second (FEV_1) (with a noninferiority margin of –50 mL) after 26 weeks. Exacerbations, health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ-C), and breathlessness as measured by the Transition Dyspnea Index also were evaluated. Of the 1,053 patients, 527 were randomized to IND/GLY and 526 to triple therapy. Their mean age was 65 years and their mean postbronchodilator FEV_1 was 1.6 L.

The researchers found that ICS withdrawal led to a mean reduction in trough FEV_1 of –26 mL, which exceeded the noninferiority margin. This difference between treatments on trough FEV_1 was driven by the subset of patients with high blood eosinophil counts at baseline (a mean of –68 mL for patients with at least 300 cells/mcL and a mean of –13 mL for patients with fewer than 300 cells/mcL). The two treatments showed similar annualized rates of moderate/severe COPD exacerbations (rate ratio, 1.08) and all (mild/moderate/severe) exacerbations (RR, 1.07). ICS withdrawal led to a small difference in SGRQ-C (1.4 U on week 26), but no differences in Transition Dyspnea Index or use of rescue medication over 26 weeks. Safety and tolerability were balanced across the two treatment groups.

"Although we found no overall increase in exacerbations with 'de-escalation,' there were, of course, exacerbations that occurred during the trial," Dr. Chapman said. "We found that they tended to occur in the minority of patients who had elevated blood eosinophil counts, especially if the counts were elevated persistently (at screening and randomization). The relevant cut-point was blood eosinophil counts above 300/UL. If exacerbations did occur in this easily identifiable subpopulation, they tended to occur early, in the first month after de-escalation. This gives physicians a simple way to identify a population they might exercise caution and a period when careful monitoring is useful."

He acknowledged certain limitations of the study, including its 6-month duration, which is shorter than most exacerbation studies. "But by recruiting at multiple sites in multiple countries and across seasons, we don't think this was an importation limitation," he said. "Of course, like most investigators, I can always think of things I wish I had tracked. My personal hunch is that FeNO [exhaled nitric oxide levels] might offer some useful information but that will be a hunch to explore in another study."

SUNSET was sponsored by Novartis. Dr. Chapman disclosed that he has received fees for research, consulting and lectures from Novartis, as well as from several other pharmaceutical companies.

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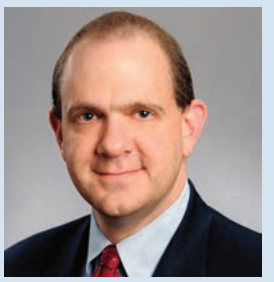
SOURCE: Chapman KR et al. ATS 2018, Abstract A1009.



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

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Female physicians face enduring wage gap

BY RICHARD FRANKI
MDedge News

Male physicians make more money than female physicians, and that seems to be a rule with few exceptions. Among the 50 largest metro areas, there were none where women earn as much as men, according to a new survey by the medical social network Doximity.

The metro area that comes the closest is Las Vegas, where female physicians earned 20% less – that works out to $73,654 – than their male counterparts in 2017. Rochester, N.Y., had the smallest gap in terms of dollars ($68,758) and the second-smallest percent difference (21%), Doximity said in its 2018 Physician Compensation Report.

The largest wage gap on both measures can be found in Charleston, S.C., where women earned 37%, or $134,499, less than men in 2017. The other members of the largest-wage-gap club are as follows: Kansas City, Mo., and Nashville, Tenn., both had differences of 32%, and Providence, R.I., and Riverside, Calif., had differences of 31%, Doximity said in the report, which was based on data from "compensation surveys completed in 2016 and 2017 by more than 65,000 full-time, licensed U.S. physicians who practice at least 40 hours per week."

A quick look at the 2016 data shows that the wage gap between female and male physicians increased from 26.5% to 27.7% in 2017, going from more than $92,000 to $105,000. "Medicine is a highly trained field, and as such, one might expect the gender wage gap to be less prominent here than in other industries. However, the gap endures, despite the level of education required to practice medicine and market forces suggesting that this gap should shrink," Doximity said.

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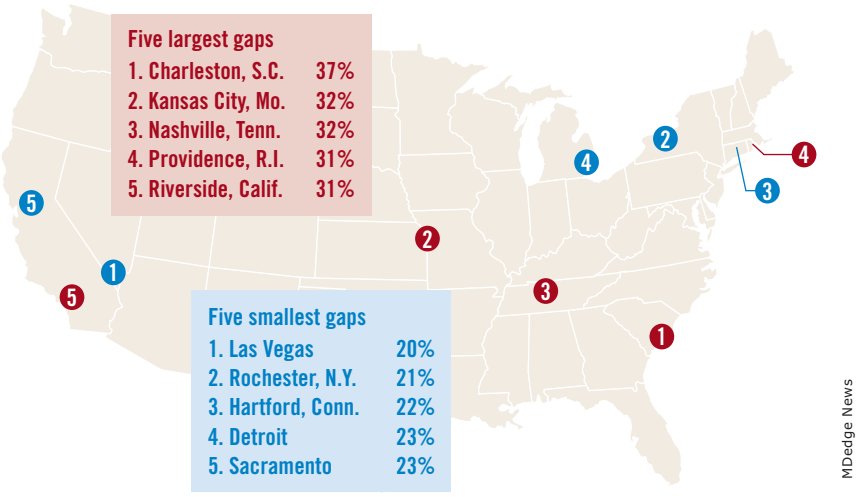

Note: Compensation surveys were completed by more than 65,000 physicians in 2016 and 2017.
Source: Doximity

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: This is a rather damning revelation about pay parity in medicine, but not unexpected given similar findings in non-medical corporate America. As I do not sit on any compensation committees or negotiate contracts for female employees, I am at a loss to explain how these levels of inequality, in ALL 50 metropolitan areas, can exist unchecked. I would suggest that it is time for all male physicians to advocate for our female colleagues.

Reducing the glucose target

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hypoglycemia," they wrote.

The retrospective cohort analysis by Dr. Hersh and his colleagues included 1,809 adult patients treated at three different ICUs in two hospitals between January 2010 and December 2015. Treatment was delivered with a computerized ICU insulin infusion protocol that allows clinicians to choose between two blood glucose targets: 80-110 mg/dL or 90-140 mg/dL. The lower target was chosen for 951 patients, and the moderate target for 858 patients.

While patients in the low blood glucose target group had a higher rate of moderate hypoglycemia, both groups had a low rate of severe hypoglycemia.

The most common primary admission diagnoses in the cohort included chest pain or acute coronary syndrome in 43.3%, cardiothoracic surgery in 31.9%, heart failure (including cardiogenic shock) in 6.8%, and vascular surgery in 6.0%.

While patients in the low blood glucose target group had a higher rate of moderate hypoglycemia, both groups had a low rate of severe hypoglycemia, at 1.16% in the low target group and 0.35% in the moderate target group ($P = .051$).

Unadjusted 30-day mortality was significantly lower in the 80- to 110-mg/dL group compared with the 90- to 140-mg/dL group (4.3% vs. 9.2%, respectively; P less than .001), according to the investigators.

Furthermore, logistic regression analysis showed that patients treated with a target of 80-110 mg/dL had a lower risk of 30-day mortality compared with patients with a target of 90-140 mg/dL (odds ratio 0.65; 95% confidence interval, 0.43-0.98; $P = .04$).

These results advance the debate over appropriate blood glucose targets in critically ill patients, as they suggest that the effects of targeting blood glucose and the effects of severe hypoglycemia "can be separated," the investigators wrote.

Current guidelines on intensive insulin therapy are based in part on findings of the NICE-SUGAR trial, which found that, among adults treated in the ICU, intensive glucose control increased mortality. However, a post hoc analysis suggested the mortality increase in NICE-SUGAR was "largely driven by a significant incidence of moderate hypoglycemia, and to a greater degree severe hypoglycemia," Dr. Hersh and his coauthors noted in their report.

"Given improvements in insulin delivery and glucose monitoring, a reassessment of potential benefits of [intensive insulin therapy] should once again be evaluated in a prospective randomized trial," they wrote.

Dr. Hersh and his coauthors declared no financial or nonfinancial disclosures related to the study.

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SOURCE: Hersh AM et al. CHEST 2018. doi: 10.1016/j.chest.2018.04.025.

Two therapies equally effective in obese OSA patients

BY KATIE WAGNER LENNON
MDedge News

The mortality rates were similar between patients using two different therapeutic regimens to treat obesity hypoventilation syndrome with severe obstructive sleep apnea, according to new research that was presented at the American Thoracic Society International Conference in San Diego.

In this multicenter open-label, randomized, controlled trial, Sanchez Quiroga et al. compared the long-term effectiveness of noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP). The researchers analyzed the results for 202 patients who used one of the two treatments for at least 3 years.

Among this study's findings were that the mortality rates and the number of cardiovascular events that occurred were similar in the two treatment groups. The mortality rate for patients who used CPAP was 14.7%, compared with 11.3% for the patients who received NIV (adjusted hazard ratio, 0.73; $P = .439$), and the cardiovascular events per 100 person-years were 5.1 for CPAP and 7.46 for NIV ($P = .315$).

The researchers concluded that both treatments are equally effective for the long term, but that CPAP should be "the preferred treatment modality," because it's cheaper and easier to implement.

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Two more and counting: Suicide in medical trainees

BY MICHAEL F. MYERS, MD

Like everyone in the arc of social media impact, I was shocked and terribly saddened by the recent suicides of two New York women in medicine – a final-year medical student on May 1 and a second-year resident on May 5. As a specialist in physician health, a former training director, a long-standing member of our institution's medical student admissions committee, and the ombudsman for our medical students, I am finding these tragedies harder and harder to reconcile. Something isn't working. But before I get to that, what follows is a bulleted list of some events of the past couple of weeks that may give a context for my statements and have informed my two recommendations.

- May 3, 2018: I give an invited GI grand rounds on stress, burnout, depression, and suicide in physicians. The residents are quiet and say nothing. Faculty members seem concerned about preventing and eradicating only burnout – and not that interested in anything more severe.
- May 5: A psychiatry resident from Melbourne arrives to spend 10 days with me to do an elective in physician health. As in the United States, there is a significant suicide death rate in medical students and residents Down Under. In the afternoon, I present a paper at the annual meeting of the American Academy of Psychodynamic Psychiatry and Psychoanalysis on the use of psychotherapy in treatment-resistant suicidal depression in physicians. There is increasing hope that this essential modality of care will return to the contemporary psychiatrist's toolbox.
- May 6: At the annual meeting of the American Psychiatric Association in New York, I'm the discussant for powerful heartfelt papers of five psychiatrists (mostly early-career psychiatrists and one resident) that talked about living with a psychiatric illness. The audience is huge, and we hear narratives about internal stigma, self-disclosure, external stigma, shunning, bullying, acceptance, rejection, alienation, connection, and love by peers and family. The authenticity and valor of the speakers create an atmosphere of safety, which enables psychiatrists in attendance from all over the world to share their personal stories – some at the microphone, some privately.
- May 7: Again at the APA, I chair and facilitate a workshop on physician suicide. We hear from four speakers, all women, who have lost a loved one to suicide – a husband, a father, a brother, a son – all doctors. Two of the speakers are psychiatrists. The stories are gripping, detailed, and tender. Yes, the atmosphere is very sad, but there is not a pall. We learn how these doctors lived, not just how they died. They all loved medicine; they were creative; they cared deeply; they suffered silently; and with shame, they lost hope. Again, a big audience of psychiatrists, many of whom share their own stories, that they, too, had lost a physician son, wife, or mother to suicide. Some of their deceased family members fell through the cracks and did not receive the life-saving care they deserved; some, fearing assaults to their medical license, hospital privileges, or insurance, refused to see anyone. They died untreated.
- May 8: Still at the APA, a psychiatrist colleague and I collaborate on a clinical case conference. Each of us describes losing a physician patient to suicide. We walk the attendees through the clinical details of assessment, treatment, and the aftermath of their deaths. We talk openly and frankly about our feelings, grief, outreach to colleagues and the family, and our own personal journeys of learning, growth, and healing. The clinician audience members give constructive feedback, and some share their own stories of losing patients to suicide. Like the day before, some psychiatrists are grieving the loss of a physician son or sibling to suicide. As mental health professionals, they suffer from an additional layer of failure and guilt that a loved one died "under their watch."
- May 8: I rush across the Javits Center to catch the discussant for a concurrent symposium on physician burnout and depression. She foregoes any prepared remarks to share her previous 48 hours with the audience. She is the training director of the program that lost the second-year resident on May 5. She did not learn of the death until 24 hours later. We are all on the edge of our seats as we listen to this grieving, courageous woman, a seasoned psychiatrist and educator, who has been blindsided by this tragedy. She has not slept. She called all of her residents and broke the news personally as best she could. Aided by "After A Suicide: A Toolkit for Residency/Fellowship Programs" (American Foundation for Suicide Prevention), she and her colleagues instituted a plan of action and worked with administration and faculty. Her strength and commitment to the well-being of her trainees is palpable and magnanimous. When the session ends, many of us stand in line to give her a hug. It is a stark reminder of how many lives are affected when someone you know or care about takes his/her own life – and how, in the house of medicine, medical students and residents really are part of an institutional family.
- May 10: I facilitate a meeting of our 12 second-year residents, many of whom knew of or had met the resident who died. Almost everyone speaks, shares their feelings, poses questions, and calls for answers and change. There is disbelief, sadness, confusion, some guilt, and lots of anger. Also a feeling of disillusionment or paradox about the field of psychiatry: "Of all branches of medicine, shouldn't residents who are struggling with psychiatric issues feel safe, protected, cared for in psychiatry?" There is also a feeling of lip service being paid to personal treatment, as in quoted statements: "By all means, get treatment for your issues, but don't let it encroach on your duty hours" or "It's good you're getting help, but do you still have to go weekly?"

In the immediate aftermath of suicide, feelings run high, as they should. But rather than wait it out – and fearing a return to "business as usual" – let me make only two suggestions:

1. We need to come together and talk about this – medical students and residents and training directors and deans. A town hall forum would be ideal. Although there are amazing innovations on wellness emanating from the Association of American Medical Colleges and Accreditation Council for Graduate Medical Education, many current medical students and residents feel frustrated – "This is taking too long" or "This is top down and being imposed on us" or "What about our voices … don't they count?" Although students and residents have representatives on faculty committees, feedback is not universal, and not all residents believe that their senior peers truly convey their concerns to those in power. They want to be present at the table and speak for themselves. Too many do not feel they have a voice.

2. In psychiatry, we need to redouble our efforts in fighting the stigma attached to psychiatric illness in trainees. It is unconscionable that medical students and residents are dying of treatable disorders (I've never heard of a doctor dying of cancer who didn't go to an oncologist at least once), yet too many are not availing themselves of services we provide – even when they're free of charge or covered by insurance. And are we certain that, when they knock on our doors, we are providing them with state-of-the-art care? Is it possible that unrecognized internal stigma and shame deep within us might make us hesitant to help our trainees in their hour of need? Or cut corners? Or not get a second opinion? Very few psychiatrists on faculty of our medical schools divulge their personal experiences of depression, posttraumatic stress disorders, substance use disorders, and more (with the exception of being in therapy during residency, which is normative and isn't stigmatized). Coming out is leveling, humane, and respectful – and it shrinks the power differential in the teaching dyad. It might even save a life.

Dr. Myers is a professor of clinical psychiatry at State University of New York, Brooklyn, and the author of "Why Physicians Die by Suicide: Lessons Learned From Their Families and Others Who Cared."

In psychiatry, we need to redouble our efforts in fighting the stigma attached to psychiatric illness in trainees. It is unconscionable that medical students and residents are dying of treatable disorders. Too many are not availing themselves of services we provide.

chestphysiciannews@chestnet.org

SYMBICORT— THE SPEED THEY WANT

WITH THE CONTROL THEY NEED

SPEED

– Majority of patients' FEV_1* improvement occurred at 5 minutes in COPD[1-3]

CONTROL

– Reduced COPD exacerbations[3]

*1-hour postdose FEV_1.

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

Please see study designs on following pages.

- SYMBICORT 160/4.5 for the maintenance treatment of COPD, and for reducing COPD exacerbations

IMPORTANT SAFETY INFORMATION

- Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA. 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 to ICS alone

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

160/4.5
Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

A reassuring sense of control

SYMBICORT 160/4.5 for the maintenance treatment of COPD

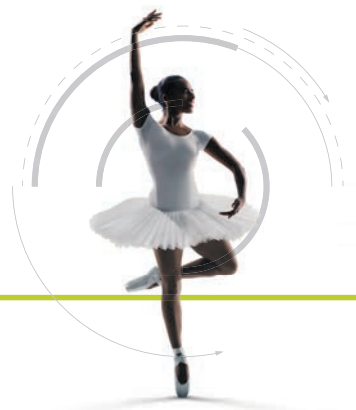
THE SPEED THEY WANT...

BETTER BREATHING—FAST[1-3]

- In a serial spirometry subset of patients taking SYMBICORT 160/4.5* in the SUN Study, the majority of patients' 1-hour postdose FEV_1 improvement occurred at 5 minutes on day of randomization, at month 6, and end of treatment[1-3]
- Sustained improvement in lung function was demonstrated in a 12-month efficacy and safety study[1,2]

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

The majority of FEV_1 improvement occurred at:



SYMBICORT 160/4.5 for reducing COPD exacerbations

...THE CONTROL THEY NEED

REDUCTION IN COPD EXACERBATIONS

- In a 12-month exacerbation clinical trial (Study 4), SYMBICORT 160/4.5* significantly reduced the annual rate of moderate/severe COPD exacerbations by 35% vs formoterol (Estimate Rate Ratio=0.65; 95% CI: 0.53, 0.80; $p<.0001$)[3,4]
  - Annual rate estimate was 0.68 for SYMBICORT 160/4.5 mcg* (n=404) vs 1.05 for formoterol 4.5 mcg* (n=403)
- In a second exacerbation clinical trial of 6-month duration (Study 3), SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (Estimate Rate Ratio=0.74; 95% CI: 0.61, 0.91; $p=.004$)[3,4]
  - Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)

- The most common adverse reactions ≥3% reported in COPD lung function clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection. The safety findings from the two exacerbation clinical trials were consistent with the lung function studies

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

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS

Study Designs

Study 2 (SUN): A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, formoterol 4.5 mcg, and placebo, each administered as 2 inhalations twice daily. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1 (coprimary endpoints). The prespecified primary comparisons for predose FEV_1 were vs placebo and formoterol, and the primary comparison for 1-hour postdose was vs placebo.

Comparator Arms in the SUN Study

Mean improvement in 1-hour postdose FEV_1 (mL/%) over 12 months (serial spirometry subset)

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%)

6 months: SYMBICORT 160/4.5 mcg (270 mL/28%), formoterol 4.5 mcg (200 mL/23%), placebo (60 mL/7%)

End of month 12 (last observation carried forward [LOCF]): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%)

SYMBICORT 160/4.5 mcg* (n=121), formoterol 4.5 mcg* (n=124), placebo* (n=125)

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg with formoterol 4.5 mcg, each administered as 2 inhalations twice daily. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg with formoterol 4.5 mcg, each administered as 2 inhalations twice daily. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

Exacerbation Definitions

In **Study 3**, COPD exacerbations were defined as worsening of ≥2 major symptoms (dyspnea, sputum volume, sputum color/purulence) or worsening of any 1 major symptom together with ≥1 of the minor symptoms (sore throat, colds [nasal discharge and/or nasal congestion], fever without other cause, increased cough or increased wheeze) for ≥2 consecutive days. COPD exacerbation severity was classified as moderate if symptoms required systemic corticosteroid (≥3 days) and/or antibiotic treatment, and severe if hospitalization was required.

In **Study 4**, COPD exacerbations were defined as worsening of COPD that required treatment with a course of oral steroids and/or hospitalization.

- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients

Symbicort® 160/4.5

(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

A reassuring sense of control

IMPORTANT SAFETY INFORMATION (CONT'D)

- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce COPD exacerbations.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. **2.** Data on File, REF-4960, AZPLP. **3.** SYMBICORT [package insert]. Wilmington, DE: AstraZeneca; December 2017. **4.** Data on File, REF-16658, AZPLP.

AstraZeneca

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION. For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. SYMBICORT 160/4.5 is also indicated to reduce exacerbations of COPD. SYMBICORT 160/4.5 is the only strength indicated for the treatment of COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. 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. 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 to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol (SYMBICORT) to budesonide *[see Clinical Studies (14.1) in the full Prescribing Information]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist

1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate / salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, 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.

Excessive Use of SYMBICORT and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications 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 SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT 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.

Pneumonia and Other Lower Respiratory Tract Infections

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

In a 6-month lung function study of 1704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month lung function study of 1964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox 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 affects 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 exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If 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 chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

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

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. 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 per day 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 SYMBICORT may provide control of asthma 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, a severe asthma attack 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, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or 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 inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma and COPD symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT 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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information].*

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10) in the full Prescribing Information]*. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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 (e.g., 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 SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month lung function study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled

corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month lung function study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications 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.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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.

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 2 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 N = 277 %**	**160/4.5 N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of ≥3% and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below reflect exposure to SYMBICORT 160/4.5 in 1783 patients. SYMBICORT 160/4.5 was studied in two placebo-controlled lung function studies (6 and 12 months in duration), and two active-controlled exacerbation studies (6 and 12 months in duration) in patients with COPD.

The incidence of common adverse events in Table 3 below is based upon pooled data from two double-blind, placebo-controlled lung function clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 3 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 3 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment[1]	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, hematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

The safety findings from the two double-blind, active-controlled exacerbations studies (6 and 12 months in duration) in which 1012 adult COPD patients (616 males and 396 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily were consistent with the lung function studies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. 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. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting $beta_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma 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 in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG 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 SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5) in the full Prescribing Information]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication 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 medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

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Americans are getting more sleep

BY KATIE WAGNER LENNON
MDedge News

Some Americans began getting more sleep over the period of 2003 through 2016, an analysis of data from the American Time Use Survey (ATUS) has suggested.

Many people living in the United States habitually sleep less than the recommended 7-9 hours each day. "Experimental studies have demonstrated that both acute total and chronic partial sleep restriction in healthy adults are associated with physiological changes that can be considered precursors of manifest diseases (e.g., decreased insulin sensitivity)," noted Mathias Basner, MD, PhD, and David F. Dinges, PhD, both of the division of sleep and chronobiology at the University of Pennsylvania, Philadelphia, in their paper.

This new study, which was published in the journal Sleep, is the first to have demonstrated that large parts of the U.S. population significantly increased their sleep between 2003 and 2016.

The investigators analyzed ATUS responses from 181,335 Americans aged 15 years and older; respondents included in the analysis were not active in the military or residing in institutions such as nursing homes or prisons. In 15- to 20-minute computer-assisted telephone interviews, the survey participants reported the activities they performed over a 24-hour period on a minute-by-minute basis. In-depth analyses included only groups "that showed a significant increase in sleep duration across survey years either on weekdays or weekends (or both): employed respondents, full-time students, and retirees."

Using this data from ATUS, Dr. Basner and Dr. Dinges found that on workdays the prevalence of people who were sleeping 7 hours or less a day decreased by 0.44% per year (*P* less than .0001), while the percentage people who were sleeping more than 9 hours a day increased by 0.48% per year (*P* less than .0001).

Overall, respondents' sleep increased by an average of 1.40 minutes during a weekday and 0.83 minutes during a weekend day every year.

These findings will be welcome news for organizations, such as the American Academy of Sleep Medicine, the Sleep Research Society, and the Centers for Disease Control and Prevention, that have been campaigning for years to increase sleep time among Americans.

The researchers also observed that the percentage of respondents in short sleep duration categories decreased significantly, and the percentage of respondents in long sleep duration categories increased significantly across survey years. One of the "most pronounced changes" occurred in the size of the group of patients receiving 6-7 hours of sleep. This group decreased by 0.23% per year. The biggest change was seen in the category of patients receiving 9-10 hours of sleep, which increased by 0.24% per year.

"[The] change in sleep duration across survey years on weekdays can mostly be explained by respondents going to bed earlier at night and, to a lesser degree, by getting up later in the morning," the researchers said. "On weekends/holidays, 'time to bed' shifted significantly to earlier bed times by 1.1 min/year across survey years, which was comparable to the shift observed on weekdays."

Study participants aged 18-24 slept the most, with hours slept having "decreased with increasing age." On weekdays, adults aged 45-54 years slept the least, and on weekends, adults aged 55-64 years got the least shuteye. Hispanic, Asian, and black respondents slept more than white and "other race/ethnicity" survey participants. The researchers also found that women overall got more sleep than men.

Dr. Basner and Dr. Dinges expressed optimism about Americans' ongoing battle against chronic sleep deficiency. "These findings presented here suggest that we are on the right track ... even if there is still a long way to go," they said.

The authors reported no conflicts of interest.

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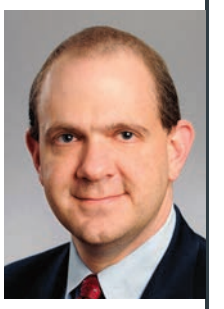
SOURCE: Basner M et al. Sleep. 2018 Apr 1;41(4):1-16.

VIEW ON THE NEWS



David A. Schulman, MD, FCCP, comments: For more than 15 years, we have had evidence that sleep deprivation is associated with not only increased accident risk, but also other common causes of mortality, including cardiovascular disease and cancer. Despite this knowledge, decades of trending in sleep patterns of the US population have continued to show declines in total sleep time, which have been attributed to multiple factors, including longer work hours and the pervasive use of electronics, which can serve both as a distraction from sleep and a contributor to circadian dysrhythmia.

The recent article by Basner and Dinges suggests, for the first time, that this trend may be reversing. Although the data suggest a minimal bump in sleep time (of approximately 1 minute per night, slightly more during weeknights than weekend nights), it is at least a move in the right direction. In a related editorial in the same issue of SLEEP, Ogilvie and Patel identify some possible problems with the paper; these include a nonvalidated tool for data collection, and the possible conflation of time in bed and sleep time. Even if the data are accurate, it is difficult to imagine that such a modest improvement in sleep duration would yield meaningful benefits in terms of daytime function and sleep-related morbidity.

While our work in improving public awareness of sleep deprivation is far from done, perhaps this study is the first sign that a new day is dawning on improved sleep health for the country.

8-Isoprostane levels predict OSA in children

BY MADHU RAJARAMAN
MDedge News

The oxidative stress biomarker 8-isoprostane (8-IsoP) predicted obstructive sleep apnea (OSA) and disease severity in children better than the fractional concentration of exhaled nitric oxide (FeNO), according to results published in Sleep Medicine.

In an analysis of 46 patients with sleep-disordered breathing and 20 controls, patients with OSA had higher levels of 8-IsoP in exhaled breath condensate (EBC) upon waking than patients with primary snoring (PS) and controls. 8-IsoP values were also correlated with apnea hypopnea index (AHI) (r, 0.40; *P* = .003) and oxygen saturation, also known as SaO_2 (r, –0.50; *P* = .001), reported Mario Barreto, MD, of the Pediatric Unit at Sant'Andrea Hospital in Rome and his coauthors.

Patients with OSA had higher levels of 8-IsoP in exhaled breath condensate upon waking than patients with primary snoring and controls. 8-IsoP values were also correlated with apnea hypopnea index and oxygen saturation.

The investigators studied 66 children aged 4.5-15.1 years, of whom 46 had sleep-disordered breathing (SDB) and were enrolled in the hospital's Pediatric Sleep Center. The 20 healthy controls had no history of sleep problems, including snoring, apneas, and restless sleep. Exclusion criteria included acute respiratory infections in the 4 weeks preceding the study, chronic respiratory comorbidities, and therapy with corticosteroids or other anti-inflammatory drugs for at least 3 weeks.

Patients with SDB had a medical examination followed by overnight standard polysomnography (PSG), and EBC 8-IsoP and FeNO measurements were collected the next morning upon waking. The SDB group also had spirometry and skin prick testing for common allergens. The children in the

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control group had the same tests and measurements done, except for PSG, Dr. Barreto and his colleagues wrote.

Central, obstructive, and mixed apnea events were counted according to American Academy of Sleep Medicine (AASM) criteria. AHI was defined as the average number of apnea and hypopnea events per hour of sleep. OSA was diagnosed with an AHI of one episode per hour and confirmed by the presence of SDB symptoms with AHI of one episode per hour.

Children with snoring and an AHI of less than one episode per hour were diagnosed with primary snoring (PS). Patients with an AHI greater than one episode per hour and less than five episodes per hour were diagnosed with mild OSA. Children with an AHI of greater than five episodes per hour were diagnosed with moderate to severe OSA, the authors said.

While 8-IsoP concentrations correlated with OSA severity for AHI and SaO_2, FeNO did not, Dr. Barreto and colleagues reported.

The difference in 8-IsoP concentrations for children with SDB and controls (mean, 39.6; $P = .006$) was increased when adjusted using multiple linear regression (mean, 43.2; $P = .007$), and the difference was even more pronounced when adjusted for all potential confounding variables (mean, 53.1; $P = .008$). The difference in FeNO levels between SDB patients and controls was not statistically significant (mean, 1.67; $P = .358$) and did not change significantly when adjusted for confounding variables.

High area under the curve values were observed for 8-IsoP as a predictor of OSA (.839; 95% confidence interval, .744-.933, $P = .000$). The sensitivity and specificity of cutoff values of 8-IsoP concentrations above the 50th percentile were 76.5% and 78.1%, respectively.

"[It] seems that biomarkers of oxidative stress reflect OSA severity in children more closely than biomarkers of atopic-eosinophilic airway inflammation," the authors concluded.

No disclosures or conflicts of interest were reported.

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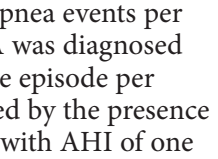
SOURCE: Barreto M et al. Sleep Medicine. 2018. doi: 10.1016/j.sleep.2018.01.011.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The field of biomarkers in different disease states has exploded over the last few years and this article is fascinating. Barreto et al. analyzed a biomarker for oxidative stress in pediatric patients who presented to their sleep lab. The concentration of 8-isoprostane in the exhaled breath condensate correlated with the severity of the OSA in these patients who were 4.5 years of age to 15.1 years of age. We screen for OSA in difficult-to-control asthma patients, so it would be interesting to repeat this study in that population, too!



Disrupted sleep tied to alexithymia

BY GINA L. HENDERSON
MDedge News

Heightened alexithymia may explain poor sleep quality, a pair of studies shows.

Alexithymia is a condition characterized by difficulty identifying and expressing one's emotions. "The mechanism by which alexithymia confers risk of disrupted sleep remains unclear, [but] suggestions include increased nocturnal arousal as a result of poor verbalization of emotions and increased light sleep," wrote Jennifer Murphy, citing previous research.

In the first study, Ms. Murphy and her associates recruited 86 men and women; 70 were included in the analyses. Participants' alexithymia scores were measured using the Toronto Alexithymia Scale, or TAS-20, which consists of three sub-

scales – difficulty describing feelings, difficulty identifying feelings, and externally oriented thinking. Sleep quality was measured using the Pittsburgh Sleep Quality Index, or PSQI, a self-report measure that asks numerous questions, including: "During the past month, when have you usually gone to bed at night?" High scores on the TAS-20 and PSQI "indicate elevated alexithymic traits and poor sleep quality, respectively," wrote Ms. Murphy, a doctoral candidate in social, genetic, and developmental psychiatry at King's College London, and her associates in the journal Personality and Individual Differences.

"The mechanism by which alexithymia confers risk of disrupted sleep remains unclear, [but] suggestions include increased nocturnal arousal as a result of poor verbalization of emotions and increased light sleep," wrote Jennifer Murphy.

The researchers found associations between total alexithymia scores and reduced sleep quality (*P* less than .001). They also found a significant association between the TAS-20 subscales and reduced sleep quality (all *P* less than .006).

In the second study, in which 73 men and women participated, Ms.

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Murphy and her associates sought to determine whether the association found in the first study was tied to depression or anxiety. Participants went online and completed three questionnaires: the TAS-20; the PSQI; and the Depression, Anxiety, & Stress Scale, or DASS-21, in a randomized order. Higher scores on the DASS-21 correlate with greater levels of depression, anxiety, and stress. None of the questionnaires asked about any aspects of sleep.

Using a regression model, Ms. Murphy and her associates found that all of the measures correlated with poor sleep quality. But only depression ($P = .011$) and alexithymia ($P = .004$) explained unique variance in sleep quality.

Ms. Murphy said in an interview that, although it might be too early to make a clear clinical recommendation, the results suggest that "clinicians should be aware of the possibility of sleep problems characterized by heightened alexithymia and more generally in those with alexithymia."

While further research is needed to confirm the direction of causality between disrupted sleep and alexithymia and how these subjective sleep reports in alexithymia map onto objectively measured sleep problems, these data suggest a link that is independent of depression and anxiety, she said.

Meanwhile, other researchers

report that alexithymia is becoming more clinically relevant. Rising rates of alexithymia are being reported in psychiatric conditions such as autism, eating disorders, schizophrenia, and alcohol and substance abuse. The condition is also seen in neurologic conditions such as multiple sclerosis and traumatic brain injury (Neuropsychologica. 2018;11:229-40).

Ms. Murphy and her associates cited several limitations of their research. One is that they did not control for factors that affect sleep quality and alexithymia such as body composition. They also cited reports of discrepancies between objective and subjective measures – such as those made by self-report – and the relatively small sample sizes.

The research was supported by the Economic and Social Research Council and the Baily Thomas Charitable Trust. No conflicts of interest were reported.

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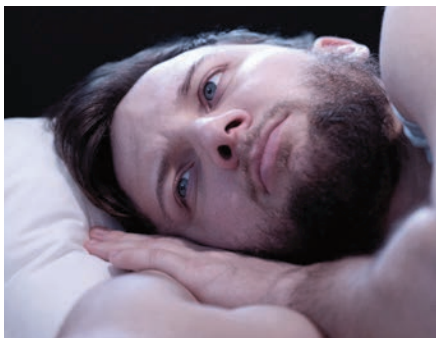
SOURCE: Murphy J et al. Pers Individ Dif. 2018 Mar 27;129:175-8.



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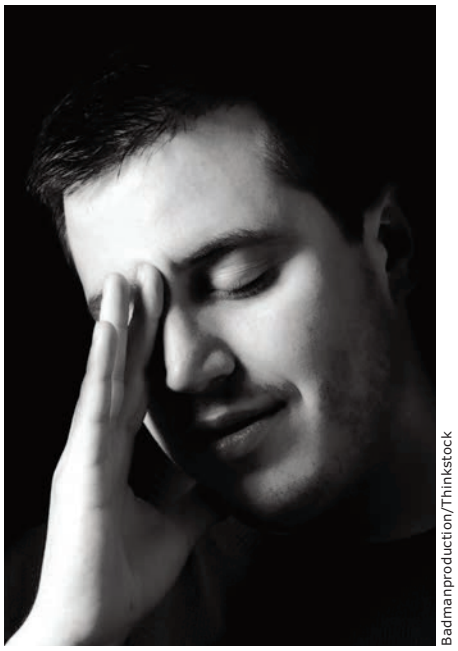
Insomnia, major depressive episode linked in U.S.

BY CHRISTOPHER PALMER
Frontline Medical News

Insomnia is prevalent among U.S. soldiers, and the highest prevalence rate is among those with current major depressive episode, according to a cross-sectional analysis.

"Psychiatric disorders moderated the relationship between insomnia and memory/concentration problems, suggesting the psychiatric disorders contribute unique variance to cognitive problems," wrote Janeese A. Brownlow, PhD, of the University of Pennsylvania, Philadelphia, and her associates. "Results highlight the importance of considering both insomnia and psychiatric disorders in the diagnosis and treatment of cognitive deficits in military soldiers."

The researchers used the All Army Study of the Army Study to Assess Risk and Resilience in Servicemembers as their data source. They used the Composite International Diagnostic Interview (CIDI) and the Posttraumatic Stress Disorder Checklist to assess psychiatric disorders; the CIDI also helped assess cognitive problems. One of the strengths of this study was its large sample size: It had an unweighted sample of 21,449 soldiers.



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Dr. Brownlow and her associates found that the prevalence of insomnia among soldiers with current major depressive episode was 85%. The prevalence was 82.6% among soldiers with generalized anxiety disorder and 69.7% among those with PTSD. The likelihood of having insomnia grew with the number of comorbid psychiatric disorders.

One of the limitations of the study was that many of the measures were self-reported; for example, the psychiatric diagnoses and the determinations regarding insomnia were based on surveys and questionnaires rather than clinical interviews and assessments. Furthermore, the absence of a comprehensive neurocognitive battery might have limited the study's ability to assess cognitive problems. Nevertheless, the researchers wrote, "addressing insomnia may increase resiliency and the ability to perform and cope with the complexities of active duty."

Read more about the study in the Journal of Affective Disorders.

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Vehicle crash risk linked to various sleep disorders

BY TARA HAELLE
MDedge News

Individuals with certain sleeping disorders may have a higher risk of crashes, near-crashes, or unsafe maneuvering prior to such events, suggests a study.

"The results confirm that some sleep disorders generally increase driving risk as defined by our dependent measures," wrote Shu-Yuan Liu, a doctoral student, and two colleagues at Virginia Tech, Blacksburg (Sleep. 2018 Apr 1. doi: 10.1093/sleep/zsy023). "Furthermore, the results also provide some insights into how risk varies across specific types of sleep disorder and some moderating factors."

The researchers analyzed data collected by the Second Strategic Highway Research Program (SHRP 2), the nation's largest Naturalistic Driving Study, on 3,541 drivers between ages 16 and 98. The participants' cars were outfitted with small cameras and other instruments that collected information on driver behavior, the driving environment, and the vehicle's movements, such as speed and braking data.

The study involved licensed drivers who drove at least 3 days a week, had an eligible vehicle in good working condition, and agreed to participate for 1-2 years. At the start and end of the study, participants filled out a questionnaire on any medical conditions they had or had been treated for in the past year, any medications they were taking, and any aids they were using for a medical condition.

Among the conditions they were able to select were narcolepsy, sleep apnea, insomnia, shift-work sleep disorder, restless legs syndrome (RLS), periodic limb movement disorder, and migraine. All of these conditions have been linked in previous studies to a higher risk of vehicle collisions.

A total of 646 participants, 18.2% of the sample, had one of those disorders: 0.14% had narcolepsy, 7.4% had sleep apnea, 4.8% had insomnia, 3.4% had RLS, 0.37% had shift-work sleep disorder, 0.23% had periodic limb movement disorder, and 8.4% had migraine.

Analysis of vehicle data found that female drivers with RLS and any drivers with insomnia had a higher risk of crashes or near-crashes (adjusted odds ratio, 2.26 and 1.49, respectively, *P* less than .05 for both). Drivers with narcolepsy had 9 times greater odds of being involved in a crash or near-crash, but the finding was not statistically significant (AOR, 10.24, *P* less than .1).

"Drivers who reported frequency of sleepy driving as 'never,' 'rarely,' and 'sometimes' also had higher a risk, indicating that crash or near-crash risk is also associated with sources other than these sleeping disorders," the authors noted. These drivers' increased odds of getting into or nearly getting into a crash ranged from 31% to 53% greater (*P* less than .05).


GummyBone/Getty Images

All drivers with shift-work sleep disorder, except for those aged 20-24, had a crash or near-crash rate that was 7.5 times greater than that of drivers without any sleeping disorders. The rate among drivers aged 20-24 with this disorder had a 90% lower rate (risk ratio, 0.1, *P* less than .05) compared with control drivers.

When the researchers analyzed the drivers' maneuvers just before a crash or near-crash, they found females with sleep apnea had a 36% greater odds of doing an unsafe maneuver in crash/near-crash circumstances (AOR, 1.36). Females with RLS and any drivers with shift-work sleep disorder were more than twice as likely to perform unsafe maneuvers (AOR, 3.38 and 3.53, respectively, *P* less than .05).

The only drivers with a sleeping disorder who were more likely to be involved in crashes of greater severity were those with periodic limb movement disorder (AOR, 1.43, *P* less than .05).

However, young drivers, senior drivers, and nighttime drivers also all had higher odds of being involved in more severe crashes and in performing unsafe maneuvers prior to a crash or near-crash. Nighttime drivers seemed to be most at risk for these, and they were linked to having more than 5 times greater odds of unsafely maneuvering their vehicles prior to getting into a crash or near-crash (AOR, 6.71, *P* less than .05).

"This is a strong piece of evidence that nighttime driving is less safe than daytime driving and limiting amount of nighttime driving could be one method to moderate road risk for some individuals," the authors wrote.

The study's limitations include its observational nature, low numbers of participants with several of the sleeping disorders (at levels below the disorder's prevalence in the general population), and the complexities involved in what causes a crash or near crash.

One limitation of this study was that sleep hygiene and sleep quality were not examined, even though these might contribute significantly to roadway safety, the researchers noted. This study also did not take into account what medications or other treatment (such as continuous positive airway pressure for those with sleep apnea) the participants might be receiving for their condition.

The study's implications include the need for physicians to advise patients with insomnia or females with sleep apnea to use caution while driving without "exaggerating risks that introduce undue fear to patients with other sleep disorders and thereby limiting mobility unnecessarily," the authors wrote. The researchers also suggested that employers consider providing alternative transportation to shift workers and/or that insurance companies offer employers lower rates for offering such alternatives.

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SOURCE: Liu S-Y et al. Sleep J. 2018 Apr 1. doi: 10.1093/sleep/zsy023.

Uvulopalatopharyngoplasty may cut CV events in OSA

BY BIANCA NOGRADY
MDedge News

Surgical remodeling of the tissues of the throat using uvulopalatopharyngoplasty (UPPP) could significantly reduce the cardiovascular complications of obstructive sleep apnea (OSA), according to a study published in Sleep Medicine.

Researchers examined the incidence of newly diagnosed myocardial infarction, congestive heart failure, and atrial fibrillation in 192,316 patients with a new diagnosis of obstructive sleep apnea – 22,213 of whom had undergone UPPP – and 961,590 controls.

The individuals who had had UPPP had a significantly lower incidence of all three cardiovascular events, compared with those who had not undergone the procedure. The hazard ratios for myocardial infarction, congestive heart failure, and atrial fibrillation among individuals with OSA who had uvulopalatopharyngoplasty, compared with controls, were 1.002, 0.757, and 1.117, respectively. By comparison, those hazard ratios in patients with OSA who had not had UPPP, compared with controls, were 1.070, 1.165, and 1.39 for myocardial infarction, congestive heart failure, and atrial fibrillation, respectively.

These figures were after accounting for confounding factors, such as age, sex, diabetes, and dyslipidemia.

The authors wrote that the most distinctive finding of their study was that uvulopalatopharyngoplasty lowered the incidence of congestive heart failure and atrial fibrillation in patients with obstructive sleep apnea to the point that they had the same level of risk as individuals without obstructive sleep apnea.

"Prior studies have evaluated the success of UPPP based on reductions of AHI [apnea-hypopnea index], with the average success rate for the surgery being low for most patients," wrote Heung-Man Lee, MD, PhD, then from the Guro Hospital at Korea University, Seoul, and his coauthors.

"However, the current study suggests that the effects of UPPP, regardless of the effects on AHI, can significantly reduce cardiac morbidity in patients with OSA."

Patients without diabetes showed more benefit from UPPP in reducing the incidence of congestive heart failure, compared with those with diabetes. However, those with diabetes showed greater reductions in the

Continued on following page

Three-pronged plan for universal flu vaccine proposed

BY NICK ANDREWS
MDedge News

Three specific research areas were proposed by the National Institute of Allergy and Infectious Diseases (NIAID) in its development plan for a universal influenza vaccine, as detailed in a report published online in the Journal of Infectious Diseases.


DR. FAUCI

Anthony S. Fauci, MD, director of the NIAID, spoke with MDedge News in an interview regarding the plan and noted that he and his colleagues felt that it was important to accelerate the effort for a universal vaccine.

The plan will focus on transmission, natural history, and pathogenesis studies utilizing prospective cohorts; influenza immunity and correlates of immune protection; and strategies in rational vaccine design to elicit broad, protective immune responses, according to Emily J. Erbelding, MD, MPH, director of microbiology and infectious diseases at the NIAID, and her associates in their report. They noted that the three research areas are not prioritized and that advances in each are expected to be interdependent.

"The strategic plan also includes a description of research resources essential to advancing these three research areas that [the] NIAID will develop, support, and provide for the scientific community," wrote Dr. Erbelding and her coauthors.

The development plan comes 8 months after scientists from academia, industry, and government convened for the NIAID Pathway to a Universal Influenza Vaccine workshop to address knowledge gaps and strategy, which was summarized last year in the journal Immunity (2017;47: 599-603). The scientists at the workshop developed criteria that would define a universal vaccine and decided that a universal vaccine for influenza should do three things: be

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risk of atrial fibrillation, compared with those without diabetes.

Similarly, the incidence of atrial fibrillation was reduced after uvulopalatopharyngoplasty but only in patients with hypertension or dyslipidemia and not in those with normal blood pressure or lipid levels.

"These differences in outcomes after UPPP are probably due to the different etiologies of cardiovascular disease," the authors wrote. Limitations included the absences of polysomnography information and information on whether patients used other sleep apnea therapies, such as CPAP or a mandibular advancing device.

The study was supported by the Korean Society of Otorhinolaryngology Head and Neck Surgery.

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SOURCE: Lee H-M et al. Sleep Med. 2018 May;45:11-6.

at least 75% effective against symptomatic influenza infection; protect against group I and II influenza A viruses; and have durable protections that lasts at least 1 year and preferably through multiple seasons.

"Clearly, a vaccine that would cover most or all seasonal strains of influenza and also provide protection during a pandemic is highly desirable," wrote Catharine I. Paules, MD, of the University of Maryland, Baltimore, and her coauthors in the workshop summary.

Dr. Fauci told MDedge News how "experts from all over the country addressed their thoughts and concerns with us last year [at the workshop], and now we have a development plan," he said. "But the next step will be doing the research and finding more resources. ... The work is yet to be done."

The development plan was published amid an ongoing historic flu season.

Dr. Fauci noted that this season had particular circumstances that made it worse than normal. "I don't think that, had we had this plan in place a year ago, it would have had an impact on this flu season," he said.

The authors reported no relevant financial conflicts and that the National Institutes of Health produced this plan.

SOURCE: Erbelding EJ et al. J Infect Dis. 2018 Feb 28. doi: 10.1093/infdis/jiy103.

Let clinical scenario guide sarcoidosis treatment

BY MICHELE G. SULLIVAN
MDedge News

SANDESTIN, FLA. – Don't be a slave to imaging when evaluating the patient with sarcoidosis.

"Sometimes, the worst-looking patients [on imaging] have the best prognosis," Daniel Culver, DO, said at the annual Congress of Clinical Rheumatology. Patients with Löfgren's syndrome are a very good example of this tenet, he said in an interview. Scans can look alarming, with multiple widespread granulomas. But Löfgren's is generally a benign condition, despite its threatening mien.

Instead of imaging, "Let two things drive your decision to treat: danger to an organ, and quality of life," said Dr. Culver, a pulmonologist and director of the Sarcoidosis Center of Excellence at the Cleveland Clinic in Ohio; he is also president of the World Association for Sarcoidosis.

He agrees with a decision schema published in 2015 (Clin Chest Med. 2015;36[4]:751-67).

"Sometimes, the worst-looking patients [on imaging] have the best prognosis," said Daniel Culver, DO, of the Cleveland Clinic.

Six factors weigh in favor of treatment:

- Symptomatic disease.
- Impaired organ function.
- Disease endangering an organ.
- Progressive disease.
- Clear-cut disease activity.
- Low likelihood of remission.

These must be balanced – with patient input as the fulcrum – against five factors that favor conservative management:

- Minimal symptoms.
- Good organ function.
- Low risk of danger to organs.
- Inactive disease.
- Higher likelihood of remission.

The decision to embark on a treatment program, usually starting with a steroid-based regimen, can't be taken lightly, Dr. Culver said. A 2017 study showed that steroids pose a cumulative risk of toxicities for sarcoidosis patients (Respir Med. 2017 Nov;132:9-14). Patients who started steroids faced more than a doubling in the risk of a toxic side effect by 96 months when compared with those who didn't. But even short-term steroid use increased the risk of a toxicity, Dr. Culver said. The study noted that problems can begin to occur in as little as 1 month, at a cumulative dose as low as 1 g.

For patients who fall onto the "treat" side of the risk teeter-totter, Dr. Culver recommended starting with an initial course of prednisone at 20-30 mg daily for no more than 4 weeks. Responders can taper to less than 10 mg/day. Those who continue to do well can maintain low-dose prednisone for up to 12 months and then complete the taper. Patients who relapse can add an immune modulator (methotrexate,

Continued on following page

Three days of beta-lactam beat clinically stable CAP

BY MICHELE G. SULLIVAN
MDedge News

MADRID – Three days of beta-lactam therapy was just as effective as 8 days for clinically stable patients presenting with community-acquired pneumonia.

In a randomized, placebo-controlled trial, 15-day cure rates were

Michele G. Sullivan/MDedge News

Dr. Aurélien Dinh

69.9% in patients who took 3 days of antibiotics and 61.2% in those who took 8 days – a nonsignificant difference, Aurélien Dinh, MD, said at the European Society of Clinical Microbiology and Infectious Diseases annual congress.

The French study was one of a series at the meeting demonstrating that, for some groups of patients, short-term antibiotic therapy is a viable – and probably healthy – alternative to the traditional longer courses, said Dr. Dinh of the University of Paris Hospital.

"Reducing treatment time now appears to be manageable and effective in a number of infectious diseases," Dr. Dinh explained. "Although there are some limits, surely, this change in practice might lead to reduced rates of multidrug-resistant bacteria, fewer adverse events, and surely lower costs."

The French PTC Trial (Short Duration Treatment of Non-Severe Community-Acquired Pneumonia) randomized 310 patients (mean age, 73.5 years) to either short- or long-course treatment with a beta-lactam antibiotic. Patients were eligible for the study if they were admitted to the hospital for community-acquired pneumonia based on respiratory signs, fever of 38° C or higher, and evidence of new infiltrate on chest radiograph.

All patients were treated with 3 days of amoxicillin/clavulanic acid (Augmentin) or third-generation cephalosporin. Those who had responded clinically by day 3 entered the 5-day randomization period, receiving placebo or 5 more days of active therapy with the same agent.

Clinical requirements for randomization included being afebrile with stable heart and respiratory rate, a systolic blood pressure of at least 90 mm Hg, and oxygen saturation of at least 90%.

The primary endpoint was clinical cure at day 15: no fever, absence of or improvement in respiratory symptoms (dyspnea, cough, purulent sputum, and cackles), and no need for additional antibiotic treatment for any indication.

Secondary endpoints were cure at day 30, 30-day mortality, adverse events, length of stay, return to usual activities by day 30, and quality of life at day 30.

Many of the generally elderly patient cohort had comorbid illnesses, including diabetes (about 20%), chronic obstructive pulmonary disease (about 35%), and coronary insufficiency (about 14%). About 20% were active smokers. Less than 10% had gotten a pneumococcal vaccine in the past 5 years.

At admission, more than half of patients were dyspneic, 80% had cough, and 39% had purulent sputum. The median PSI/PORT Score was 82.

After 3 days of treatment, clinical cure was not significantly different between the 3- and 8-day groups, either in the intent-to-treat analysis (69.9% vs. 61.2%) or in the per-protocol analysis (75.7% vs. 68.7%).

"Reducing treatment time now appears to be manageable and effective in a number of infectious diseases. [This] change in practice might lead to reduced rates of multidrug-resistant bacteria, fewer adverse events, and surely lower costs."

Because the trial had closed days before the ECCMID meeting, only the primary endpoints were available for discussion, Dr. Dinh said. Investigators are analyzing the secondary endpoint data, which he said would be published at a later date.

Despite the positive results, Dr. Dinh cautioned against using the study as justification for a one-size-fits-all treatment for community-acquired pneumonia.

"Although I think we demonstrated that 3 days of treatment with beta-lactam is not inferior to 8 days, this cannot be imposed without regard to individual patient status," he cautioned. Such a treatment paradigm would not be advisable for patients with moderately severe pneumonia, who were excluded from the study, or those with compromised immune systems.

Nor does Dr. Dinh expect wholesale clinical embracing of the encouraging results, which bolster the ever-accumulating data in favor of shorter courses of antibiotics for some infectious diseases.

"I think there is a chance that clinicians who normally treat for 9 or 10 days may now feel comfortable reducing to 7," he said with a chuckle.

The French Ministry of Health sponsored the study. Dr. Dinh had no competing financial interests.

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azathioprine, leflunomide, or mycophenolate).

Those who have an inadequate response to the initial prednisone course should then get an immune modulator. If they do well, that can be maintained; a second modulator can be brought on board if necessary.

For those who don't respond at all to the initial prednisone course, it's necessary to proceed immediately to an immunosuppressive regimen to prevent irreversible fibrosis.

Dr. Culver noted associations with multiple pharmaceutical companies, but said none were relevant to his talk. A video interview with Dr. Culver is available on mdedge.com/chestphysician.

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Four-meter gait speed predicts mortality in IPF

BY DOUG BRUNK
MDedge News

SAN DIEGO – Among patients with idiopathic pulmonary fibrosis (IPF), an improvement in 4-meter gait speed with pulmonary rehabilitation is an independent predictor of all-cause mortality at 1 year, suggest results from a multicenter study presented at an international conference of the American Thoracic Society.

The authors of the study found that patients who improved their gait speed had a longer survival time. In all, 11% of patients died within 1 year of completing pulmonary rehabilitation.

"Mortality is an attractive endpoint in IPF clinical research but requires large sample sizes and long follow-up duration, making clinical trials expensive and challenging to undertake," lead study author Claire M. Nolan, MSc, said at the conference. "Consequently, there is much interest in surrogate endpoints of mortality. In the elderly population, a lot of work has been done on performance measures, in particular the 4-meter gait test. It's a simple test to do from the assessor's perspective, because you just need a 4-meter corridor and a stopwatch. From the patient's perspective, they only have to walk at their usual speed, making it feasible in most settings."

The study by Ms. Nolan, a National Institute for Health Research fellow, and her associates, involved recruiting 90 IPF patients referred to three outpatient pulmonary rehabilitation programs in London. All patients underwent the following assessments before and after 8 weeks of pulmonary rehabilitation: spirometry, Medical Research Council dyspnea score; anthropometry, 4-meter gait speed, incremental shuttle walk test, and King's Brief Interstitial Lung Disease questionnaire. Ms. Nolan, a respiratory physiotherapist with the Harefield Pulmonary Rehabilitation and Muscle Research Group, Royal Brompton and Harefield NHS Foundation Trust, London, and her associates drew from national databases to obtain data on all-cause mortality 1 year following pulmonary rehabilitation.

"We also identified a cutpoint, so if patients improved their walking speed by 0.009 meters per second or above, that was associated with a longer survival time at 1 year (area under the curve of 0.76, for sensitivity of 69.6% and a specificity of 70%; *P* less than 0.01)," she said. "Among patients who achieved that cutpoint or exceeded it, only 5% of them died in the 1-year follow-up period, compared with 23% in the group that didn't achieve that cutpoint. That's quite a big difference, but this requires external validation in another population."

To determine the 4-meter gait speed change cut-off that best discriminated between patients who died and survived, the investigators plotted receiver operating characteristic curves. For validation, they conducted a Kaplan-Meier analysis to assess time to death, with significance assessed via the log-rank test. Finally, they used a multivariate Cox proportional hazards model to characterize the relationship between 4-meter gait speed change and all-cause mortality, adjusting for independent predictors of mortality (age, previous respiratory hospitalizations in the past year, forced vital capacity percent predicted) and baseline 4-meter gait speed.

At baseline, 70% of the 90 patients were male, mean age was 74 years, mean forced vital capacity was 72.8% predicted, and mean Medical Research Council dyspnea score was 3. In addition, mean body mass index was 27.2 kg/m^2, mean 4-meter gait speed was 0.92 meters per second, mean incremental shuttle walk test measurement was 271 meters, and mean King's Brief Interstitial Lung Disease total score was 56.4. Following 8 weeks of pulmonary rehabilitation, the patients' 4-meter gait speed improved significantly by a mean of 0.15 meters per second (*P* less than .001). All other variables also improved significantly, with the exception of forced vital capacity.

Doug Brunk/MDedge News

"[It's] plausible that change in gait speed may be a surrogate marker for, say, improvement in exercise capacity or health status. But the precise mechanism requires verification," noted Claire M. Nolan.

In an interview, Ms. Nolan characterized the results as "one piece of the puzzle in answering whether 4-meter gait speed is a useful test for clinicians and researchers. It needs to be taken in the context of 4-meter gait speed in other populations as well as with what we're finding in patients with IPF. We know that this test is reliable, valid, and responsive to treatment. Now we know that it has predictive capacity as well."

During her presentation, she cited potential reasons why change in gait speed is associated with survival. "Firstly, gait speed has been described as a clinical indicator of multisystem well-being and the 'sixth vital sign,'"she said. "Walking ability and speed rely on multiple factors and the integration of many systems, cardiovascular and otherwise. We know that pulmonary rehab has multiple benefits and improves these systems, and it's plausible that change in gait speed may be a surrogate marker for, say, improvement in exercise capacity or health status. But the precise mechanism requires verification."

Ms. Nolan acknowledged certain limitations of the study, including the fact that contemporaneous measurement of full lung function testing and pulmonary hypertension diagnosis were not available at the time of the study. "Therefore, we were unable to account for [diffusing capacity of the lung for carbon monoxide] and pulmonary hypertension diagnosis," she said. "Secondly, we were unable to identify the precise cause of death from the national database of harm and care records, but this corroborates previous data which suggest that it's difficult to reliably discern if a death is IPF- or non-IPF related. Lastly, we know that the benefits of pulmonary rehab experienced by IPF patients tend to wane after 6 months. It would be interesting to compare the short-term improvements in gait speed that we observed to more sustained improvements, to identify whether this impacts prognostability."

National Institute for Health Research funded the study.

Ms. Nolan reported having no financial disclosures.

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New ILD diagnostic test now available

BY KATIE WAGNER LENNON
MDedge News

A 190-gene test for interstitial lung diseases (ILD), including idiopathic pulmonary fibrosis (IPF), is now available through an early-access program.

IPF can be difficult to distinguish from other ILDs, S. Samuel Weigt, MD, of the University of California, Los Angeles, and director of UCLA Health's Interstitial Lung Disease Center, said in a statement from Veracyte, the company marketing the test.

In fact, more than half of patients with ILDs were misdiagnosed at least once, according to a study published by the Pulmonary Fibrosis Foundation.

The new test, known as the Envisia Genomic Classifier, combines RNA sequencing and machine learning to help physicians differentiate IPF from ILDs in samples obtained through transbronchial biopsy. Its specificity and sensitivity for detecting the genomic pattern of usual interstitial pneumonia, are 88% and 70%, respectively, according to the Veracyte statement.

"Multiple studies have demonstrated that the Envisia Genomic Classifier supports more confident IPF diagnosis and optimal patient management," Bonnie Anderson, chairman and CEO of Veracyte, said in the statement.

A benefit of the new test is that its use does not require patients to undergo risky, expensive surgery, which may not even be possible for some patients, noted Dr. Weigt. "We are pleased to be one of the few medical facilities in the country to have access to this breakthrough technology."

More information about the Envisia Genomic Classifier and how to enter the early-access program can be obtained through emailing Veracyte at support@veracyte.com or by calling 844-464-5864.

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Ivacaftor reduced hospitalizations in CF

BY MADHU RAJARAMAN
MDedge News

Ivacaftor, a therapy that targets the G551D CFTR gene mutation to treat cystic fibrosis, significantly reduced hospital admission rates in patients with cystic fibrosis with a variety of mutations, according to results published May 7 in Health Affairs.

The study involved 143 patients being treated with ivacaftor (Kalydeco), which is manufactured for Vertex Pharmaceuticals, between February 2012 and February 2015. In 2014, the FDA expanded its approval for the use of ivacaftor by cystic fibrosis patients to include nine additional mutations, and patients with these mutations were included in this study.

The overall rate of inpatient admissions dropped by 55%, and cystic fibrosis–related admissions rates fell by 78% (*P* less than .0001) between the period 12 months before treatment and 12 months after the first filled prescription, wrote Lisa B. Feng and her coauthors.

Ms. Feng, who is senior director for policy and advocacy at the Cystic Fibrosis Foundation and her colleagues analyzed administrative claims data from the Truven Health Analytics Market Scan Commercial Research Database. All of the claims were for patients from the United States with employer-sponsored insurance plans. Eligibility criteria included an ICD-9 CM diagnosis of cystic fibrosis on one or more inpatient claims or two or more outpatient claims at least 30 days apart, a prescription claim for ivacaftor monotherapy, being at least 6 years of age at the time of the first filled prescription, and 12 months of continuous enrollment before and after the first filled prescription.

The "pre-ivacaftor" period was defined as the 12 months before the first filled prescription. The "post-ivacaftor" period was defined as the 12 months after the first filled prescription. For each period, the numbers and percentages of patients hospitalized were calculated, for any reason and for cystic fibrosis–related reasons. Hospitalization rates also were calculated as numbers of admissions per person-year. Data were analyzed for two subcohorts: the 86 patients who started using ivacaftor between Feb. 6, 2012, and Feb. 21, 2014, under the initial Food and Drug Administration label; and the 57 patients who initiated use between Feb. 22, 2014, and Dec. 31, 2015, under the expanded FDA label, which included nine additional genetic mutations.

Of the 143 patients who had filled

Continued on following page

Declines in hospital admissions also were similar between the initial label and the expanded FDA label groups, with declines in overall admissions of 59% and 57%, respectively. Hospital admissions related to cystic fibrosis decreased by 78%.

RSV immunoprophylaxis doesn't prevent asthma

BY CATHERINE COOPER NELLIST
MDedge News

Respiratory syncytial virus immunoprophylaxis in premature infants does not appear to prevent asthma at age 6 years, reported Nienke M. Scheltema, MD, of Wilhelmina Children's Hospital, Utrecht, the Netherlands, and associates.

In a study of 395 otherwise healthy premature infants who were randomized to receive palivizumab for respiratory syncytial virus (RSV) immunoprophylaxis or placebo and followed for 6 years, 14% of the 199 infants in the RSV prevention group had parent-reported asthma, compared with 24% of the 196 in the placebo group (absolute risk reduction, 9.9%). This was explained mostly by differences in infrequent wheeze, the researchers said. However, physician-diagnosed asthma in the past 12 months was not significantly different between the two groups at 6 years: 10.3% in the RSV prevention group and 9.9% in the placebo group.

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SOURCE: Scheltema NM et al. Lancet. 2018 Feb 27. doi: 10.1016/S2213-2600(18)30055-9.

Continued from previous page

prescriptions for ivacaftor, 63% were aged 18 years or older. The rate of overall inpatient admissions decreased 55%, from 0.57 admissions per person-year in the pre-ivacaftor period to 0.26 admissions per person-year in the post-ivacaftor period.

The declines in hospital admissions also were similar between the initial label and the expanded FDA label groups, with declines in overall admissions of 59% and 57%, respectively.

Hospital admissions related to cystic fibrosis also decreased significantly, by 78%. Admissions with principal diagnosis codes for cystic fibrosis decreased from 42 in the preprescription period, to 8 after filling the prescription. Rates per person per year decreased by 82% in patients aged 6-17 years and 80% among adults aged 18 years and older. Additionally, patients who filled at least 10 prescriptions during the study period experienced a 68% reduction in inpatient admissions, compared with 45% for those with 3-9 prescriptions filled.

Ivacaftor also was associated with 60% lower per-person inpatient spending overall, with a greater proportional reduction in hospital costs for adults (68%) than for children (45%), and an absolute per-person reduction of $10,567.

"To deliver the right care to the right patient," the authors concluded, "cystic fibrosis care must continue to account for other aspects unique to individuals such as environment, physiology, patients' preferences, and lifestyle."

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SOURCE: Feng LB et al. Health Aff. 2018 May 8. doi: 10.1377/hlthaff.2017.1554.

As-needed budesonide-formoterol prevented exacerbations in mild asthma

BY AMY KARON
MDedge News

Stockbyte/Thinkstock

Formoterol plus budesonide prevented exacerbations when inhaled as needed by patients with mild persistent asthma, according to the results of two large, double-blind, 52-week, randomized phase 3 trials.

In the SYGMA1 (Symbicort Given as Needed in Mild Asthma) trial, the regimen outperformed as-needed terbutaline in terms of asthma control (34.4% vs. 31.1% of weeks; $P = .046$) and exacerbations (rate ratio, 0.36; 95% confidence interval, 0.27-0.49). In the SYGMA2 study, it was noninferior to twice-daily budesonide for preventing severe exacerbations (RR, 0.97; upper one-sided 95% CI, 1.16). The findings were published in two reports in the New England Journal of Medicine.

Asthma often is undertreated because many patients adhere poorly to maintenance glucocorticoids, noted Paul M. O'Byrne, MD, of McMaster University in Hamilton, Ont., and his associates from SYGMA1 (NCT02149199). Instead, patients often rely on short-acting beta$_2$-agonists for symptom control, but these drugs don't stop exacerbations or treat underlying inflammation. "One potential strategy to address these issues is the use of a combination of a fast-acting beta$_2$-agonist and an inhaled glucocorticoid taken only on an as-needed basis," the researchers wrote.

Accordingly, they randomly assigned 3,849 patients aged 12 years and up who had mild persistent asthma (mean forced expiratory volume in 1 second [FEV$_1$] before bronchodilator use, 84% of predicted value) to receive one of three regimens: twice-daily placebo plus terbutaline (0.5 mg) used as needed, twice-daily placebo plus budesonide-formoterol (200 mcg of budesonide and 6 mcg of formoterol) used as needed, or maintenance twice-daily budesonide (200 mcg) plus as-needed terbutaline (0.5 mg), all for 52 weeks.

In the final analysis of 3,836 patients, annual rates of severe exacerbations were 0.20 with terbutaline, significantly worse than with budesonide-formoterol (0.07) or maintenance budesonide (0.09). Using budesonide-formoterol (Symbicort) as needed improved the odds of having well-controlled asthma by about 14%, when compared with using terbutaline as needed (odds ratio, 1.14; 95% CI, 1.00-1.30; $P = .046$).

Although maintenance budesonide controlled asthma best (44.4% of weeks; OR vs. budesonide-formoterol, 0.64; 95% CI, 0.57-0.73), 21% of patients did not adhere to it, the researchers reported. "Patients are often more concerned [than their health care providers] about adverse effects of inhaled glucocorticoids, even when low inhaled doses are used," they wrote. Notably, the budesonide-formoterol as-needed group received a median daily dose of only 57 mcg inhaled glucocorticoid, 17% of that received by the budesonide maintenance group.

In SYGMA2 (NCT02224157), 4,215 patients with mild persistent asthma aged 12 years and up were randomly assigned to receive either twice-daily placebo plus as-needed budesonide-formoterol or twice-daily maintenance budesonide plus as-needed terbutaline. Doses were the same as in the SYGMA1 trial. The regimens resembled each other in terms of severe exacerbations (annualized rates, 0.11 and 0.12, respectively) and time to first exacerbation, even though budesonide-formoterol patients received a 75% lower median daily dose of inhaled glucocorticoid, reported Eric D. Bateman, MD, of the University of Cape Town, South Africa, and his associates.

Results from both trials suggested that as-needed budesonide-formoterol provided better symptom control than did terbutaline but worse symptom control than did twice-daily budesonide. In SYGMA1, the change from baseline on the Asthma Control Questionnaire-5 (ACQ-5) favored budesonide-formoterol over terbutaline by an average of 0.15 units and similarly favored twice-daily budesonide over budesonide-formoterol. In SYGMA2, the budesonide maintenance group averaged 0.11 units greater improvement on the ACQ-5 and 0.10 better improvement on the standardized Asthma Quality of Life Questionnaire, compared with as-needed budesonide-formoterol recipients.

Finally, lung function assessments favored as-needed budesonide-formoterol over terbutaline but not over maintenance budesonide. SYGMA1, mean changes (from baseline) in FEV$_1$ before bronchodilator use were 11.2 mL with terbutaline, 65.0 mL with budesonide-formoterol, and 119.3 mL with maintenance budesonide. In SYGMA2, these values were 104 mL with budesonide-formoterol and 136.6 mL with maintenance budesonide.

AstraZeneca provided funding. For SYGMA1, Dr. Byrne disclosed ties to AstraZeneca, Novartis, GlaxoSmithKline, Medimmune, and Genentech. For SYGMA2, Dr. Bateman disclosed ties to AstraZeneca, Novartis, Cipla, Vectura, Boehringer Ingelheim, and a number of other pharmaceutical companies.

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SOURCES: O'Byrne PM et al. N Engl J Med. 2018;378(20):1865-76. Bateman ED et al. N Engl J Med. 2018;378(20):1877-87.

VIEW ON THE NEWS

'Two out of three ain't bad'

In the SYGMA1 and SYGMA2 trials, as-needed budesonide-formoterol (Symbicort) prevented exacerbations and loss of lung function, the two worst outcomes of poorly controlled asthma, concluded Stephen C. Lazarus, MD, FCCP, in an editorial accompanying the studies in the New England Journal of Medicine.

"As-needed treatment was similar, or at least noninferior, to regular maintenance therapy with inhaled glucocorticoids with regard to the prevention of exacerbations, and exacerbations are the main contributor to loss of lung function, death, and cost," wrote Dr. Lazarus.

Patients typically received only 17%-25% as much inhaled glucocorticoid as did those on maintenance budesonide, which would help prevent side effects and would make the regimen more acceptable to "glucocorticoid-averse patients," he added. Another benefit to patients with mild persistent asthma using as-needed budesonide-formoterol instead of inhaled glucocorticoid maintenance therapy is that it would result in nearly $1 billion in cost savings in the United States yearly.

Budesonide-formoterol did not control symptoms as well as did maintenance budesonide, but patients might accept "occasional mild symptoms and inhaler use if it [freed] them from daily use of inhaled glucocorticoids while preventing loss of lung function and exacerbations," he concluded. "For these patients, 'Two out of three ain't bad!' "

Dr. Lazarus is in the department of medicine and at the Cardiovascular Research Institute, University of California, San Francisco. He reported having no conflicts of interest. This comments are from his editorial (N Engl J Med. 2018 May 17. doi: 10.1056/NEJMe1802680).

In PAH trials, clinical worsening risk rose with time

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST® ▪ Current clinical trials evaluating combination therapy for pulmonary artery hypertension (PAH) may be longer than what is needed to demonstrate treatment benefit, results of a recent meta-analysis suggest.

In PAH trials of combination therapy, the absolute risk reduction of clinical worsening beyond 6-12 months was relatively constant, according to results of the study published in the May issue of the journal *Chest®*.

That finding "questions the requirement for longer-term event-driven trials beyond that duration in an orphan disease such as PAH," wrote investigator Annie C. Lajoie, MD, of the Pulmonary Hypertension Research Group, Quebec

VIEW ON THE NEWS
Long-term follow-up questioned

Results of this study by Lajoie and colleagues question the need for long-term follow-up beyond 12 months in clinical trials of combination therapy in pulmonary arterial hypertension (PAH), according to authors of an editorial.

"While very short term follow-up trials fail to detect important patient-centered outcomes and adverse events, very long term follow-up may impact trial feasibility without improving power to detect meaningful efficacy," wrote Rogerio Souza, MD, PhD, and Juliana C. Ferreira, MD, PhD.

The study also shows that relative risk of worsening is influenced by the duration of the trial. That suggests looking at relative risk in isolation may not be the optimal approach to evaluating the benefits of combination therapies for PAH, the authors added.

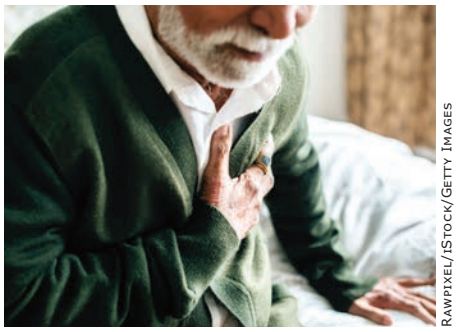
These findings, collectively, should inform the development of future clinical trials, they said. In particular, those trials could evaluate multiple markers of PAH improvement and a "time-limited observation" of morbidity events.

That "potential alternative" approach could make future studies more feasible, without compromising the robustness of findings, Dr. Souza and Dr. Ferreira said in their editorial.

Rogerio Souza, MD, PhD, and Juliana C. Ferreira, MD, PhD, are with the University of São Paulo, pulmonary division. These comments are derived from their editorial appearing in the journal Chest®. Dr. Ferreira reported speaker fees from Medtronic, and Dr. Souza reported speaker and consultancy fees from Actelion, Bayer, GSK, and Pfizer.

City, and her coauthors.

The meta-analysis by Dr. Lajoie and her colleagues included 3,801 patients enrolled in 1 of 15 previously published randomized clinical trials. Of those trials, four were long-term, event-driven studies, with a mean duration of 87 weeks, while the remainder were shorter studies with a mean duration of 15 weeks.



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For the long-term, event-driven trials, the mean number needed to treat (NNT) was 17.4 at week 16, gradually decreasing to 8.8 at 52 weeks of follow-up, remaining stable after that, according to investigators.

Consistent with that finding, the mean relative risk of clinical worsening was 0.38 at 16 weeks, and similarly, 0.41 at 26 weeks, investigators reported. After that, the relative risk progressively increased to 0.54 at 52 weeks and 0.68 at 104 weeks.

Looking at all trials combined, Dr. Lajoie and her colleagues observed that longer trial duration had a positive correlation with relative risk of clinical worsening ($P = .0002$).

Pragmatically, these results raise

Continued on following page

Continued from previous page

the possibility that PAH combination therapy trials could be shorter in duration. Some recent event-driven studies have lasted up to 6 years, with patients on treatment for about 2 of those years, investigators noted.

"In the context of an orphan disease with limited and competing recruitment for trials and the rapidly changing treatment paradigm in PAH, the optimal duration of future trials should be revisited," Dr. Lajoie and her colleagues wrote in a discussion of their findings.

Longer trial duration had a positive correlation with relative risk of clinical worsening.

They also cautioned that NNT, a measure of how many patient treatments are needed to prevent one additional adverse event, could be "misleading" despite its value as a simple measure of treatment impact.

Dr. Lajoie's coauthors had disclosures related to Actelion Pharmaceuticals, Bayer, and GlaxoSmithKline, among others.

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SOURCE: Lajoie AC et al. Chest. 2017 May;153(5):1142-52.

Stroke-smoking link is dose-dependent in young men

BY JIM KLING

MDedge News

In men younger than 50 years, even just a reduction in the number of cigarettes smoked may decrease the risk of ischemic stroke, according to a population-based, case-control study.

The odds ratio for a stroke was 1.21 for men who smoked fewer than 11 cigarettes per day, compared with nonsmokers, and 5.24 for those who smoked 40 or more per day, reported Janina Markidan and her coinvestigators in Stroke.

A prior study showed a similar relationship in young women, but the researchers decided to conduct a follow-up study in men in order to eliminate hormonal confounders (Stroke. 2008 Sep;39[9]:2439-43).

Ms. Markidan and her colleagues used data from the Stroke Prevention in Young Men Study, which recruited 615 men who had experienced a stroke in the previous 3 years, and compared these men with 530 age-, ethnicity-, and geography-matched controls.

There were some statistically significant differences in the two populations: Cases had lower levels of education and had greater incidences of hypertension, diabetes, myocardial infarction, angina, and obesity (all $P < .05$).

Current smokers were identified as those who had smoked more than 100 cigarettes in their lifetime and who had smoked a cigarette in the 30 days preceding the stroke. Never smokers were those who had smoked fewer than 100 cigarettes in their lifetime or who had never smoked five packs.

Compared with never smokers, current smokers had an odds ratio for stroke of 1.88 (95% confidence interval, 1.44-2.44). When the researchers stratified smokers by the number of cigarettes smoked, the stroke risk appeared to be dose dependent in the fully adjusted models: The OR for 1-10 cigarettes/day was 1.21 (95% CI, 0.83-1.77), 1.64 for 11-20 cigarettes/day (95% CI, 1.10-2.43), 3.51 for 21-39 cigarettes/day (95% CI, 1.65-7.45), and 5.24 for 40 or more cigarettes/day (95% CI, 1.90-14.42).

The study cannot prove causation and did not include smoking of nontobacco products, alcohol consumption, or physical activity.

chestphysiciannews@chestnet.org

SOURCE: Markidan J et al. Stroke. 2018 May;49(5):1276-8.

TERROA/ISTOCK/GETTY IMAGES

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

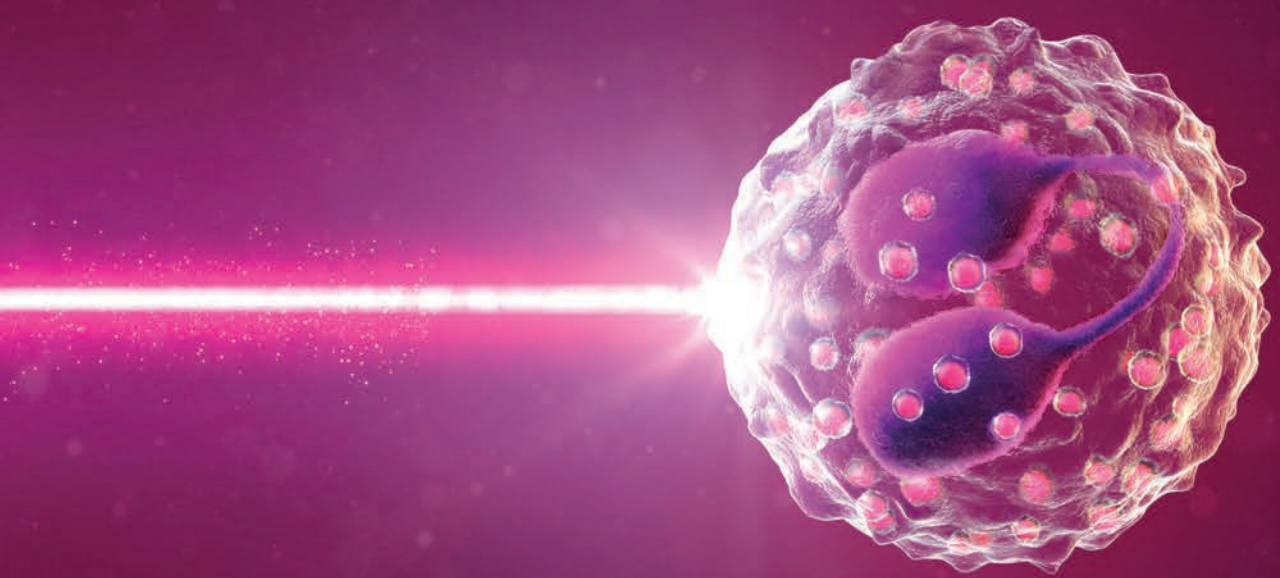
Hypersensitivity Reactions

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

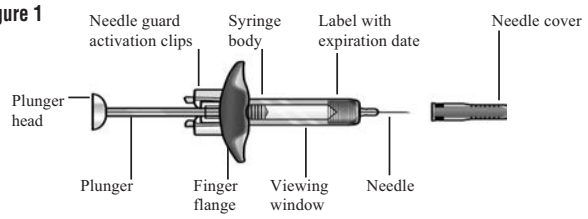
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

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.

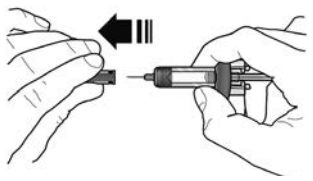
Figure 1



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

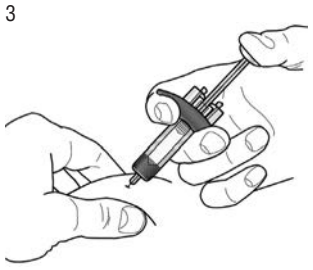
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain 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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ED visits higher among pediatric asthma patients with comorbid depression, anxiety

BY DOUG BRUNK
MDedge News

TORONTO – Children with asthma who have a comorbid diagnosis of anxiety or depression are significantly more likely to make asthma-related visits to the emergency department, compared with their peers who do not have a mental health condition, results from a large administrative data analysis showed.

"There has been a fair bit of research on how comorbid mental health conditions can affect health care utilization for asthma in adults, but few studies have examined how comorbid mental health conditions like anxiety or depression can affect children with asthma," one of the study authors, Caroline Neel, said in an interview in advance of the Pediatric Academic Societies meeting.

In an effort to assess whether anxiety or depression is associated with asthma-related ED usage in pediatric patients, Ms. Neel, a clinical research coordinator in the department of pediatrics at the University of California, San Francisco, and her associates evaluated data from the Massachusetts All Payer Claims Database for 2014-2015. They used the technical specifications from the Pediatric Quality Measures Program to measure the rate of asthma-related ED visits. This measure identifies patients aged 2-21 years with asthma using ICD 9 and 10 codes and tracks ED utilization over the measurement year. Next, the researchers conducted univariate and multivariate analyses to assess the relationship between ED visit rate and an established diagnosis of comorbid anxiety or depression.

"We were surprised to see that anxiety and depression seemed to increase asthma emergency department visits as much as other medical chronic illnesses," said Caroline Neel, a clinical research coordinator.

In all, the researchers identified 71,326 patients with asthma, with an overall rate of 16.3 ED visits per 100 child-years. Among these, children with a diagnosis of depression had significantly higher rates of ED visits (21.5 visits per 100 child-years; *P* less than .01), as did those with a diagnosis of anxiety (19.5 ED visits per 100 child-years; *P* less than .01). Being enrolled in a Medicaid managed care plan or Medicaid fee-for-service plan also increased the rates of asthma-related ED visits (20.3 and 21.5 ED visits per 100 child-years, respectively; *P* less than .01 for both associations.)

"We were surprised to see that anxiety and depression seemed to increase asthma emergency department visits as much as other medical chronic illnesses like cystic fibrosis or sickle cell disease, and that kids on Medicaid, who tend to be our poorer kids, also had an independent risk of going to the emergency department," Ms. Neel said. "Having Medicaid as well as anxiety or depression were independently related to going to the emergency room for asthma, so the study suggests that some of our highest-risk kids for asthma have multiple different contributors to getting sick and needing to go to the emergency room for an asthma attack."

She acknowledged certain limitations of the analysis, including its reliance on administrative claims data to identify whether or not children had a diagnosis of anxiety or depression. "This doesn't necessarily identify all the kids who may have these mental health conditions, since sometimes providers are less likely to document a diagnosis of a mental health conditions for children," she said. "However, we still saw a significant association between a comorbid mental health condition and emergency department use for asthma, despite the potential that mental health conditions may have been under reported."

The study's senior author was Naomi Bardach, MD. The researchers reported having no financial disclosures.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is a robust study and I am not surprised at all. Adding in the information about pediatric patients who have Medicaid and anxiety or depression is also not surprising. This is why the Cystic Fibrosis Foundation now recommends that adolescent CF patients should be screened at every routine visit to a CF clinic. Maybe we should do the same for our asthma patients.

Interferon-gamma release assay trumps tuberculin skin test in school-aged children

BY HEIDI SPLETE
MDedge News

The interferon-gamma release assay (IGRA) was significantly more sensitive than a tuberculin skin test (TST) as an adjunct tuberculosis diagnosis of children aged 5 years and older, according to data from a population-based study of 778 cases.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Our pediatric infectious disease colleagues are using the IGRA test for the specific age groups cited in this article. The TB skin test has such variability in regards to how it is placed and read, so this is a welcomed method for the diagnosis of tuberculosis at least in many parts of the United States.

IGRAs have shown greater specificity than do TSTs, but data on their sensitivity to TB in children are limited, wrote Alexander W. Kay, MD, of the California Department of Public Health and his colleagues in a study published in Pediatrics.

The researchers reviewed data on children and teens aged 18 years and younger from the California TB registry for 2010-2015. Of 778 reported cases of TB, 360 were laboratory confirmed, and 95 children had both an IGRA and TST with complete results. Of these, IGRA was significantly more sensitive than TST (96% vs. 83%) in children aged 5-18 years. The sensitivities of IGRA and TST were similar in children aged 2-4 years (91% for both) and not significantly different in children younger than 2 years (80% vs. 87%, respectively).

Children younger than 1 year of age and those with CNS disease were significantly more likely to have indeterminate IGRA results, the researchers noted.

The study results were limited by the use of mainly enzyme-linked immunosorbent assay–based IGRA, which limited the data on enzyme-linked immunospot tests, the researchers said. The findings also were limited by the small number of children younger than 5 years.

However, the study is the largest North American analysis of IGRA in children, and based on the findings, "we argue that an IGRA should be considered the test of choice when evaluating children 5-18 years old for TB disease in high-resource, low-TB burden settings," Dr. Kay and his associates wrote.

The study was funded by the Centers for Disease Control and Prevention. Coauthor Shamim Islam, MD, disclosed financial support from Qiagen, maker of the QuantiFERON test. Dr. Kay and the other investigators had no financial conflicts to disclose.

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SOURCE: Kay AW et al. Pediatrics. 2018 May 4. doi: 10.1542/peds.2017-3918.

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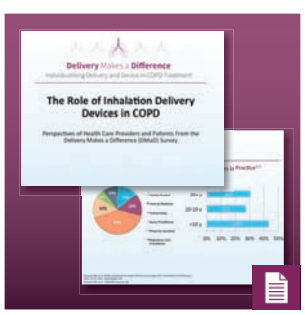

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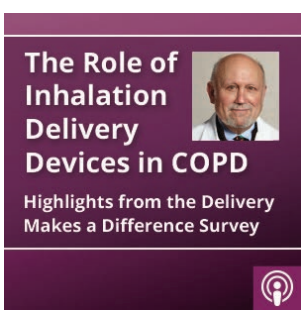

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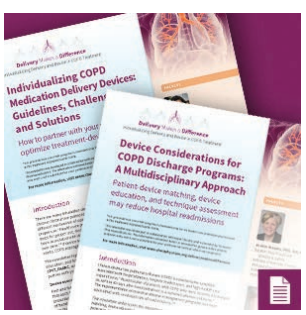

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Lung cancer palliative care may reduce suicides

BY KATIE WAGNER LENNON
MDedge News

Veterans with advanced-stage lung cancer who received palliative care were less likely to commit suicide, according to new research presented at the international conference of the American Thoracic Society.

"Suicide is a significant national public health problem, especially among lung cancer patients and among veterans," said lead author, Donald R. Sullivan, MD, of the division of pulmonary and critical care medicine at Oregon Health & Science University and a member of the OHSU Knight Cancer Institute, in a statement.

Dr. Sullivan, who also is a core investigator at the Center to Improve Veteran Involvement in Care at Portland Veterans Affairs, and his colleagues analyzed data on patients in the VA Healthcare System who were diagnosed with advanced-stage lung cancer (IIIB & IV) from January 2007 to December 2013.

The investigators found that veterans who experienced at least one "palliative care encounter" after learning they had lung cancer were 82% less likely to die by suicide (odds ratio, 0.18; 95% confidence interval, 0.07-0.46; *P* less than .001), when compared with veterans who were diagnosed with lung cancer but did not receive palliative care.

The suicide rate for the advanced stage lung cancer patients was 200/100,000 patient-years, five times higher than for all veterans using VA health care.

The suicide rate for the advanced-stage lung cancer patients was 200/100,000 patient-years, which was more than five times higher than the suicide rate – adjusted for age, sex, and year – for all veterans using VA health care (37.5/100,000), according to the study abstract.

Of the 20,900 lung cancer patients analyzed, 30 committed suicide. Only six (20%) of the patients who died by suicide had received palliative care. Overall, most patients (18,192 or 87%) in the registry died of lung cancer. Other cancers, heart disease, and chronic obstructive pulmonary disease were some of the other common causes of death for the lung cancer patients, according to the abstract.

While several medical societies recommend palliative care for all patients with advanced-stage lung cancer, there is a gap between those recommendations and practice, noted Dr. Sullivan. "There are many barriers to palliative care, and unfortunately, some are related to clinician referrals. Not all doctors are aware of the benefits of palliative care," he said in the statement.

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Delay of NSCLC surgery can lead to worse prognosis

BY RANDY DOTINGA
MDedge News

SAN DIEGO – A study suggests a delay of surgery in certain cases of non–small cell lung cancer (NSCLC) can mean patients will be upstaged and consequently have worse prognoses.

"There is significant upstaging with time from completion of clinical staging to surgical resection, with a 4% increase of upstaging per week for the overall study population," said study coauthor Harmik J. Soukiasian, MD, FACS, of Cedars-Sinai Medical Center, Los Angeles, in an interview. "Upstaging impacts lung cancer prognosis as more advanced stages portend to a poorer prognosis."

Dr. Soukiasian presented the study findings at the annual meeting of the American Association for Thoracic Surgery.

An estimated 80%-85% of lung cancer patients have NSCLC, according to the American Cancer Society, and Dr. Soukiasian said surgery offers a chance at a cure for those diagnosed at stage I.

"National Cancer Comprehensive Network (NCCN) Guidelines recommend surgery within 8 weeks of completed clinical staging for NSCLC to limit cancer progression or upstaging," Dr. Soukiasian said. "Although these guidelines are well established and widely adopted, our study performs a more granular analysis, studying time as a predictor of upstaging for those patients diagnosed with stage I NSCLC."

"Although these guidelines are ... widely adopted, our study performs a more granular analysis," said Dr. Harmik J. Soukiasian.

For the new study, Dr. Soukiasian and colleagues tracked 52,406 patients in a cancer database who had stage I NSCLC but had not undergone preoperative chemotherapy. The researchers tracked their clinical stages for up to 12 weeks from initial staging.

Researchers found that, while staging levels rose with each successive week, just 25% of patients underwent surgery by 1 week, and only 79% had surgery in accordance with NSCLC guidelines by week 8. At 12 weeks, 9% had still not undergone surgery.

Upstaging was common: 22% at 1 week, 32% after 8 weeks, and 33% after 12 weeks.

"We demonstrate that patients diagnosed with stage I NSCLC benefit from surgery sooner than the 8-week window recommended by the NCCN guidelines," Dr. Soukiasian said. "Exclusive of the rate of progression and in addition to time to surgery, our study also demonstrated academic centers, higher lymph node yield during surgery, and left-sided tumors to be independent predictors of upstaging."

The study design doesn't provide insight into why surgery is often delayed. However, "we can theorize factors associated with delays to surgery may be due to patient factors (personal scheduling, availability of support systems, etc.), delays in follow-up, operating room availability or scheduling, and issues with insurance approval," Dr. Soukiasian said.

In his presentation, Dr. Soukiasian emphasized the role of the mediastinum. "Given the clinical impact of stage III disease, we analyzed upstaging rates of stage I NSCLC to stage IIIA and revealed a 1.3% increase per week of upstaging specifically to stage IIIA. Additionally, almost 5% of patients initially diagnosed with stage I NSCLC upstaged to IIIA disease. The significant rate of upstaging to IIIA disease makes the case for more accurate and aggressive mediastinal staging prior to surgical resection."

No disclosures were reported.

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Nivolumab shows promise in early-stage resectable NSCLC

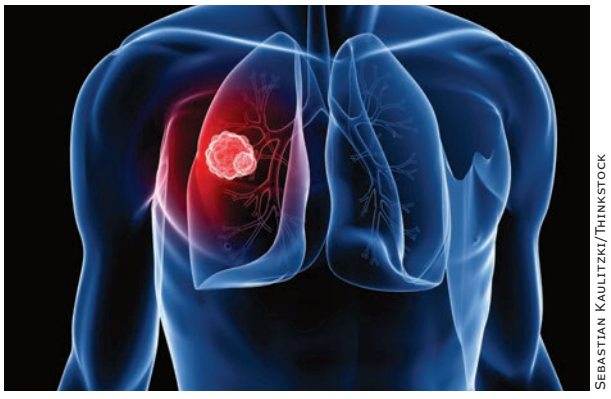
BY AMY KARON
MDedge News

Neoadjuvant nivolumab did not delay surgery and produced at least 90% tumor regression in nearly half of early-stage, resectable non–small cell lung cancers (NSCLC), according to the results of a 21-patient pilot trial.

Eighty percent of patients were alive and recurrence free a year after surgery, said Patrick M. Forde, MBBCh, and his colleagues from Johns Hopkins University, Baltimore. The only grade 3 or higher adverse event was treatment-related pneumonia, which did not prevent surgery. The findings were reported at the annual meeting of the American Association for Cancer Research and simultaneously in the New England Journal of Medicine.

Nivolumab targets the programmed cell death 1 (PD-1) pathway and is approved in several tumor types, including advanced NSCLC that has progressed despite platinum-based or epidermal growth factor receptor or anaplastic lymphoma kinase–targeted therapy. That approval was based on the CHECKMATE-057 trial, in which nivolumab significantly outperformed docetaxel in metastatic NSCLC (median overall survival, 12.2 vs. 9.4 months; $P = .002$). However, programmed cell death 1 inhibition in resectable NSCLC remained unexplored, Dr. Forde and his colleagues noted.

For the study (NCT02259621), 21 patients with treatment-naive, stage I, II, or III NSCLC received two preoperative doses of nivolumab (3 mg/kg) 2 weeks apart, with surgery timed for 4 weeks after the first dose. In all, 62% of patients had adenocarcinoma, 81% had stage II or IIIa disease, and 86% were current or former smokers. Patients were followed for a median of 12 months after surgery (range, 0.8-19.7 months), and the researchers assessed safety, tumor response, programmed death ligand 1 mutational burden, and T-cell response.



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Among 20 patients with evaluable resected primary tumors, nine (45%) showed a major pathologic response, defined as having 10% or fewer residual viable tumor cells. Twelve-month, recurrence-free survival was 83% (95% confidence interval, 66%-100%). The three progressors included one patient with 75% residual tumor at resection who subsequently developed a brain lesion, a patient with 5% residual tumor at resection who developed mediastinal lymph node recurrence, and a patient with 80% residual tumor at resection. The first two patients had durable responses to stereotactic radiotherapy or chemoradiotherapy, while the third patient developed fatal distal metastatic disease.

Sequencing of 11 completely resected tumors linked major pathologic response with higher tumor mutational burden ($P = .01$). Mutational burden did not correlate with tumor programmed death ligand 1 expression. Deep sequencing of T-cell receptor–beta chain CDR3 regions also correlated major pathologic response with increased clonality of tumor-infiltrating T-cell clones that also expanded into peripheral blood. "Many of these clones were not detected in peripheral blood before treatment," the investigators wrote.

In all, five (23%) patients developed treatment-related adverse events, and many developed more than one side effect. Grade 1-2 anorexia, taste distortion, vomiting, and diarrhea were most common, with isolated cases of grade 1-2 fever, infusion reaction, abdominal pain, abnormal liver function, dry skin, and delirium. The case of grade 3 pneumonia developed after the first dose of nivolumab.

The funders included Cancer Research Institute–Stand Up 2 Cancer; Johns Hopkins Bloomberg–Kimmel Institute for Cancer Immunotherapy; Bristol-Myers Squibb; International Immuno-Oncology Network, LUNGevity Foundation; International Association for the Study of Lung Cancer; and Lung Cancer Foundation of America. Bristol-Myers Squibb makes nivolumab and supplied the study drug. Dr. Forde disclosed study grant support from Bristol-Myers Squibb. He reported ties to Bristol-Myers Squibb, AbbVie, and other pharmaceutical companies outside the submitted work.

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SOURCE: Forde PM. AACR Annual Meeting 2018. Forde PM et al. N Engl J Med. 2018 Apr 16. doi: 10.1056/NEJMoa1716078.

LUNG CANCER

Malignant pleural mesothelioma guidelines often ignored

BY RANDY DOTINGA
MDedge News

SAN DIEGO – National guidelines for the treatment of malignant pleural mesothelioma (MPM) often are not followed, a new study showed, with fewer than a third of patients receiving cancer-directed surgery.

Another 32% received no treatment, although that didn't seem to have an impact on median months of survival.

Still, "there can be a wide variation in median survival time, depending on clinical factors and tumor characteristics," said study coauthor Harmik Soukiasian, MD, of Cedars-Sinai Medical Center, Los Angeles, at the annual meeting of the American Association for Thoracic Surgery. "Given the variation in prognosis, it is quite astonishing that over 30% of MPM patients are not receiving any form of treatment. As clinicians armed with these data, we need to investigate why that is."

MPM, a rare cancer, is mainly linked to asbestos exposure. "MPM is almost always a fatal disease, and the prognosis can only be modestly influenced by oncological treatments," according to the authors of guidelines released in 2013. "The diagnostic process can be complex, with highly specialized advice frequently required to arrive at a definite diagnosis. Treatment varies from therapeutic nihilism to radical combined-modality treatment approaches" (J Thorac Dis. 2013 Dec;5[6]:E254-307).

Surgical resection is a controversial treatment for MPM, Dr. Soukiasian said. It is "based on the principle of macroscopic resection of solid tumor with adjuvant therapy to treat micrometastatic disease," he explained. "Cancer-directed surgery for MPM is usually reserved for localized epithelial type histology and is associated with a 5-year survival rate of 15%."

For the new study, the investigators tracked 3,834 patients in the National Cancer Database (2004-2014) diagnosed with MPM clinical stages I-III. Most had epithelioid MPM (69%), with sarcomatoid (17%) and mixed subtype (15%) making up the rest. They examined whether patient treatment complied with the National Comprehensive Cancer Network (NCCN) guidelines, which recommend surgery in resectable epithelioid MPM.

"Our study revealed significant lack of compliance with NCCN guidelines, as well as many disparities in the management of MPM," Dr. Soukiasian said. "For the overall cohort, 32.3% of patients did not receive any treatment, 18.1% had surgery plus chemotherapy, 38.6% chemotherapy alone, and only 7% received trimodality therapy. In patients with epithelial histology, surgery was significantly underutilized, with only 30% of patients receiving cancer-directed surgery."

In addition, he said, "our study reveals several disparities that affect compliance with NCCN guidelines. Treatment disparities were observed in women, octogenarians, the uninsured, the Medicaid-insured, and in patients with comorbidities. Guideline adherence was significantly increased in academic and high-volume hospitals with an associated increase in survival."

But the study also found that median survival estimates were similar regardless of treatment: 10 months for no treatment, 15 months for chemotherapy only, 17 months for surgery only, and 22 months for surgery plus chemotherapy.

During the AATS presentation, an audience member asked about how performance status – a measure of a person's ability to perform everyday activities – affects the eligibility for surgery.

"It's quite common for low performance status to exclude someone from surgery," the audience member said.

Dr. Soukiasian acknowledged that performance status was not included in the data. The study was focused on the gap between guidelines and real-world practice, and generated questions of why and about the potential opportunity for improved treatment of these patients.

"Although our research does not provide data or conclusions on quality of life or cost, these topics will be important to address in follow-up studies to elucidate possible barriers in the treatment of MPM and the initiation of future educational opportunities for our patients," Dr. Soukiasian noted.

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Diagnosis and management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI): Updated guidelines 2017

BY STEPHEN M. PASTORES, MD, FCCP

Critical illness-related corticosteroid insufficiency (CIRCI) was first introduced in 2008 by a task force convened by the Society of Critical Care Medicine (SCCM) to describe the impairment of the hypothalamic-pituitary-adrenal (HPA) axis during critical illness (Marik PE, et al. *Crit Care Med*. 2008;36(6):1937).

CIRCI is characterized by dysregulated systemic inflammation resulting from inadequate cellular corticosteroid activity for the severity of the patient's critical illness. Signs and symptoms of CIRCI include hypotension poorly responsive to fluids, decreased sensitivity to catecholamines, fever, altered mental status, hypoxemia, and laboratory abnormalities (hyponatremia, hypoglycemia). CIRCI can occur in sepsis and septic shock, acute respiratory distress syndrome (ARDS), severe community-acquired pneumonia, and non-septic systemic inflammatory response syndrome (SIRS) states associated with shock, such as trauma, cardiac arrest, and cardiopulmonary bypass surgery. Three major pathophysiologic events constitute CIRCI: dysregulation of the HPA axis, altered cortisol metabolism, and tissue resistance to glucocorticoids (Annane D, Pastores SM, et al. *Crit Care Med*. 2017;45(12):2089; Intensive Care Med. 2017;43(12):1781). Plasma clearance of cortisol is markedly reduced during critical illness, due to suppressed expression and activity of the primary cortisol-metabolizing enzymes in the liver and kidney. Furthermore, despite the elevated cortisol levels during critical illness, tissue resistance to glucocorticoids is believed to occur because of insufficient glucocorticoid receptor alpha-mediated anti-inflammatory activity.

Reviewing the Updated Guidelines

Against this background of recent insights into the understanding of CIRCI and the widespread use of corticosteroids in critically ill patients, a panel of experts of the SCCM and the European Society of Intensive Care Medicine (ESICM) recently updated the guidelines for the diagnosis and management of CIRCI in a two-part guideline document (Annane D, Pastores SM, et al. *Crit Care Med*. 2017;45(12):2078; *Intensive Care Med*. 2017;43(12):1751; Pastores SM, Annane D, et al. *Crit Care Med*. 2018;46(1):146; Pastores SM, Annane D, et al. *Intensive Care Med*. 2018;44(4):474). For this update, the multidisciplinary task force used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to formulate actionable recommendations. The recommendations and their strength (strong or conditional) required the agreement of at least 80% of the members. The task force spent considerable time and spirited discussions on the diagnosis of CIRCI and the use of corticosteroids for clinical disorders that most clinicians associate with CIRCI: sepsis/septic shock, ARDS, and major trauma.

Diagnosis

The task force was unable to reach agreement on a single test that can reliably diagnose CIRCI. However, they acknowledged that a delta cortisol less than or equal to 9 µg/dL at 60 minutes after administration of 250 µg of cosyntropin and a random plasma cortisol level of less than or equal to 10 µg/dL may be used by clinicians. They also suggested against the use of plasma-free cortisol or salivary cortisol level over plasma total cortisol. Unequivocally, the panel acknowledged the limitations of the current diagnostic tools to identify patients at risk for CIRCI and how this may impact the way corticosteroids are used in clinical practice.

Sepsis and Septic Shock

Despite dozens of observational studies and randomized controlled trials (RCTs), the benefit-to-risk ratio of corticosteroids to treat sepsis and septic shock remains controversial with systematic reviews and meta-analyses either confirming (Annane D, et al. *Cochrane Database Syst Rev*. 2015;12:CD002243) or refuting (Volbeda M, et al. Intensive Care Med. 2015;41:1220) the survival benefit of corticosteroids. Based on the best available data, the task force recommended using corticosteroids in adult patients with septic shock that is not responsive to fluids and moderate-to-high vasopressor therapy but not for patients with sepsis who are not in shock. Intravenous hydrocortisone less than or equal to 400 mg/day for at least greater than or equal to 3 days at full dose was recommended rather than high dose and short course. The panel emphasized the consistent benefit of low-dose corticosteroids on shock reversal and the low risk for superinfection.

Since the publication of the updated CIRCI guidelines, two large RCTs (more than 5,000 combined patients) of low-dose corticosteroids for septic shock were reported: The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial (Venkatesh B, et al. *N Engl J Med*. 2018;378:797) and the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial (Annane D, et al. *N Engl J Med*. 2018;378:809). The ADRENAL trial included 3,800 patients in five countries and did not show a significant difference in 90-day mortality between the hydrocortisone and the placebo groups (27.9% vs 28.8%, respectively, P=.50). In contrast, the APROCCHSS trial, involving 1,241 patients, reported a lower 90-day mortality in the hydrocortisone-fludrocortisone group compared with the placebo group (43% vs 49.1%, P=.03). Both trials showed a beneficial effect of hydrocortisone in the number of vasopressor-free and mechanical ventilation-free days. Blood transfusions were less common in the hydrocortisone group than those who received placebo in ADRENAL. Besides hyperglycemia, which was more common in the hydrocortisone group in both trials, the overall rates of adverse events were relatively low.

It is important to highlight the key differences between these two RCTs. First, in APROCCHSS, oral fludrocortisone (50-µg once daily for 7 days) was added to hydrocortisone to provide additional mineralocorticoid potency, although a previous study had shown no added benefit (Annane D, et al. *JAMA*. 2010;303:341). Second, hydrocortisone was administered as a 50-mg IV bolus every 6 hours in APROCCHSS and given as a continuous infusion of 200 mg/day for 7 days or until death or ICU discharge in ADRENAL. It is noteworthy that the subjects in ADRENAL had a higher rate of surgical admissions (31.5% vs 18.3%), a lower rate of renal-replacement therapy (12.7% vs 27.6%), lower rates of lung infection (35.2% vs 59.4%) and urinary tract infection (7.5% vs 17.7%), and a higher rate of abdominal infection (25.5% vs 11.5%). Patients in APROCCHSS had high Sequential Organ Failure Assessment (SOFA) scores and Simplified Acute Physiology Score (SAPS) II values suggesting a sicker population and probably accounting for the higher mortality rates in both hydrocortisone and placebo groups compared with ADRENAL. In view of the current evidence, the author believes that survival benefit with corticosteroids in septic shock is dependent on several factors: dose (hydrocortisone less than or equal to 400 mg/day), longer duration (at least 3 or more days), and severity of sepsis. "The more severe the sepsis, the more septic shock the patient is in, the more likely it is for corticosteroids to help these patients get off vasopressors and mechanical ventilation. I consider the addition of fludrocortisone as optional."

Dr. Pastores is Program Director, Critical Care Medicine, Vice-Chair of Education, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center; Professor of Medicine and Anesthesiology, Weill Cornell Medical College, New York, NY.

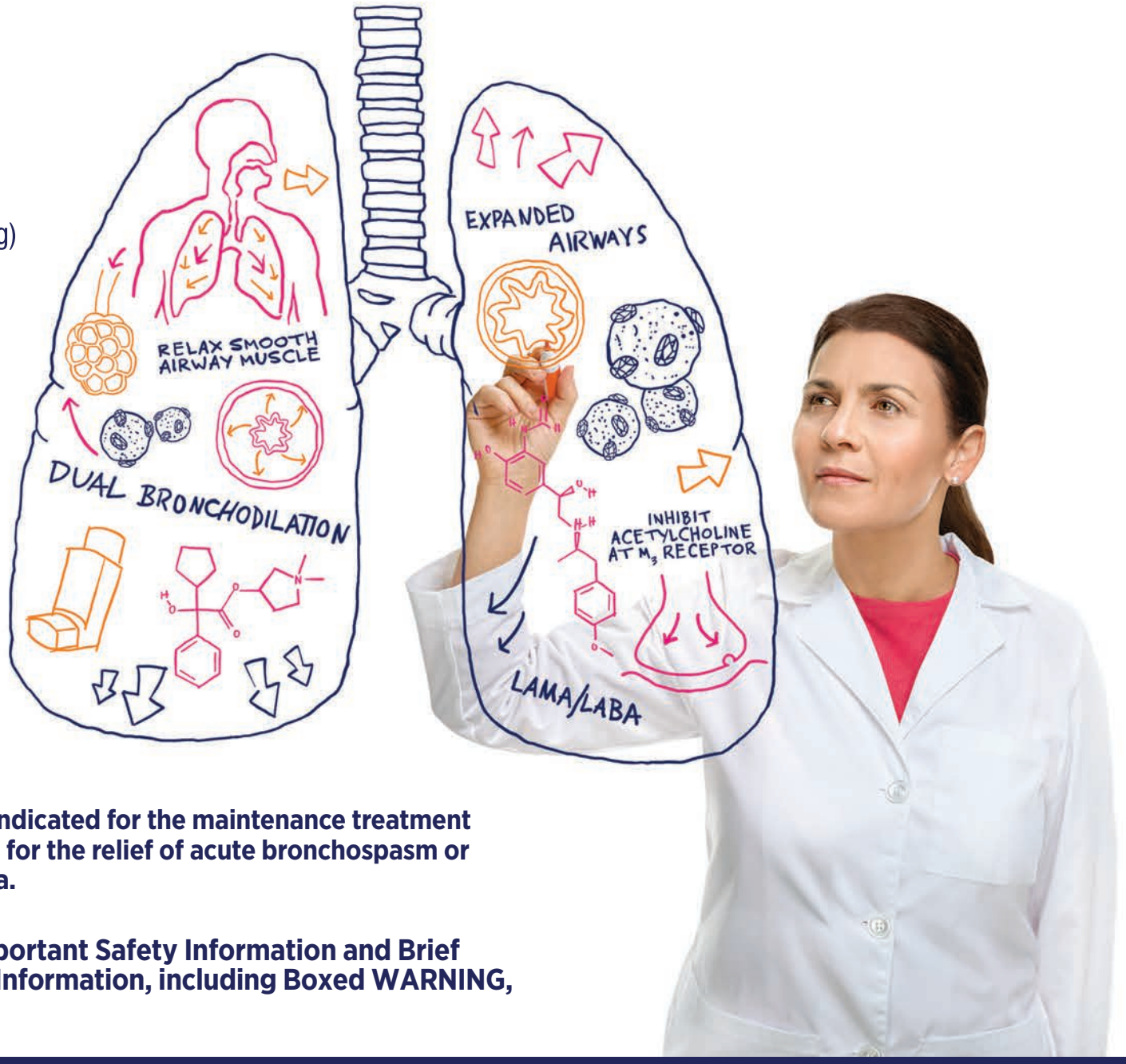
ARDS

In patients with early moderate-to-severe ARDS (PaO_2/FIO_2 of less than or equal to 200 and within 14 days of onset), the task force recommended the use of IV methylprednisolone in a dose of 1 mg/kg/day followed by slow tapering over 2 weeks to prevent the development of a rebound inflammatory response, and adherence to infection surveillance. In patients with major trauma and influenza, the panel suggested against the use of corticosteroids. Corticosteroids were recommended for severe CAP (less than or equal to 400 mg/day of IV hydrocortisone or equivalent for 5 to 7 days), meningitis, adults undergoing cardiopulmonary bypass surgery, and adults who suffer a cardiac arrest. The task force highlighted that the quality of evidence for use of corticosteroids in these disease states was often low and that additional well-designed RCTs with carefully selected patients were warranted.

To conclude, as with any clinical practice guideline, the task force reiterated that the updated CIRCI guidelines were not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Good clinical judgment should always prevail!

BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting beta$_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

CONTRAINDICATIONS: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating chronic obstructive pulmonary disease (COPD), which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions occur, in particular, angioedema, urticaria, or skin rash, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- 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
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

2018 GOLD Report

LAMA/LABAs RECOMMENDED

1ST-LINE FOR MOST PATIENTS*

MAXIMIZE BRONCHODILATION[1,2†]

Improved lung function including predose FEV_1 and peak FEV_1 at 24 weeks[1,2‡]

In a separate study vs placebo, improvement in peak inspiratory capacity at Day 29[3§‖]

INTELLIGENT FORMULATION[1¶]

Intelligent formulation for a pMDI using patented, phospholipid-based AEROSPHERE™ Delivery Technology[1]

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

*Initial treatment in Group B patients with severe breathlessness and in Group D patients.

†Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).

‖In a separate Phase IIIb trial (n=35), there was a significant improvement in the primary endpoint, FEV_1 AUC_{0-24}, on Day 29 vs placebo. Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint. Similar results seen in a second Phase IIIb trial (n=75).

¶BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.

- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore, BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Learn more at DUALBRONCHODILATION.COM

‡**Pinnacle 1 & 2 Pivotal Trials:** Two 24-week efficacy and safety studies were conducted in patients with moderate to very severe COPD (n=3699). Primary endpoint: change from baseline in trough FEV_1 at Week 24 for BEVESPI 18 mcg/9.6 mcg BID vs placebo BID (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; $P<0.0001$ for all treatment comparisons.[1,2] Trial 1 included open-label active control.[1] Statistically significant results also seen in Trial 2.[1,2] Secondary endpoint: change from baseline in peak FEV_1 at Week 24 for BEVESPI BID vs placebo BID (291 mL), glycopyrrolate 18 mcg BID (133 mL), and formoterol fumarate 9.6 mcg BID (93 mL); results are from Trial 1; $P<0.0001$ for all comparisons.[1,2] Statistically significant results also seen in Trial 2.[1,2]

§**Separate Phase IIIb Trials (Study A & B):** Two Phase IIIb crossover studies were conducted to evaluate 24-hour lung function profile of BEVESPI 18 mcg/9.6 mcg BID vs placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing. Study B included open-label active control.[3] Primary endpoint, FEV_1 AUC_{0-24}: Study A – BEVESPI (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both $P<0.0001$.[4] Secondary endpoint, Peak IC (evening): Study A – BEVESPI (n=34) vs placebo (n=30) = 381 mL (baseline evening IC 1.980 L and 1.939 L, respectively); Study B – BEVESPI (n=62) vs placebo (n=63) = 312 mL (baseline evening IC 1.877 L and 1.913 L, respectively); both $P<0.0001$.[4]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2017. **2.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357. **3.** Reisner C, Gottschlich G, Fakih F, et al. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res*. 2017;18:157. **4.** Data on File, REF-4976, AZPLP.

*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.*

AstraZeneca

BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) 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 all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs 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 LABAs.

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; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE 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 BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, 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 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 BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of 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 dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, 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) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE 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.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications 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$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

BEVESPI AEROSPHERE 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 physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

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

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions: Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG 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 $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

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

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE 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 medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom
or By: AstraZeneca Dunkerque Production (AZDP), Dunkerque France

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Seven days of antibiotics is enough

BY MICHELE G. SULLIVAN
MDedge News

MADRID – Seven days of antibiotic therapy was just as effective as 14 days for patients with gram-negative bacteremias.

The shorter course was associated with similar cure rates and a faster return to normal activities, Dafna Yahav, MD, said at the European Society of Clinical Microbiology and Infectious Diseases annual congress.

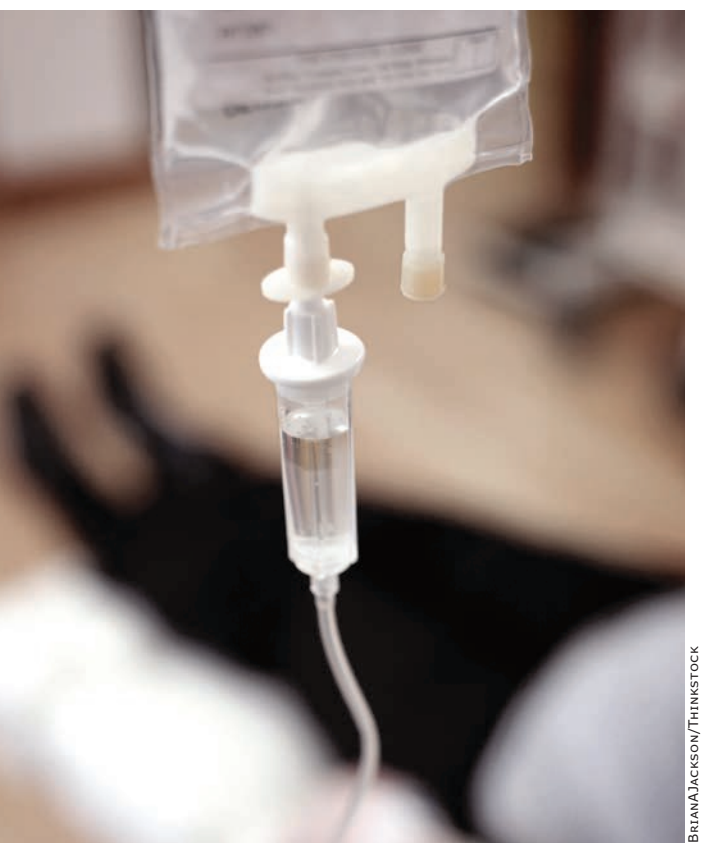
"In patients hospitalized with gram-negative bacteremia and sepsis, a course of 7 antibiotic days was not inferior to 14 days, and resulted in a more rapid return to baseline activity, " said Dr. Yahav of the Rabin Medical Center, Petah Tikva, Israel. "This could lead to a change in accepted management algorithms and shortened antibiotic therapy. Potentially, though we did not show this in our trial, it may lead to reduced cost, reduced development of resistance, and fewer adverse events."

During the past few years, a new dogma has emerged in antibiotic treatment paradigms, she said: Shorter is better. Brad Spellberg, MD, described this concept in his 2016 editorial in JAMA Internal Medicine, "The new antibiotic mantra" (Sep 1;176[9]:1254-5).

In it, Dr. Spellberg, of the University of Southern California, Los Angeles, addressed the long-held view that a full 10- or 14-day course of antibiotics was necessary to decrease the risk of creating a resistant strain, even if clinical symptoms were long resolved.

However, he noted, there is little evidence supporting the idea that longer courses suppress the rise of resistance – and, in fact, some data support the opposite.

"To the contrary, specifically for pneumonia, studies have shown that longer courses of therapy result in more emergence of antibiotic resistance, which is consistent with everything we know about natural selection, the driver of antibiotic resistance," he noted. "In only a few types of infections does resistance emerge at the site of infection; rather, resistance typically emerges off target, among colonizing flora away from the site of infection. Thus, all that is achieved by treating an infection with antibiotics for longer than the patient has symptoms is increased selective pressure driving antibiotic resistance among our colonizing microbial flora."



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The European Union and Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have all recently updated their antibiotic stewardship guidelines to include a strong recommendation for the shortest effective duration of antimicrobial therapy.

However, most of the supporting data were drawn from randomized, controlled studies of patients with lung, skin, and kidney infections. Short-course treatments have not been adequately studied in bacteremia patients, Dr. Yahav said.

The aim of her study, which was investigator initiated and received no external funding, was to demonstrate the noninferiority of 7 days of antibiotic therapy, compared with 14 days, in patients with bacteremia arising from gram-negative infections.

The randomized, open-label study comprised 604 patients in three hospitals: two in Israel and one in Italy. Patients were eligible if they had an aerobic gram-negative bacteremia of any infection source that was either community or hospital acquired. The medication choice was left up to the treating physician. Patients were assessed at discharge, and at days 30 and 90.

The primary outcome was a composite 90-day endpoint of all-cause mortality, clinical failure (relapse, new local complications, or distant complications), and readmission or hospital stay longer than 14 days. There were a number of secondary outcomes, including new infection, emergence of antibiotic resistance, total hospital and total antibiotic days, time to return to baseline activity, and adverse events.

The cohort was a mean of 71 years old. About 60% were functionally independent, and the mean Charlson comorbidity score was 2. Most of the infections (90%) were nosocomial. The urinary tract was the largest source of infection (69%). Other sources were abdominal, respiratory, central venous catheter, and skin or soft tissue.

Escherichia coli was the most common infective organism (62%), followed by Klebsiella species and Enterobacteriaceae. A small number of patients had Acinetobacter and Pseudomonas infections.

In the intent-to-treat analysis, the primary composite outcome of all-cause mortality or extended hospital stay occurred in 46% of the 7-day group and 50% of the 14-day group – not significantly different. The results were nearly identical in the per-protocol analysis (46% vs. 49.6%).

Likewise, none of the secondary outcomes posted a significant difference in favor of one treatment arm, including relapse (2.9% vs. 2.7%) and resistance development (10.8% vs. 9.7%).

Dr. Yahav pointed out that total antibiotic-use days were significantly less in the 7-day group, (5 days) than in the 14-day group (10 days). Patients in the short-duration group returned to their normal activities a day earlier than those in the longer-term group (2 days vs. 3 days), a difference that was statistically significant.

Michele G. Sullivan/MDedge News

For gram-negative bacteremia and sepsis, 7 days of antibiotics was not inferior to 14 days, noted Dr. Dafna Yahav.

The total hospital stay from randomization to day 90 was only half a day shorter in the short-term group (mean, 3 days vs. 3.5 days). That was not a significant finding.

There were some differences in adverse events, although none was statistically significant. The short-duration arm had slightly more cases of kidney injury (0.5%), fewer cases of liver function abnormalities (–1.5%), and half as many rashes (two vs. four). There were two cases of *Clostridium difficile* in the short-use arm and one in the long-use arm, also not a significant difference.

A subgroup analysis looked at outcomes among the different sources of infection (urinary tract vs. other), whether empirical antibiotics were used, and whether the induced resistance was multidrug or non-multidrug. All of those differences hovered close to the null, but generally favored short antibiotic treatment, Dr. Yahav noted.

"I would conclude from these data that it is generally safe to stop antibiotics after 7 days of covering antibiotics for gram-negative bacteremia patients, if they are hemodynamically stable and nonneutropenic at 7 days, and have no uncontrolled source of infection," she concluded.

The investigator-initiated study had no outside funding.

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Adding vasopressin in distributive shock may cut AF risk

BY ANDREW D. BOWSER
MDedge News

In patients with distributive shock, the risk of atrial fibrillation may be lower when vasopressin is administered along with catecholamine vasopressors, results of a recent systematic review and meta-analysis suggest.

The relative risk of atrial fibrillation was reduced for the combination of vasopressin and catecholamines versus the current standard of care, which is catecholamines alone, according to study results published in JAMA.

Beyond atrial fibrillation, however, findings of the meta-analysis were consistent with regard to other endpoints, including mortality, according to William F. McIntyre, MD, of McMaster University, Hamilton, Ont., and his coinvestigators.

The current study is one of the first to directly compare the combination of vasopressin and catecholamine to catecholamines alone, which is the current standard of care, wrote William F. McIntyre, MD, of McMaster Univeristy, and his coinvestigators, in their paper published in JAMA.

Mortality was lower with the combination approach when all studies were analyzed together. Yet, when the analysis was limited to the studies with the lowest risk of bias, the difference in mortality versus catecholamines alone was not statistically significant, investigators said.

Nevertheless, the meta-analysis does suggest that vasopressin may offer a clinical advantage regarding prevention of atrial fibrillation in patients with distributive shock, a frequently fatal condition most often seen in patients with sepsis.

Vasopressin is an endogenous peptide hormone that decreases stimulation of certain myocardial receptors associated with cardiac arrhythmia, the authors noted.

"This, among other mechanisms, may translate into a reduction in adverse events, including atrial fibrillation, injury to other organs, and death," they said in their report.

Dr. McIntyre and his colleagues included 23 trials that had enrolled a total of 3,088 patients with distributive shock, a condition in which widespread vasodilation lowers vascular resistances and mean arterial pressure. Sepsis is its most common cause. The current study is one of the first to directly compare the combination of vasopressin and catecholamine to catecholamines alone, which is the current standard of care, the investigators wrote.

They found that the administration of vasopressin was associated with a significant 23% reduction in risk of atrial fibrillation.

"The absolute effect is that 68 fewer people per 1,000 patients will experience atrial fibrillation when vasopressin is added to catecholaminergic vasopressors," Dr. McIntyre and his coauthors said of the results.

Pooled data showed administration of vasopressin along with catecholamines was associated with an 11% relative reduction in mortality, according to the investigators.

The atrial fibrillation finding was judged to be high-quality evidence, they said, noting that two separate sensitivity analyses confirmed the benefit.

Mortality data were less consistent, they said.

Pooled data showed administration of vasopressin along with catecholamines was associated with an 11% relative reduction in mortality. In absolute terms, 45 lives would be saved for every 1,000 pa-

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tients receiving vasopressin, they noted.

However, the mortality findings were different when the analysis was limited to the two studies with low risk of bias. That analysis yielded a relative risk of 0.96 and was not statistically significant.

Studies show patients with distributive shock have a relative vasopressin deficiency, providing a theoretical basis for vasopressin administration as part of care, investigators said.

The current Surviving Sepsis guidelines suggest either adding vasopressin to norepinephrine to help raise mean arterial pressure to target or adding vasopressin to decrease the dosage of norepinephrine. Those are considered weak recommendations based on moderate quality of evidence, Dr. McIntyre and colleagues noted in their report.

Authors of the study reported disclosures related to Tenax Therapeutics, Orion Pharma, Ferring Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb, among other entities.

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SOURCE: McIntyre WF et al. JAMA. 2018;319(18):1889-900.

CHEST past president honored by AACN

Curtis Sessler, MD, FCCP, has been honored with the American Association of Critical-Care Nurses (AACN) Pioneering Spirit Award. As one of AACN's Visionary Leadership Awards, it recognizes significant contributions that influence high-acuity and critical care nursing regionally and nationally and relates to AACN's mission, vision, and values.

Dr. Sessler is the Orhan Muren Distinguished Professor of Medicine at the Virginia Commonwealth University (VCU) Health System, Richmond. He also serves as director of VCU's Center for Adult Critical Care, medical director of critical care, and medical director of the medical respiratory ICU. He has enjoyed a long career in critical care medicine focusing on patient care, teaching, clinical research, and advancing collaborative care of critically ill patients. He has a long-term collaboration with research colleagues from VCU School of Nursing, studying a variety of clinical problems, including ICU sedation,

DR. SESSLER

prevention of nosocomial infection, mechanical ventilation, and procedural competency. Under his leadership, the interprofessional group created and validated the Richmond Agitation-Sedation Scale, which is used worldwide to help improve the management of pain, sedation, and delirium in critically ill patients.

Besides serving as CHEST President in 2014-2015, Dr. Sessler has held numerous leadership roles at CHEST and has been recognized for his research, leadership, and service with many honors, including the 2017 Distinguished CHEST Educator Award, 2016 Art Wheeler Memorial Lecture Award, and 2010 Roger C. Bone Memorial Lecture Award.

Dr. Sessler has also participated in many activities of the Critical Care Societies Collaborative, which links the leaders of AACN, CHEST, the American Thoracic Society, and the Society of Critical Care Medicine. This group has addressed numerous issues central to critical care, such as research priorities, workforce shortage, clinical competencies, Choosing Wisely in Critical Care, and, most recently, burnout among critical care health-care professionals.

CHEST congratulates Dr. Sessler on this distinguished honor!

NAMDRC legislative and regulatory agenda once again focuses on patient access

BY PHIL PORTE
Executive Director, NAMDRC

NAMDRC's Mission Statement declares, "NAMDRC's primary mission is to improve access to quality care for patients with respiratory disease by removing regulatory and legislative barriers to appropriate treatment." This mission is clear as we review our legislative and regulatory agenda on an ongoing and continuing basis.

Home Mechanical Ventilation: Close to 20 years ago, HCFA (now CMS) was faced with an important reality: advances in technology

DR. PORTE

related to home mechanical ventilation are triggering an exponential growth in availability of these life supporting devices, but a price would be paid. At that time, Medicare law was quite explicit, indicating that certain ventilators would be paid under a "frequent and substantial servicing" payment methodology, authorizing payment on an ongoing basis as long as the prescribing physician documented medical necessity. To circumvent that statutory reality, the agency created a new category of medical device – a respiratory assist device/RAD – and declared that these devices are no longer ventilators and are now subject to capped rental rules and regulations.

NAMDRC was determined to work within the system, but roadblocks were consistently encountered, ie, contractor policies that did not reflect current medical standards of care, peer reviewed literature, etc. Even defining a "respiratory assist device" was (and still is) a challenge, as the term does not appear in the medical literature or in FDA vernacular.

Spin forward to 2018 and numerous realities come into play. Physicians still struggle with the concept

of RADs without a definitive, consistent definition and no FDA language to guide usage. Today, it is easier to secure a ventilator if a physician documents the patient experiences some level of respiratory failure than it is to prescribe a simple ventilator with a back-up rate. Because of that dichotomy, the growth of life support ventilator usage is well documented.

NAMDRC was determined to work within the system, but roadblocks were consistently encountered, such as contractor policies that did not reflect current medical standards of care.

If one takes the approach that a device should be paired with the actual clinical characteristics/medical need of the patient, changes in policy are necessary. While CMS clearly has the authority to act to improve policy and match clinical need to patient access, years and years of back and forth have signaled a definite unwillingness of the agency to

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move in that direction; therefore, the only genuine recourse is to seek legislative relief.

NAMDRC is working closely with the United States Senate, particularly the Finance Committee, Senator Cassidy (R-LA), and the Office of Senate Legislative Counsel to craft legislative language to address the myriad of issues associated with home mechanical ventilation.

Home Oxygen Therapy: In 1986, Congress revamped the statute governing coverage and payment of home oxygen. Pondering the reality of a segment of pulmonary medicine that has seen dramatic technological improvements and enhancements over the past 30-plus years, coupled with a payment system that is stuck with e-cylinders and competitive bidding, it is no wonder that both patients and physicians experience ongoing frustration trying to match a patient's needs with an oxygen system that reflects the patient's needs.

It's a challenge to even consider where to start a reasonable discussion of home oxygen therapy. While the concept of supplemental oxygen is well accepted, the actual clinical evidence relies heavily on a very small number of studies. While virtually no one challenges the concept of the therapy, the actual science has progressed modestly in 30-plus years. But the technology surrounding oxygen therapy has become an industry all to itself. There are concentrators, portable oxygen concentrators, liquid systems, transfill systems, transtracheal oxygen therapy, and so on.

NAMDRC is working with the Senate Finance Committee, Senator Cassidy (R-LA), and the Office of Senate Legislative Counsel to craft legislative language to address the myriad of issues associated with home mechanical ventilation.

Add to the environment the growing demand for high flow systems that would deliver continuous flow oxygen at rates in excess of 4 L/min, and you begin to realize that the current payment system is a barrier to access. After all, the current payment system has problematic characteristics:

1. A flawed competitive bidding methodology;
2. Payment tied to liter flow pegged at a baseline of 2 L/min, regardless of actual patient need;
3. The major shift from a "delivery model" of care to a nondelivery model that reflects these newer technologies;
4. Virtual disappearance of liquid system availability as an option for physicians/patients;
5. The total failure of CMS to monitor, let alone act on, patient concerns.

Again, taking the NAMDRC Mission Statement into context, NAMDRC is working with all the key societies to craft a broad strategy to address these problems, acknowledging that it will likely take a mix of legislative and regulatory actions to bring home oxygen therapy into the 21st century, let alone to reflect realities of care in 2018.

PULMONARY PERSPECTIVES®

From ECMO to post-ICU discharge clinics

BY JOHN MADARA, MD, AND MICHAEL BARAM, MD, FCCP

As extracorporeal membrane oxygenation (ECMO) is utilized more frequently,[1] there will be more survivors of prolonged hospitalizations with new challenges that they will need to face. As health-care providers, we must be involved with establishing a system to deal with the longitudinal effects of the expanding treatment options. Some of the interventions to improve post-ECMO quality of life require hospital-based initiatives but also should incorporate post-hospital discharge care.

The ECMO patient population represents some of the sickest patients in the hospital. With the average ECMO patient having an APACHE II score of greater than 25, this carries an estimated mortality rate of at least 55%.[2, 3] When the decision is made that the patient no longer needs ECMO support and is removed from the circuit, there still remains a possibility of a multitude of complications during their hospitalization. One of the more common occurrences after ECMO is a continued systemic inflammatory response syndrome (SIRS).[4] A meta-analysis published in 2013 reported frequent ECMO complications, such as renal failure requiring hemodialysis (52%), pneumonia (33%), liver disease (16%), and GI bleeding (7%).[5] Many patients require tracheostomy for prolonged mechanical ventilation and percutaneous enteral access. There are high rates of critical care-related myopathies and neuropathies that usually require prolonged treatment courses of physical therapy and occupational therapy. This is not to mention one of the more dreaded complications of prolonged ICU stays—delirium, leading to posttraumatic stress disorder (PTSD). Due to the pharmacokinetics of the ECMO circuit and high levels of discomfort, higher amounts of opioids and benzodiazepines are required when compared with the general critical care population. It is common to see patients receiving high doses of continuous IV infusions of lorazepam, fentanyl, and ketamine. ICU delirium leads to increased days in the ICU, adds the additional risks of developing complications seen from long hospitalizations, and contributes to long-term cognitive deficits.

Once these critically ill patients are discharged from the hospital, they are left with a multitude of long-term medical, psychological, and cognitive deficits. Post-Intensive Care Unit Syndrome (PICS) is becoming more recognized as a group of health problems that patients suffer after a prolonged course of treatment in the ICU. Recent studies have shown the long-term negative deficits in critically ill patients. Iwashyna and colleagues demonstrated that survivors of severe sepsis revealed increased rates of cognitive impairments and functional disabilities.[6] The same phenomena that patients with septic shock suffer are seen in ECMO survivors, as well. ECMO survivors are frequently left with residual cognitive, psychological, and medical complications.

It is known that patients who survive long ICU stays suffer from PICS, and patients who survive ECMO are at high risk for developing complications, but there is a dirth of literature examining the long-term outcomes in these patients. High levels of sedation are required while on pump increases delirium that is a known risk factor for cognitive impairments in the long term. Prolonged bedrest, paralytics, and steroids are frequently needed for these patients, all risk factors in developing ICU-acquired weakness. An article published by Schmidt and colleagues[7] in 2013 showed that survivors of ECMO had decreased SF-36 scores, which is a single measure patient health-related quality of life questionnaire, indicating worse quality of life when compared with the general population. Hodgson and colleagues[8] also noted a similar decrease in SF-36 scores in ECMO survivors at 8 months postdischarge. Beyond the cognitive and quality of life impairments, significant long-term psychiatric issues develop. A case-series published in 2013 showed an extremely high prevalence (71%) of mental disorders in ECMO survivors.[9]

During a long and complicated hospital course for these patients, there is often a major component to the care of the patient that goes overlooked. While the patient remains sedated with anti-anxiety, analgesics, and amnesic medications throughout their ICU stay, the family members and caregivers of the patient remain at bedside, often for hours, days, or weeks on end. It is sometimes difficult to explain the nuisances, risks, and details of the care of ECMO patients to other health-care practitioners, yet alone family members who are undergoing one of the most stressful periods of their life, leaving anxiety amongst decision makers. An article published in 2016,[10] demonstrated that the long-term negative outcomes affect not only the patients but their caregivers, as well. Primary caregivers of critically ill patient survivors suffered from high rates of depression that persisted for the year of the study. It has been shown that including family members in daily discussions and scheduling frequent family meetings helps to avoid confusion and stress.

Dr. Madara and Dr. Baram (pictured) are with the Division of Pulmonary Care, Department of Medicine, Jefferson University, Philadelphia, Pennsylvania.

To further hospital-based strategies to reduce PICS, there have been several interventions proposed and implemented to decrease these long-term negative outcomes. Daily rounds are performed to identify who may benefit from physical therapy, and patients are receiving early treatments. Emphasis is placed on minimizing sedation, as well as daily sedation holidays to decrease the amount of pharmacologics that patients are receiving. Family members are incorporated into rounds and updated daily to decrease uncertainty in their loved one's care. Time is

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spent to make sure medications are reconciled, specialist recommendations are incorporated, and then patients are discharged from the hospital with follow-up plans usually to their primary care physician. Historically, the intensivist role in caring for the patient classically ends there—this is changing. The newest literature about PICS supports longer engagement by intensivists. Intensivists are the ones who have identified this is an issue and increasingly are involved with the patient care and family after discharge.

Post-ICU discharge clinic

We have begun a post-ICU discharge clinic at our institution to start screening our patient population for the cognitive, psychological, and medical disease processes that are common, yet underrecognized. Incorporating the health-care providers who care for the critically ill patients in the hospital will help give us an understanding of what challenges and difficulties these patients may face once discharged. A lot of focus in the medical literature is on mortality benefits. We argue that if we are having more patients survive critical illness, our focus should broaden on how to deal with the complications that our survivors are left with. We can work together to help our patients and their families in their most vulnerable time in their lives. Patients should be provided an ongoing service after they leave the ICU and focus on improving their quality of life.

Models for a post-ICU clinic vary per site. But the goals of these clinics are to help bridge the gaps as patients try to rebuild their lives. A prolonged critical illness can leave a devastated life that needs to be restructured. Using multiple services, the goal of the clinic is to recognize the difficulties of recovering from critical care. Internists often do not realize the stress that surviving ICU can leave. Some people look at surviving ARDS as a miracle, while others carry financial, social, physical, and emotional scars as indicated by SF-36 scores. The goal of the clinic is to acknowledge deficits left by a prolonged stay with multidisciplinary services being involved. There are screening tools to identify PTSD; rehabilitation medicine specialists; and pharmacists to help address issues. Although many of the identified issues will not be addressed directly in clinic, the goal is to refer patients to specialists who can provide long-term care. In many ways, the goal of the clinic is to offer patients recognition/substantiation of what they have gone through (which is a plus in itself) but also refers patients to subspecialty services that our university program can provide.

Each person in the clinic has a unique role. The physician presence is to describe to the patient and their loved ones the ongoing medical complications from the hospitalization. Families are informed that cognitive and psychological problems are common in this particular condition. A critical care pharmacist can review lists of medications and doses to ensure no problems occurred in the transition to outpatient. Physical and occupational therapy are present to screen for both neuromuscular and cognitive defects and provide tips and exercises to help rebuild patients' strength of muscle and mind. We also involve one of the most important parts of the patients care while in the ICU, critical care-trained nurses and nurse practitioners. These are the members of the team who the patients and families are always happiest to see. Also, seeing patients in the outpatient setting, after significant recovery has occurred, comes as a significant morale booster for the health-care practitioners who deal with so much stress and anxiety on a daily basis. The team feels gratified that all of their energy spent in the ICU yields very meaningful outcomes.

Utilizing the expertise of multiple disciplines, our post-ICU clinic is to help ICU survivors gain control over their lives. The Society of Critical Care Medicine (SCCM) has embraced the idea of treating PICS. As intensivists we embrace the idea of helping our survivors regain independence in life, support family members through their needs, and help fulfill our own need to see survivors achieve a higher quality of life.

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This month in the journal *CHEST*®

Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, the journal CHEST®

GIANTS IN CHEST MEDICINE
Dirkje S. Postma, MD, PhD.
By Dr. Huib A. M. Kerstjens.

ORIGINAL INVESTIGATIONS
Beta-Blockers in COPD: A Cohort Study From the TONADO Research Program.
By Dr. F. Maltais, et al.

The Risk of TB in Patients With Type 2 Diabetes Initiating Metformin vs Sulfonylurea Treatment.
By Dr. S-W Pan, et al.

CHEST NETWORKS

Sinus rhythm, physician burnout, difficult-to-treat pulmonary infections, and more

Cardiovascular Medicine and Surgery

Sinus rhythm is superior for heart failure with atrial fibrillation

It is a question that is frequently asked: is rhythm or rate control better for non-valvular atrial fibrillation (AFib)? The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) [*N Engl J Med.* 2002;347[23]:1825-33) and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) (Van Gelder et al. *N Engl J Med.* 2002;347[23]:1834-40] trials demonstrated that the strategies are equivalent. However, AFib and heart failure are concurrent in up to 50% of patients (Santhanakrishnan et al. *Circulation.* 2016;133[5]:484-92) and several trials have shown that decreasing the time spent in AFib leads to improved left ventricular ejection fraction (LVEF), 6-minute walk distance (6MWD), quality of life, and may even reduce mortality and hospitalizations (Khan et al. *N Engl J Med.* 2008;359[17]:1778-85; Hunter et al. *Circ Arrhythm Electrophysiol.* 2014[1];7:31-8; DiBiase et al. *Circulation.* 2016;133[17]:1637-44). The AFFIRM trial demonstrated a reduced mortality in those achieving sinus rhythm, but this was negated by adverse effects from antiarrhythmic medications. The Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial examined the benefits of rhythm control in patients with AFib and CHF via pulmonary vein ablation (Marrouche et al. *N Engl J Med.* 2018;378[5]:417-27). This was a multicenter, randomized, open label trial that included patients with symptomatic AFib, an LVEF less than or equal to 35%, and at least NYHA class II heart failure. Results demonstrated a significant reduction in all-cause mortality and heart failure hospitalizations in those undergoing ablation (NNT of 9). Exploratory results also demonstrated reduced cardiovascular death, decreased AFib burden, increased 6MWD, and improved LVEF with ablation. Post-ablation patients received anticoagulation therapy for at least 6 months. However, the study did have some limitations: it was not blinded, there was no sham group, the sample size was relatively small, and experienced, high volume medical centers performed the procedures (*N Engl J Med.* 2018;378:468-469). CASTLE-AF provides additional evidence for the benefits of reducing the burden of AFib in congestive heart failure while avoiding the detrimental effects of antiarrhythmic medications.

David J. Nagel, MD, PhD
Steering Committee Member

Follow-up study of HeartMate 3 LVAD

Since commercially available in 2008, enthusiasm for continuous flow LVADs as treatment of end-stage heart failure has increased with over 22,000 implantations to date. However, the 2-year survival rate of 70% is limited mostly by neurologic complications - the consequence of the perilous imbalance between thrombosis and bleeding (Kirklin et al. *JHLT* 2017;36[10]:1080).


DR. SHAH

In this context, the MOMENTUM 3 trial (Mehra et al. *N Engl J Med.* 2018;378:1386), a head-to-head study of the HeartMate 3 (newest durable LVAD) vs HeartMate II (the first and most popular model) is a significant milestone. In this trial, compared with the HM II, patients with HM 3 had fewer strokes and reoperation for pump malfunction at 2 years. Although rate of severe strokes was similar in both arms, HM 3 has the lowest rate of overall strokes or pump thrombosis compared with other continuous flow device trials thus far. The rates of bleeding were the

Continued on following page

Continued from previous page

same among the two models in this trial, but given the low rate of pump thrombosis, lower anticoagulation targets might be considered for the HM 3. Whether new modifications of the anticoagulation strategy reduce bleeding complications down the road remains to be seen. Currently, the HM 3 is FDA-approved for bridge to transplant only, but, after this trial, the indication will likely expand to include destination therapy.

As technological breakthroughs lead to improved long-term patient survival, we will inevitably be tending to a growing number of LVAD implanted patients in our clinics and units.

Nimesh S. Shah, MD, FCCP
Steering Committee Member

Chest Infections

Inhaled antibiotics for difficult-to-treat pulmonary infections

That the lungs constantly interface with the environment is both a blessing and a curse: while the lungs are continually exposed to environmental pathogens and irritants, this also provides a relatively unique route for delivery of effective medications directly to the site of disease. For chronic lung diseases characterized by recurrent infections, such as cystic fibrosis (CF) and non-CF bronchiectasis, this means delivery of antimicrobials via inhalation.

DR. KEYT

For individuals with CF, inhaled antibiotics are considered standard of care in the management of Pseudomonal infections. A recent Cochrane review concluded that inhaled anti-pseudomonal treatments improve lung function and reduce exacerbation rates in this population (Smith, et al. *Cochrane Database Syst Rev.* 2018;Mar 30;3:CD001021).

What is the next frontier for inhaled antimicrobial therapies in CF? The focus is now on increasingly common and difficult-to-treat pathogens, such has methicillin-resistant Staphylococcus aureus (MRSA) and nontuberculous mycobacteria (NTM). Vancomycin inhalation powder (AeroVanc TM) is an inhaled dry powder version of vancomycin, which significantly reduced sputum MRSA density in a recent phase 2 trial; a phase 3 trial is currently underway. For infections caused by NTM, inhaled amikacin has been shown to be safe and efficacious in small subsets of patients with CF and non-CF bronchiectasis (Yagi, et al. *BMC Infect Dis.* 2018;17[1]:558). Other inhaled therapies currently under investigation for use in CF pulmonary infections include fosfomycin/tobramycin inhalation and a new inhaled glycopolymer (SNSP113) that disrupts bacterial biofilms.

In non-CF bronchiectasis, the evidence showing benefit for use of inhaled antibiotics is not as well established. A recent Cochrane review reported no evidence indicating whether oral or inhaled antibiotics are better for non-CF bronchiectasis (Spencer, et al. *Cochrane Database Syst Rev.* 2018; Mar 27;3:CD012579). The heterogeneity of this population limits the ability to extend positive findings in a small subgroup to the population at large; however, investigation in this area is ongoing.

Inhaled antibiotics have been studied and used for decades in patients with chronic infections, and interest in the development of even more efficacious and better-tolerated medications is stronger than ever. Look for more information on this topic at the upcoming CHEST 2018 Annual Meeting in San Antonio this October.

Holly Keyt, MD
Steering Committee Member

Clinical Pulmonary Medicine

Prevent and treat burnout now

Burnout is a work-related syndrome that manifests with symptoms of emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment (Moss, et al. *Chest.* 2016;150[1]:17-26). In a 2018 Medscape survey, critical care physicians had the highest rates of burnout at 48%, with pulmonary medicine physicians reporting rates at 41% (Medscape. https://www.medscape.com/sites/public/lifestyle/2018. Accessed Apr 13, 2018). Studies show approximately 25% to 33% of critical care nurses experience burnout (Shanafelt, et al. *Arch Intern Med.* 2012;172[18]:1377-1385). Resident and fellow trainees also have a high prevalence (60%) of burnout (Dyrbye, et al. *Acad Med.* 2014;89[3]:443-451). Burnout has been shown to contribute to staff turnover and, thus, impact access to care, patient satisfaction, and quality of care. Excessive staff turnover rates also increase health-care costs. Replacing a critical care nurse and primary care physician is estimated to cost at least $65,000 and $250,000, respectively. Drivers of burnout (ie, excessive workload, lack of work support, lack of work-home integration, loss of control and autonomy, and loss of meaning from work) can be solved with organizational (ie, optimizing electronic medical records) and individual solutions (ie, prioritizing tasks and mindfulness) (West, et al. *J Intern Med.* 2018; Mar 5. doi: 10.1111/joim.12752 [Epub ahead of print]).

DR. DOO

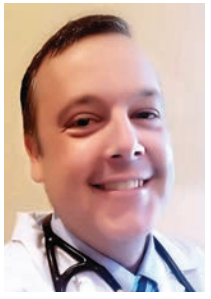
The American College of Chest Physicians is part of the Critical Care Societies Collaborative (CCSC), which was convened to acknowledge and raise awareness of burnout in the healthcare community (Moss M, et al. *Chest.* 2016;150[1]:17-26). To combat this crisis, all stakeholders in healthcare must work together to develop evidence-based strategies to prevent and treat burnout.

Saiprakash B. Venkateshiah, MD, FCCP
Vice-Chair
Kathleen Doo, MD
Fellow-in-Training Member

Interprofessional Team

When standard ACLS fails for the hospitalized patient

The current standard of care for the management of hospitalized adult patients who suffer cardiac arrest is standard ACLS. This population still suffers significant mortality even after the incorporation of rapid response teams (Solomon et al. *J Hosp Med.* 2016 Jun;11(6):438-45. doi: 10.1002/jhm.2554. Epub 2016 Feb 1). Addition of technology and mechanical support with chest compression devices has also demonstrated survival improvement (Couper, et al. *Resuscitation.* 2016 Jun;103:24-31. doi: 10.1016/j.resuscitation.2016.03.004. Epub 2016 Mar 11). As ECMO becomes more commonplace in various centers (Abrams and Brodie. *Chest.* 2017;152[3]:639–649), expanding those programs to provide E-CPR services has become the next step in some facilities. ELSO registry reports demonstrate an approximate 40% survival rate for adults treated with ECPR (Extracorporeal Life Support Organization. 2017. *ECLS Registry Reports.* Retrieved from https://www.elso.org/Portals/0/Files/Reports/2017/US%20Summary%20July%202017.pdf). This potentially represents fertile ground hospitals to improve in-hospital arrests. Guidelines exist for consideration of ECPR when standard measures fail. A two-physician model has been described; however, this resource may not always be available. Models have been described whereby advanced practice providers (APPs) can be key leaders in critical care and to initiate ECPR (Baeten, et al. Shifting the paradigm towards advanced practice providers managing the coronary care units. SCAI 40th Annual Scientific Sessions, May 10-13, 2017, New Orleans, LA). Limiting factors for expedient cannulation can include the time for arrival of a perfusionist and/or ECMO-capable physician.



DR. BAETEN

A multiprofessional approach, including RTs, RNs, APPs, and MDs can be used to optimize appropriate resources. In-house staff, including a respiratory therapist to secure and manage the airway, nurses ensure appropriate compressions or operation of a chest compression device, and APPs to determine ECMO/ECPR candidacy in conjunction with the appropriate physician. While the physician is en route, ACLS continues; however, the patient is prepped and draped and initial femoral venous-arterial access is achieved. This facilitates rapid catheter exchange to large peripheral VA-ECMO cannulas immediately upon arrival of the ECMO physician.

Robert Baeten II, PA-C
Steering Committee Member

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Catching up with our CHEST past presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians, leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's strategic initiatives. Let's check in with Dr. D. Robert McCaffree, Master FCCP.

D. Robert McCaffree, MD, MSHA, Master FCCP
CHEST President 1997 - 1998

Dr. Mary Anne McCaffree and Dr. D. Robert McCaffree

I received the chain of office (yes, there is an actual chain) from Dr. Bart Chernow in New Orleans during CHEST 1997. I remember this time as being a time of beginnings, challenges, and changes. Bart had been the stimulus for the CHEST Foundation and the form and function of this foundation was being developed. The women's caucus (probably not the official name) was becoming more organized and more of a force under the leadership of Dr. Diane Stover and Dr. Deborah Shure and others, and the Woman, Girls, Tobacco, and Lung Cancer educational program was being refined. It was this program that got my wife, Mary Anne, involved with CHEST, and she became a Fellow (FCCP). The American College of Chest Physicians was in the midst of the national tobacco settlement efforts at this time. Our involvement began when Mike Moore, Attorney-General of Mississippi, filed the first suit against the tobacco industry in 1994. Under the stimulus of Dr. John Studdard, our current President, the college was the only medical organization to file an *amicus curiae* brief supporting this, thus thrusting us into the midst of the tobacco settlement debates and in a leadership position. During the time I was President-elect and President, I was fortunate to represent us both in the ENACT Coalition (composed of national health groups, such as the American Cancer Society), as well as on the Koop-Kessler Congressional Advisory Committee. I also testified before Congress on the tobacco issues and met at the White House with DHHS Secretary Donna Shalala. On a different front, our international activities were not as developed as now, but we did make two memorable trips to India. Many thanks to Dr. Kay Guntupalli for helping make those trips so memorable. After this absolutely wonderful year, I passed the chain to Dr. Allen Goldberg in Toronto.

My experiences with tobacco control continue to influence my life. After the national tobacco settlement failed, there was enacted the multistate tobacco settlement. Oklahoma was the only state to place the majority of those settlement dollars into a constitutionally protected trust fund, the Oklahoma Tobacco Settlement Endowment Trust Fund (TSET). I was fortunate to be appointed to the Board of Directors of TSET by our Attorney General and was elected the first chair. Since then, the corpus has grown to over one billion dollars, and TSET has been able to effect many positive changes toward helping tobacco control in Oklahoma. One of these was to fund the Oklahoma Tobacco Research Center (OTRC) as part of the Stephenson Cancer Center at Oklahoma University. I stepped off the TSET Board to join Dr. Laura Beebe in this endeavor, which started with two people and one office and has now grown to occupy over 15,000 square feet with nine faculty and several postdoctoral students.

Among other activities, I was Chief of Staff at the Oklahoma City VAMC for 18 years, retiring from that position in 2009. I was honored by having the MICU at the VA named after me. In the community, I helped start the Hospice of Oklahoma County and then the Hospice Foundation of Oklahoma, both of which I served as first chairman. I also helped start Palliative Care Week on the OUHSC campus. I am currently the vice-chair of the Health Alliance for the Uninsured in Oklahoma City, which helps support the many free clinics in our city. My wonderful wife, Mary Anne, is also involved in many community activities. On a personal level, we try to see our two children and two grandchildren as often as possible, which is not often enough. My free time activities include reading, playing the piano, fly fishing (not often enough), and exercise.

My time as President of the American College of Chest Physicians was one of the best and most important experiences of my life. My memories of working with Al Lever, David Eubanks, Marilyn Lederer, Lynne Marcus, Steve Welch, and all the other staff and physician leaders during that time remain very dear to me. The influence of CHEST continues to this very day. I can never repay all that I have gained from this experience. I wish I had the space allowance to expand on my experiences. But while my word allowance is limited, my gratitude is unlimited.

Explore the Culture in San Antonio During CHEST 2018

With the level of history and culture in San Antonio, there are plenty of options when experiencing what the city has to offer. Here are a few ways you can enjoy the arts and culture of San Antonio.

San Antonio Museum of Art
200 West Jones Avenue
The San Antonio Museum of Art contains the largest and most comprehensive collection of ancient Egyptian, Greek, Roman, and Asian art in the southern United States. The museum also has a significant collection of Latin American art. Also, check out the growing contemporary art collection with notable Texan and regional art, special exhibitions, films, concerts, gallery talks, and more!

Centro de Artes
101 S. Santa Rosa Avenue
Monday: Closed
Tuesday to Sunday: 11:00 a.m. to 6:00 p.m.
Head over to Centro de Artes to experience local and regional art, as well as history and culture, revealing the story of the Latino experience in the United States with a focus on San Antonio and South Texas.

King William Historic District
122 Madison Street
Historic King William District spans 25 blocks of downtown San Antonio. In the late 1800s, the King William District was considered the most elegant residential area in the city and zoned as the state's first historic district. You can now view these 19th century residences on the south bank of the San Antonio River where some have been preserved and reincarnated into cafes, art galleries, museums, and shops.

GO RIO River Shuttle
Daily: 10:00 a.m. to 9:00 p.m.
Want an open tour of San Antonio? Look for the GO RIO River Shuttle signs and boats (labeled with GO RIO) along the River Walk from downtown to Museum Reach. Shuttles run approximately every 60 minutes with tickets available for purchase on the boat, online, or at any GO RIO ticket booth.

Market Square
514 W. Commerce Street
Open Daily: 10:00 a.m. to 6:00 p.m.
Explore the Historic Market Square where you'll find authentic handcrafted art and the gourmet Mexican cuisine of old Mexico at over 100 locally owned shops and stalls, all at a festive indoor mall. There's also the Farmers Market Food Court where you can enjoy a show on the stage.

City Sightseeing San Antonio Bus Tours
Get a double decker view starting from Alamo Plaza, then head north toward the San Antonio Museum of Art, the Pearl Brewery Entertainment Complex, and more. There are 18 stops where you can get off and explore. Then, just go back to where you were dropped off, and wait for the next bus to arrive. There's a bus every 20 minutes at each stop during the operating hours from 8:40 a.m. to 5:30 p.m..

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THE SECTION OF PULMONARY, CRITICAL CARE & SLEEP MEDICINE, YALE SCHOOL OF MEDICINE, IS SEEKING OUTSTANDING INDIVIDUALS FOR THE FOLLOWING POSITIONS:

Associate Clinic Director

Section of Pulmonary, Critical Care and Sleep Medicine, Yale School of Medicine (Yale PCCSM), is seeking candidates for Associate Director of our rapidly growing Ambulatory Pulmonary program (Winchester Chest Clinic). This academic position will be filled at a rank of: Instructor, Assistant Professor, or Associate Professor commensurate with qualifications. The successful candidate is expected to assist the Clinic director with the day to day management of the Winchester Chest Clinic, as well as develop initiatives to improve and optimize patient care and experience in the clinic. The candidate is expected to see patients in the Comprehensive Pulmonary Program but may also work in our sub-specialty practices as well dependent on interest. All candidates are expected to have outstanding skills in the clinical and educational arena, will take an active role teaching and mentoring fellows and residents and other opportunities for career development in the thriving academic environment of Yale PCCSM. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. Minimum requirements include: board eligibility or certification in pulmonary diseases and critical care medicine. Experience in pulmonary ambulatory care, medical education and management is encouraged.

All applications materials should be submitted electronically to:
http://apply.interfolio.com/41048

Review of applications will begin immediately, and will continue until the position is filled.

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For more information on Yale PCCSM
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FRONTLINE MEDICAL COMMUNICATIONS

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THE SECTION OF PULMONARY,
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YALE SCHOOL OF MEDICINE,
IS SEEKING OUTSTANDING INDIVIDUALS
FOR THE FOLLOWING POSITION

Ambulatory Clinician

Section of Pulmonary, Critical Care and Sleep Medicine at Yale School of Medicine (Yale PCCSM), is seeking applicants to practice in our Ambulatory Pulmonary program (Winchester Chest Clinic) and satellite practices. The successful candidate is expected to see the majority of their patients in the general comprehensive pulmonary practice but may also work in our sub-specialty practices as well dependent on interest. All candidates are expected to have outstanding skills in the clinical and educational arena and will have the opportunity to take an active role teaching and mentoring fellows and residents. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. Minimum requirements include: board eligibility or certification in pulmonary diseases and critical care medicine.

Review of applications will begin immediately, and will continue until the position is filled.

Yale University is an affirmative action/equal opportunity employer. Yale values diversity in its faculty, students, and staff and especially welcomes applications from women, persons with disabilities, protected veterans and members of minority groups.

For more information please contact Dr. Jonathan Siner, Clinical Chief, Yale PCCSM e-mail, **jonathan.siner@yale.edu** or phone 203-737-4523

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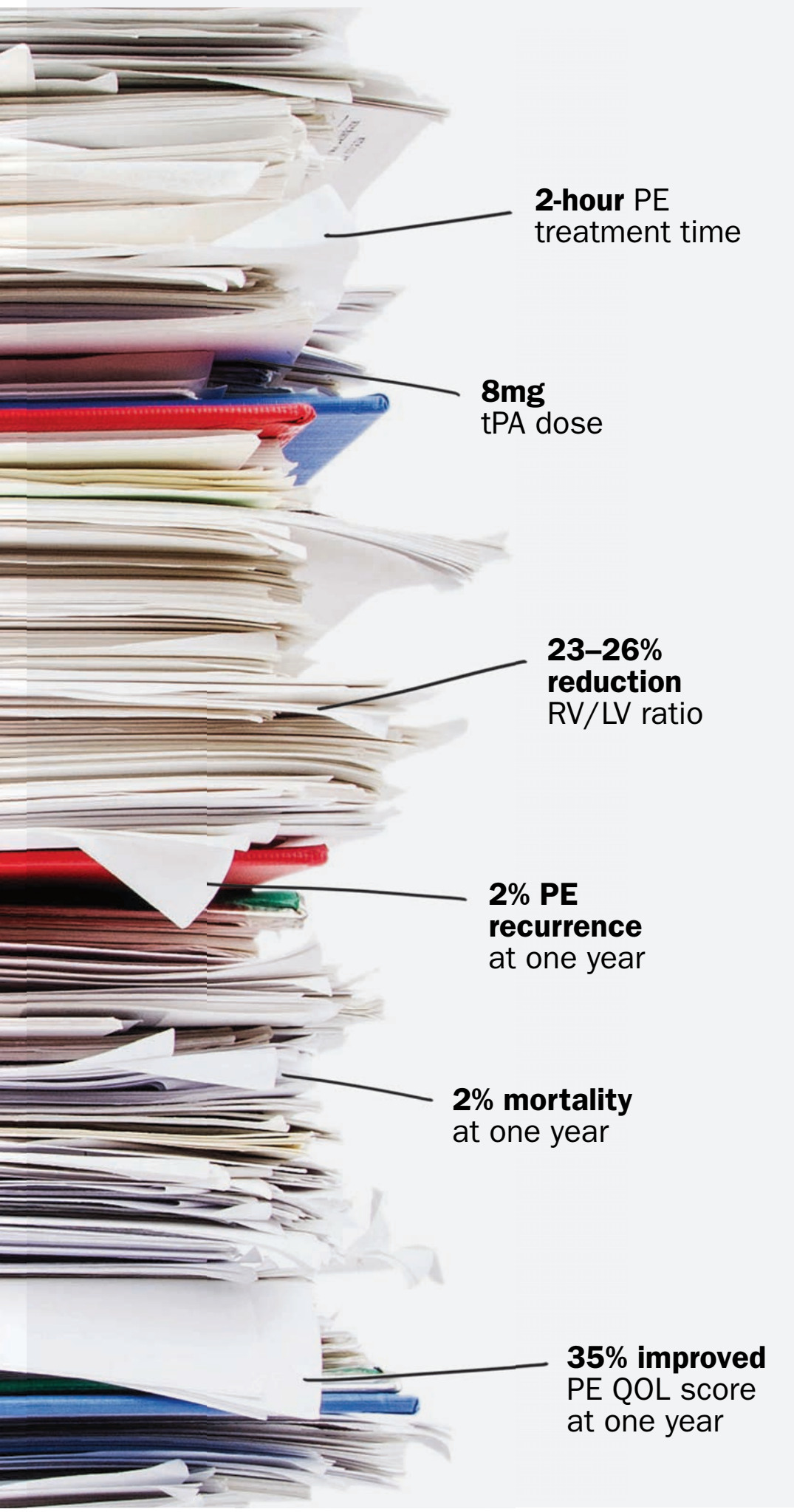

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*Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL. Feb 2018.

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See back for study design information and continued footnotes.

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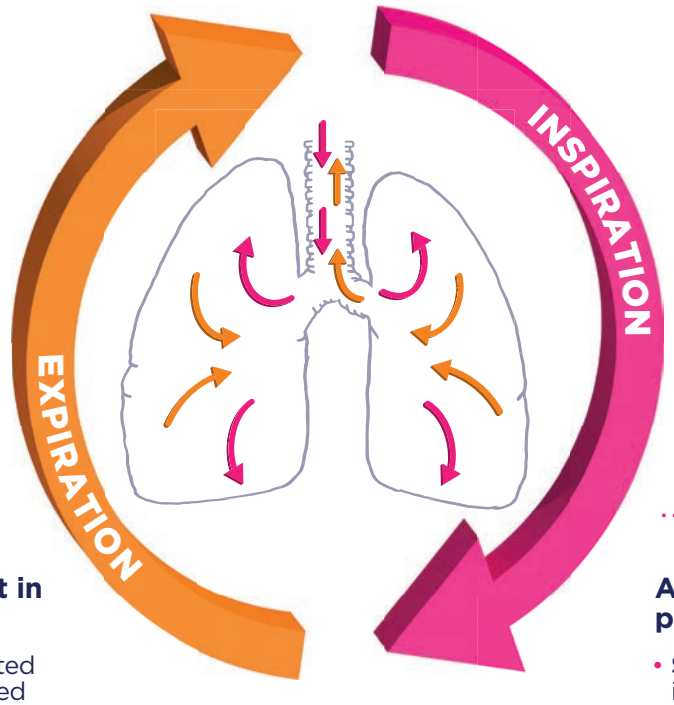

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- **Primary endpoint:** Mean improvements in FEV_1 $AUC_{0\text{-}24}$ on Day 29 for BEVESPI vs placebo were 249 mL and 265 mL (for Study A and Study B, respectively; both $P<0.0001$)[4¶]
- **Secondary endpoint:** Mean changes from baseline in peak FEV_1 on Day 29 (evening) for BEVESPI vs placebo were 293 mL and 337 mL (for Study A and Study B, respectively; $P<0.0001$)[3]

...THROUGH INSPIRATION

Achieved a 381 mL improvement in peak inspiratory capacity vs placebo[3]

- **Secondary endpoint (continued):** Mean improvements in peak IC from baseline on Day 29 (evening) for BEVESPI vs placebo were 381 mL (19.4%) and 312 mL (16.5%) (for Study A and Study B, respectively; both $P<0.0001$)[4,5#&]
- Adverse events were numerically similar across treatment arms[3]

All study treatments were administered BID

*Improvements in lung function relative to its individual components and placebo in two 24-week pivotal trials.
‖Initial treatment in Group B patients with severe breathlessness and in Group D patients.

IMPORTANT SAFETY INFORMATION *(Continued)*

- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore, BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, either visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

†PINNACLE 1 & 2 PIVOTAL TRIALS

Study Design: The clinical development program for BEVESPI AEROSPHERE included two 24-week, randomized, double-blind, placebo-controlled, parallel-group trials in patients with moderate to very severe COPD. Both trials evaluated BEVESPI AEROSPHERE 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, and placebo administered BID. Trial 1 also included an open-label active control.[1] The primary endpoint for Trial 1 and Trial 2 was change from baseline in trough FEV_1 at Week 24 compared with placebo, glycopyrrolate 18 mcg BID, and formoterol fumarate 9.6 mcg BID.[1]

The comparison of BEVESPI AEROSPHERE with glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg was assessed to evaluate the contribution of the individual components to BEVESPI AEROSPHERE.[1] Change from baseline in peak FEV_1 at Week 24 was a secondary endpoint.[1,2] Inclusion criteria: a clinical diagnosis of COPD, between 40 to 80 years of age, a history of smoking ≥10 pack-years, a post-albuterol FEV_1 of <80% of predicted normal values, and a ratio of FEV_1/FVC <0.7.[1]

Primary endpoint: In Trial 1, the change from baseline in predose FEV_1 at Week 24 with BEVESPI (n=429) was 150 mL vs placebo (n=161), 59 mL vs glycopyrrolate 18 mcg (n=344), and 64 mL vs formoterol fumarate 9.6 mcg (n=367); $P<0.0001$ for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[2]

Secondary endpoint: In Trial 1, the change from baseline in peak FEV_1 at Week 24 for BEVESPI (n=428) was 291 mL vs placebo (n=160), 133 mL vs glycopyrrolate 18 mcg (n=343), and 93 mL vs formoterol fumarate 9.6 mcg (n=367); $P<0.0001$ for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[2]

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

SEPARATE PHASE IIIB TRIALS (STUDY A AND STUDY B)

Study Design: Two randomized, Phase IIIb, double-blind, multicenter, crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI AEROSPHERE 18 mcg/9.6 mcg BID compared with placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and B). Study B also included an open-label active control.[3] The primary endpoint was the change from baseline in FEV_1 $AUC_{0\text{-}24}$ on Day 29 for BEVESPI AEROSPHERE BID compared with placebo BID. Secondary endpoints included peak change from baseline in FEV_1 and inspiratory capacity following the evening dose on Day 29.[3] Inclusion criteria were consistent with the two 24-week pivotal trials.[1,3]

¶ Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A - BEVESPI AEROSPHERE n=35; Placebo n=31 (Baseline FEV_1 1.382 L and 1.345 L, respectively) and Study B - BEVESPI AEROSPHERE n=65; Placebo n=65 (Baseline FEV_1 1.328 L and 1.333 L, respectively).

Secondary endpoint, peak IC (evening): Study A - BEVESPI AEROSPHERE n=34; Placebo n=30 (Baseline evening IC 1.980 L and 1.939 L, respectively) and Study B - BEVESPI AEROSPHERE n=62; Placebo n=63 (Baseline evening IC 1.877 L and 1.913 L, respectively).

& *P*-value is based on treatment comparison of absolute mean change from baseline for BEVESPI AEROSPHERE vs placebo.

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2017. **2.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357. **3.** Reisner C, Gottschlich G, Fakih F, et al. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res*. 2017;18:157.
4. Data on File, REF-4976, AZPLP.
5. Data on File, REF-8618, AZPLP.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

BEVESPI AEROSPHERE®
(glycopyrrolate 9 mcg/ formoterol fumarate 4.8 mcg) Inhalation Aerosol

AstraZeneca

BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) 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 all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs 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 LABAs.

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; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE 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 BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, 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 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 BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of 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 dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, 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) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE 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.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications 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$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

BEVESPI AEROSPHERE 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 physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

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

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions: Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG 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 $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

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

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE 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 medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

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By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom
or By: AstraZeneca Dunkerque Production (AZDP), Dunkerque France

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