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The outcomes of 'GOLD 2017'

"Most practicing physicians are frequently asked about prognosis by patients, and I am not sure if the 2017 reclassification really helps with that," noted Dr. Imran Iftikhar.

Courtesy Dr. Imran Iftikhar

BY DOUG BRUNK
MDedge News

After the Global Initiative for Chronic Obstructive Lung Disease released updated recommendations for grading COPD patients' level of disease in November of 2016, Imran Iftikhar, MD, FCCP, tried to incorporate them into his practice, but he encountered problems.

For one thing, the new classification system, which became known as GOLD 2017, uncoupled spirometry results from the ABCD treatment algorithm. "I found it wasn't really helping me in terms of prognostication or COPD management," said Dr. Iftikhar, section chief of pulmonary and critical care at Emory Saint Joseph's Hospital, Atlanta. "Although the purpose of the GOLD classification was not really meant for prognostication, most practicing physicians are frequently asked about prognosis by patients, and I am not sure if the 2017 reclassification really helps with that."

The GOLD 2017 classification simplified the chronic obstructive pulmonary disease staging that was available from 2011 to 2015 from three variables (spirometry thresholds, exacerbation risk, and dyspnea scale) to two variables (exacerbation risk and dyspnea scale). In the 2017 report, authors of the new guidelines characterized forced expiratory volume in 1 second (FEV_1) as "a poor predictor of disease status" and proposed

COPD GUIDELINES // *continued on page 6*

Adjunct treatments assist with persistent asthma

BY HEIDI SPLETE
MDedge News

Asthma patients who struggle with poor control despite using inhaled corticosteroids can benefit from additional treatment with long-acting muscarinic antagonists (LAMAs) or single maintenance and reliever therapy, suggest data from a pair of systematic reviews and meta-analyses.

Asthma control remains a problem for many patients despite the daily use of inhaled corticosteroids. The current preferred adjunct therapy for patients aged 12 years and older is long-acting beta-agonists (LABAs), wrote Diana M. Sobieraj, PharmD, of the University of Connecticut School of Pharmacy, Storrs, and her colleagues in a study published in JAMA. The researchers examined the efficacy of other adjunct therapies and therapeutic regimes, including the use of a LAMA, in two studies of patients with persistent asthma.

In one of their analyses, the researchers evaluated LAMAs as an add-on therapy for patients with poorly controlled asthma. They

ADJUNCT THERAPY // *continued on page 13*

INSIDE HIGHLIGHT

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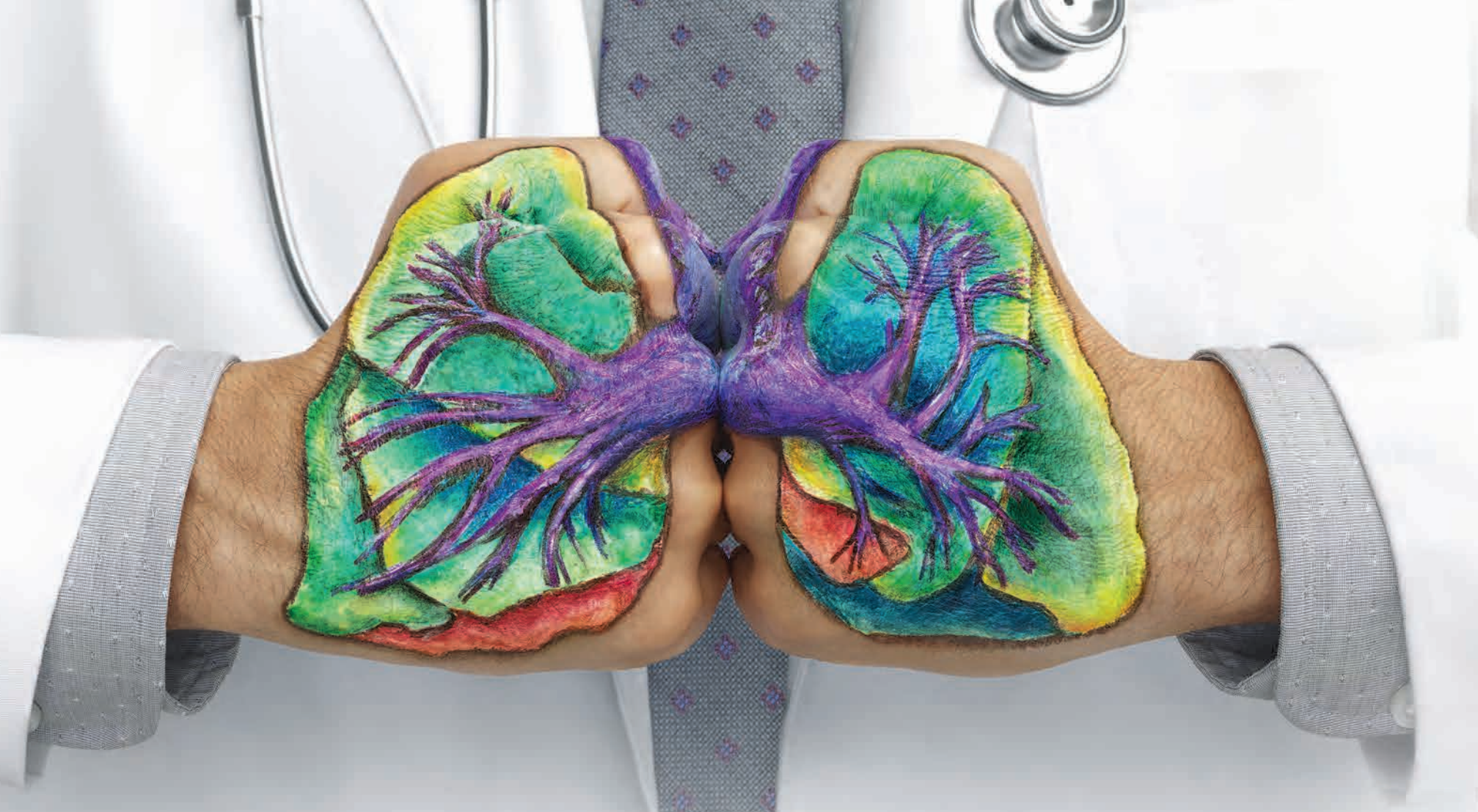

Indication

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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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]

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§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]

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New strains recommended for next flu season

BY IAN LACY
MDedge News

SILVER SPRING, MD. – In an effort to better match the vaccine to the virus, federal advisers have recommended two new strains be swapped into the 2018-2019 quadrivalent influenza vaccine.

The updates should be the influenza A(H3N2) component and the influenza B components.

Singapore A(H3N2) and the B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) are recommended be added to A/Michigan/45/2015 (H1N1)pdm09-like virus and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) for the upcoming season, according to a near-unanimous vote at a meeting of the Food and Drug Administration Vaccines and Related Biological Products Advisory Committee.

Trivalent vaccines should include the same strains, with the exception of B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage), the committee recommended.

The panel voted separately on the strains, and all votes were unanimous, except for the vote on the B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) in the trivalent vaccine, which was supported with 11 positive votes with 1 abstention.

The advisory committee's recommendation is identical to the recommendations recently made by the World Health Organization for next season's influenza vaccines in the Northern Hemisphere. The WHO recommended that trivalent vaccines contain A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage). WHO also recommended that quadrivalent vaccines contain all of the above strains and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) as the second influenza B strain.

Most of the influenza activity in the United States this season is due to influenza A(H3N2) viruses (67%), according to Lisa Grohskopf, MD, asociate chief for policy & liaison in the Influenza Division at the Centers for Disease Control and Prevention. Fortunately, the majority of circulating strains are similar to those contained in the 2017-2018 vaccine. Only strains with B/Victoria lineage displayed antigenic drift, but represented less than 1% of all circulating viruses.

Hospitalization rates for laboratory-confirmed influenza this season have been markedly higher among people aged 65 years and older, compared with younger age groups, and have increased since last season. As of Feb. 17, the preliminary estimate of hospitalizations in this age group was 322.7 cases per 100,000 people, compared with about 290.5 per 100,000 during the 2016-2017 season. There have been 97 pediatric deaths associated with influenza, compared with 110 reported during the 2016-2017 season, 93 during 2015-2016, and 148 during 2014-2015.

With H3N2 strains of influenza A predominating, questions on the effectiveness of the newly recommended Singapore A(H3N2) were raised by the committee. Jacqueline Katz, PhD, director of the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, reassured the committee.

"Yes, in fact, it does cover them very well. The majority of the viruses that we've tested at the CDC were that emerging 3C2a2 [clade of H3N2] group, and the Singapore virus covered those very well. In general, that's why we went with Singapore," she said.

Dr. Katz added that one of the reasons Singapore is so effective is because it can be found on the base of the phylogenetic tree; "it's not on the tip of the tree where things are changing, so it's a more conservative selection."

The CDC estimate of current vaccine effectiveness (VE) against influenza A(H3N2) viruses is 25%, as of Feb. 3. Effectiveness is even higher for all influenza viruses, with an estimated VE of 36%, indicating that the flu vaccine reduced a person's risk of having to seek medical care at a doctor's office for flu illness by 36% (MMWR. 2018;67:180-5).

While the FDA usually follows the recommendations of its panel members, it is not obligated to do so. None of the committee members disclosed relevant financial conflicts of interest.

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COPD Guidelines

// continued from page 1

that clinicians derive ABCD groups exclusively from patient symptoms and their exacerbations. FEV_1 is an "important parameter at the population level" in predicting hospitalization and mortality, the authors wrote, but keeping results separate

"All guidelines need to be modified as further research becomes available. I think that the frontiers of this area are going to be to incorporate new elements such as tobacco history, more emphasis on clinical signs and symptoms, and use of markers other than spirometry, such as eosinophil count, to categorize patients with COPD," Dr. Ouellette added.

"Clinicians have indicated that they like the flexibility the system provides in separating spirometry, symptoms, and exacerbation risk as this more accurately reflects the heterogeneity we see in the COPD patient population," reported Dr. Han.

"acknowledges the limitations of FEV_1 in making treatment decisions for individualized patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD."

According to MeiLan Han, MD, MS, a member of the GOLD Science Committee, since release of the 2017 guidelines, "clinicians have indicated that they like the flexibility the system provides in separating spirometry, symptoms, and exacerbation risk as this more accurately reflects the heterogeneity we see in the COPD patient population." Nevertheless, how this approach influences long-term outcomes remains unclear.

Dr. MeiLan Han

Daniel Ouellette, MD, FCCP, a pulmonologist with the Henry Ford Health System in Detroit, described the GOLD 2017 criteria as "a good step forward" but said he wasn't sure whether the optimal or perfect tool exists for categorizing COPD patients' level of disease.

"I think what we see is an effort to use all of these criteria to help us better treat our patients. I think it's a good classification, but we should always view such guidelines as a work in progress," he said in an interview.

In an analysis of the GOLD 2017 criteria applied to 819 COPD patients in Spain and the United States, published online Nov. 3, 2017, in the American Journal of Respiratory and Critical Care Medicine, Carlos Cabrera López, MD, and his colleagues concluded that the mortality risk was better predicted by the 2015 GOLD classification system than by the 2017 iteration (Am J Respir Crit Care Med. 2018 Feb. doi: 10.101164/rccm.201707-1363OC).

The distribution of Charlson index scores also changed. Whereas group D was higher than B in 2015, they become similar in the 2017 system. For her part, Dr. Han emphasized that the primary goal of the GOLD ABCD classification system is to categorize patients with respect to treatment groups. "Current therapy targets symptoms and exacerbations, which are the key current elements of the classification schema," she said in an interview. "The results of the Cabrera López analysis are not necessarily unexpected, as FEV_1 is associated with mortality."

In a prospective, multicenter analysis, Portuguese researchers compared the performance of GOLD 2011 and 2017 in terms of how 200 COPD patients were reclassified, the level of agreement between the two iterations, and the performance of each to predict future exacerbations (COPD. 2018 Feb;15[1]; 21-6). They found that about half of patients classified as GOLD D under the 2011 guidelines became classified as GOLD B when the 2017 version was used, and the extent of agreement between the two iterations was moderate (*P* less than .001). They also found that the two versions of the guidelines were equivalently

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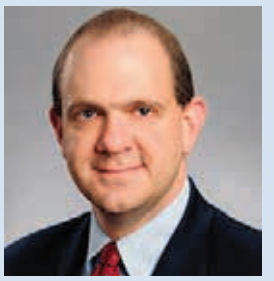

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Mary Jo Dales/MDedge News

Dr. Daniel Ouellette remarked that "the fact that GOLD criteria doesn't improve mortality shouldn't make us think that it's not a useful tool."

When the spirometric stages 1-4 were combined with the A-D groupings based on symptoms and exacerbations, the 2017 classification predicted mortality with greater accuracy, compared with previous iterations.

Continued from previous page

effective at predicting exacerbations (69.7% vs. 67.6% in the 2011 and 2017 iterations, respectively). In addition, patients who met the criteria for a GOLD B grouping in the 2017 iteration exacerbated 17% more often and had a lower percent predicted postbronchodilator FEV_1 than did those who met the criteria for a GOLD B classification under the 2011 guidelines.

Dr. Han, who is also an associate professor of medicine at the University of Michigan Hospital, acknowledged that GOLD 2017 has resulted in the reclassification of some previously group D patients as group B patients. "Our primary goal is to aid clinicians with the diagnosis and management of patients with COPD," she said. "We look forward to additional data coming in from ongoing clinical trials that will provide longer term data to further refine treatment algorithms."

In a recent study of more than 33,000 Danish patients older than age 30 with COPD, researchers led by Anne Gedebjerg, MD, found that the GOLD 2017 ABCD classification did not predict all-cause and respiratory mortality more accurately than previous GOLD iterations from 2007 and 2011. Area under the curve for all-cause mortality was 0.61 for GOLD 2007, 0.61 for GOLD 2011, and 0.63 for GOLD 2017, while the area under the curve for respiratory mortality was 0.64 for GOLD 2007, 0.63 for GOLD 2011, and 0.65 for GOLD 2017 (Lancet Respir Med. 2018 Jan;6[3]:204-12).

However, when the spirometric stages 1-4 were combined with the A-D groupings based on symptoms and exacerbations, the 2017 classification predicted mortality with greater accuracy, compared with previous iterations (*P* less than .0001). "My practice is very much like this paper," Dr. Iftikhar said. "I use both the spirometric grade and the ABCD grouping to specify which 'group' and 'grade' my patient belongs to. I think future investigators need to combine ABCD with spirometry classification to see how we can improve the classification system."

In a commentary published in the same issue of the Lancet Respiratory Medicine as the large Danish study, Joan B. Soriano, MD, PhD, wrote that the 2011 GOLD guideline's collapse of four spirometric thresholds (greater than 80%, 50%-80%, 30%-50%, and less than 30%) into just two (greater than 50% or 50% or less) "reduced the system's ability to inform and predict mortality from the short term up to 10 years" (Lancet Respir Med. 2018 Jan;6[3]:165-6).

"Lung function remains the best available biomarker for life expectancy in both patients with COPD and the general population," wrote Dr. Soriano, a respiratory medicine researcher based in Madrid.

GOLD 2017 ABCD classification vs. 2007 and 2011

	Area under the receiver operating curve		
	GOLD 2007	GOLD 2011	GOLD 2017
All-cause mortality (n = 33,765)	0.61	0.61	0.63
Respiratory mortality (n = 22,621)*	0.64	0.63	0.65

MDedge News

*Subcohort of patients with cause-specific mortality data available.

Note: Based on data for patients aged 30 years or older from the Danish registry for COPD.

Source: Lancet Respir Med. 2018 Jan;6(3):204-12

Additional important outcomes for COPD patients

Dr. Ouellette noted that, while mortality is an important outcome for COPD patients, it's not the only outcome of interest. "In addition to [trying to] help people live longer, which is certainly a desirable goal, we also want to make people be able to be more functional during their life, have fewer hospitalizations, and have less of a need of other types of supportive medical care for worsening of their disease," he said. "The fact that the current guidelines don't improve mortality more than the previous ones may not be a negative thing. It may tell us that the previous guidelines already did a pretty good job of helping us to improve mortality."

Dr. Ouellette was quick to add that none of inhaled drugs currently available to treat COPD have been conclusively shown to improve mortality. "The only things we know that improve mortality for COPD patients are quitting smoking and using oxygen if a patient meets predefined goals for oxygen," he said. "So the fact that GOLD criteria doesn't improve mortality shouldn't make us think that it's not a useful tool. We already know that the medicines may not help people live longer."

Dr. Han pointed out that spirometry "is still used to further clarify the choice of therapy recommended based on the nature and degree of airflow obstruction in light of severity of patient symptoms. The data are still designed to be used in conjunction to personalize therapy for patients."

She added that the GOLD Science Committee "welcomes additional data analyses so that future recommendations can be further refined."

Dr. Han disclosed that she has consulted for Boehringer Ingelheim, AstraZeneca, and GlaxoSmithKline. She has also received in-kind research support from Novartis and Sunovion.

Dr. Iftikhar reported having no financial disclosures. Dr. Ouellette is a member of *CHEST*® *Physician*'s editorial advisory board. He disclosed being part of a federally funded study being carried out by the Patient-Centered Outcomes Research Institute.

There was no industry involvement in the GOLD 2017 report, but many of its authors and board members had pharmaceutical company ties, and GOLD's treatment advice relies on data from industry-sponsored studies.

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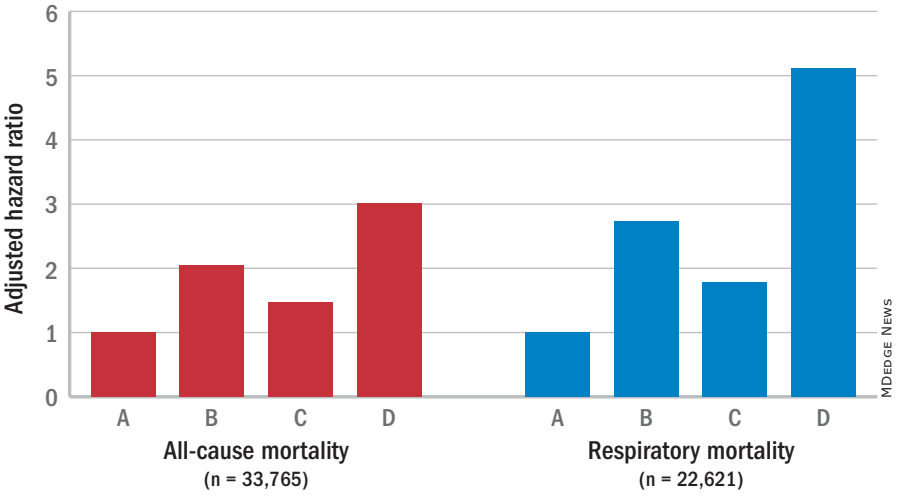
Mortality risk over 3 years by GOLD 2017 ABCD group



Note: Based on data for patients aged 30 years or older from the Danish registry for COPD.

Source: Lancet Respir Med. 2018 Jan;6(3):204-12

Four-gene signature predicted TB progression

BY AMY KARON
MDEdge News

The four-gene signature dubbed RISK4 performed similarly well in four diverse cohorts of HIV-negative household contacts of TB patients in sub-Saharan Africa, reported Sara Suliman, PhD, of the University of Cape Town, South Africa, and her associates. Testing for such a signature could be a cost-effective, point-of-care method to prioritize recipients of prophylactic treatment, the researchers said.

Worldwide, about 1.7 people are infected with *Mycobacterium tuberculosis*, but only 5%-20% of these individuals develop TB. Finding a reliable biomarker for increased risk of progression would be "an important step forward towards better TB control," especially in resource-strapped areas, the investigators said. Unfortunately, the predictive value of a positive tuberculin skin test or a positive interferon gamma release assay is too low to be useful for this purpose, they wrote in the American Journal of Respiratory and Critical Care Medicine.

Accordingly, the investigators searched for gene transcripts whose upregulation or downregulation reliably predicted progression to TB disease. To do so, they compared whole-blood PCR test results from 79 cases (who developed TB after exposure to a household index case) and 328 controls (household contacts who did not progress to TB disease). Progressors developed TB disease within 3-24 months of exposure. Nonprogressors were matched by site, sex, age, and year of recruitment.

The RISK4 signature comprised four unique genes: GAS6 and SEPT4, which were upregulated in progressors compared with matched controls, and CD1C and BLK, which were downregulated, the researchers reported. For the overall data set, RISK4 predicted TB progression with an area under the curve (AUC) of 0.67 (95% confidence interval, 0.57-0.77; $P = .0002$). The AUC for individual sites ranged from 0.66 to 0.72 (P less than .03) and was 0.69 ($P = .0004$) among household contacts who were tested within 2 months of index case diagnosis. Furthermore, RISK4 performed comparably in an external cohort South African adolescents who tested positive on IGRA or TST (AUC, 0.69; 95% CI, 0.62 to 0.76; $P = .0003$).

The groups in this study represented diverse genetic backgrounds, TB epidemiology, and circulating strains of *M. tuberculosis*, which suggested that RISK4 reliably predicts TB progression among household contacts across sub-Saharan Africa, the researchers said. Previously published TB signatures (which include DIAG3, DIAG4, and ACS COR) performed as well as RISK4 on the overall test cohort, but not at individual sites, they added.

In unblinded post hoc analyses, two of the four transcripts (SEPT4 and BLK) performed as well as the four-gene RISK4 signature, according to the investigators. Upregulation of the complement C1q C-chain (C1QC) with downregulation of T-cell receptor alpha variable gene 27 (TRAV27) predicted progression even more reliably, with AUCs exceeding 0.76 at all study sites. However, this transcript pair did not perform as well in the separate adolescent cohort (AUC, 0.57).

"Importantly, samples from household contact progressors were collected mostly at enrollment, immediately following exposure to the respective TB index cases, thus possibly representing a signature of recent M.tb exposure," the researchers noted. "The next steps include assessment of the performance of RISK4 and the 2-transcript C1QC/TRAV27 signature in other settings, including non-African populations, and [determining] the feasibility of developing a near-patient test for targeted intervention."

Funding sources included the Bill and Melinda Gates Foundation, the National Institutes of Health, the South African Medical Research Council, the Carnegie Corporation of New York, the South African National Research Foundation, and the Claude Leon Foundation.

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SOURCE: Am J Respir Crit Care Med. 2018 Apr 6. doi: 10.1164/rccm.201711-2340OC.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Given the poor performance of our current latent TB testing to predict progression to active TB, this is a very welcome development. Refinement of these personalized approaches not only allows resource-limited areas to target their efforts, but holds the potential to minimize therapeutic harm in those not at high risk for developing active disease. It should be noted that this modality was tested in a particular area and in non–HIV infected people – and adapting its use to other populations may be inappropriate (especially the immunocompromised).

Good definitions, research lacking for COPD-asthma overlap

BY THOMAS R. COLLINS
MDEdge News

ORLANDO – Experts agreed that asthma and chronic obstructive pulmonary disease (COPD) overlap syndrome, referred to as ACOS, is an area in dire need of more careful study to give clinicians data they can actually use.

The topic is even more pressing given the growing interest and research into biological treatments for asthma and consideration of their possible use in COPD, experts said at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization. Their remarks came in what was ostensibly a "debate" on whether ACOS is a distinct entity requiring special treatment but largely turned into a discussion about gaps in knowledge on the topic.

DR. PEEBLES

DR. TASHKIN

The dilemma, they said, is that the research tends to look almost exclusively at extreme cases, with asthma studies excluding COPD patients and COPD studies excluding asthma patients.

"The problem here is that it has not been defined in a way that everyone agrees on – that does create a problem because, if there's no consensus on the diagnostic criteria, then it may be difficult to study this overlap," said Donald Tashkin, MD, director of the pulmonary function laboratories at the University of California, Los Angeles. "Because there is no agreement on how to diagnose ACOS, it hasn't been studied with respect to its responsiveness to different treatment options."

R. Stokes Peebles Jr., MD, professor of allergy, pulmonary, and critical care medicine at Vanderbilt University Medical Center, Nashville, Tenn., said that, although the number of published articles on ACOS has skyrocketed over the last several years, review articles have outnumbered original research articles.

There is disagreement in published definitions: One set of definitions includes a criterion of fractional exhaled nitric oxide not seen in any other definitions, whereas some other definitions require a history of smoking while others don't, he said.

"How does one manage a disease without a definition and without clinical studies? It's impossible for me to know," Dr. Peebles said.

A commentary piece published in 2016, he noted, called for the term ACOS to be "abandoned" and then replaced when new phenotypes and underlying subtypes are identified and when "a new taxonomy of airway diseases is generated." Dr. Peebles said he agreed with this suggestion.

Jeffrey Drazen, MD, the Distinguished Parker B. Francis Professor of Medicine at Harvard Medical School, Boston, and the editor of the New England Journal of Medicine, also lamented the polar nature of the research. "We all treat patients in the middle; everybody does, all the time – and we would love more guidance," he said.

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Multidisciplinary teams improve diagnoses in ILDs

BY RANDY DOTINGA
MDedge News

FROM THE JOURNAL *CHEST*® ▪ New research provides strong statistical support for the use of dynamic multidisciplinary discussion in the diagnosis of patients who may have interstitial lung diseases (ILDs).

Multidisciplinary discussion (MDD) provided a diagnosis in 80% of referred cases when referring physicians couldn't come up with one, and it changed the diagnosis in 41% of the other cases.


DR. ANTIN-OZERKIS

The American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association adopted joint guidelines for the treatment of idiopathic pulmonary fibrosis (IPF) in 2015, and the ATS and ERS updated guidelines for the classification and terminology for idiopathic interstitial pneumonias in 2013. A previous study published in The Lancet Respiratory Medicine after these guidelines were adopted showed that, in IPF, MDDs lead to a "higher level of agreement on diagnoses, assign diagnoses with higher confidence more frequently, and provide diagnoses that have nonsignificant greater prognostic separation than do clinicians or radiologists in most cases" (Walsh SLF et al. 2016;4[7]:557-65).

In the new study, MDD failed to produce a diagnosis or suggestions about a way forward in only 3.5% of patients, according to the study, which appeared March 30 in *CHEST*®.

"Several previous studies have demonstrated that MDD improves the accuracy of ILD diagnosis, particularly as compared with the referring physician's initial diagnosis," said pulmonologist Danielle Antin-Ozerkis, MD, of Yale University, New Haven, Conn., in an interview. "The current study supports the use of this team approach."

According to Dr. Antin-Ozerkis, accurate diagnosis of ILD is crucial to treatment, but it can be challenging to achieve. The MDD approach has been recommended since 2002 by the ATS and ERS, she said.

The study authors, led by Laurens J. De Sadeleer, MD, of Belgium's University Hospitals Leuven, define the MDD approach as one "in which expert ILD clinicians, radiologists, and pathologists integrate all available clinical data, laboratory results, high-resolution computed tomography [HRCT] findings, and lung biopsy [when performed]."

For the study, the researchers tracked pre-MDD and MDD diagnoses of 938 consecutive patients with possible ILD who were discussed during 2005-2015. Of these patients, referring physicians made preliminary diagnoses in 49% of cases; in the rest, physicians either failed to develop a diagnosis or offered multiple possible diagnoses.

MDD teams produced a change in diagnosis in 191 – 42% – of patients with a pre-MDD diagnosis. Another condition was diagnosed in 118 of these patients, and the MDD teams declined to classify the other 73 patients pending further investigation.

The MDD teams also were able to produce diagnoses in 80% of cases when referring physicians could not come up with diagnoses.

"Discrepancy between pre-MDD diagnosis before work-up and discussion was remarkable," the study authors wrote, estimating that MDD added value for 70% of referred patients.

"We believe MDD should be a common practice in the diagnosis of every patient with suspected ILD," the researchers said.

The study doesn't examine the challenges of putting MDD into practice, but Dr. Antin-Ozerkis provided some perspective. "It may be difficult for physicians to take the time from a busy practice to meet with a multidisciplinary team. It can require resources to gather the data necessary to comprehensively assess each patient case. Additionally, maintaining staff with experienced pulmonologists, radiologists and pathologists may be costly."

She added that "there are various ways in which MDD may occur" and that the pros and cons of different methods have not been well studied. "This practice will likely evolve with the development of new biomarkers and other diagnostic strategies in IPF."

Still, she said, "this joint undertaking is clearly vital in helping to guide clinical practice, including therapeutic decisions and discussion of prognosis. For now, any discussion between clinician, radiologist, and pathologist is of benefit."

Eric Gartman, MD, FCCP, compared the use multidisciplinary discussions for diagnosing ILD to cancer tumor boards.

"Similar to the concept of cancer tumor boards providing a multi-specialty approach to the evaluation and treatment of a complex disease, the benefit of utilizing a similar modality for interstitial lung disease patients can be substantial," he said. "In addition to prior work, this study underscores the importance of these discussions and how they impact care, and potentially can alter a patient's treatment and prognosis."

A very important point is raised regarding access to such groups for a large segment of pulmonary practitioners – and novel mechanisms need to be established to ensure quality of care for these patients (e.g., an electronic multi-disciplinary review system or mandatory referral to an interstitial lung disease center)," added Dr. Gartman, who is an assistant professor of medicine at Brown University, Providence, R.I. and serves on the editorial advisory board for *CHEST*® *Physician*.

Research Foundation-Flanders and University Hospitals Leuven funded the study. Some study authors reported various disclosures. Dr. Antin-Ozerkis disclosed serving as an investigator on several clinical trials for IPF and other ILDs by Boehringer, Fibrogen, Promedior, and Roche. She noted that payments go directly to the university with no direct payments to the investigator.

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SOURCE: De Sadeleer LJ et al. Chest. 2018 Mar 30. doi: 10.1016/j.chest.2018.03.026.

VIEW ON THE NEWS

MDD strategy is crucial for accurate ILDs diagnoses

The field of interstitial lung diseases (ILDs) is challenging, with more than 200 disorders as possible diagnoses for patients who present to clinicians with similar symptoms and chest x-ray findings. The multidisciplinary discussion (MDD) strategy is very important for attaining an accurate ILD diagnosis.

We have had routine, formal, multidisciplinary discussions at our center since 2008. My guesstimate is that at least a third of patients referred as having idiopathic pulmonary fibrosis or another form of ILD by pulmonologists had been given the wrong diagnosis. Frequently, this was because of incorrect impressions provided by local radiologists and/or pathologists along with the clinician's own limited knowledge of ILD.

In my experience, some patients described their pulmonologists as becoming irate with them when they asked for a second opinion, and I have had to try to avoid confrontations with referring physicians when trying to explain why the referral diagnosis was inaccurate.

Challenges to instituting the multidisciplinary discussion approach include coverage by health plans for a second-opinion evaluation, the willingness of physicians (for example, pulmonologists) outside of academic referral centers to refer patients to a center capable of adequately conducting an MDD, and patients' desire to undergo an evaluation at centers of excellence where an MDD can be performed.

One must have also adequate resources to perform a proper MDD. But even in centers that refer patients, pulmonologists should confer with their colleague radiologists – and pathologists when appropriate – to try to make the most accurate diagnosis. And they should continue to question their diagnosis at follow-up appointments, as new symptoms and findings may arise or additional crucial information can become available over time that can point to an alternative diagnosis.

Kenneth C. Meyer, MD, MS, served as medical director of the lung transplant program and head of ILD at the University of Wisconsin–Madison. He reported no relevant disclosures.

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Indication

REVATIO is a phosphodiesterase-5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Limited published data from randomized controlled trials, case-controlled trials, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy. There are risks to the mother and fetus from untreated PAH.

Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation.

The most common side effects of REVATIO greater than or equal to 3% were epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

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INDICATION AND USAGE

REVATIO is a phosphodiesterase (PDE-5) indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [*see Warnings and Precautions*], Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children [*see Use in Specific Populations*].

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational case-crossover study evaluated risk of NAION when PDE-5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to the PDE-5 inhibitor in a prior time period. The results suggest an approximately 2-fold increase in the risk of NAION with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO® (sildenafil)-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed dose titration study (Study 2) of REVATIO (starting with recommended dose of 20 mg and increased to 40 mg and then 80 mg all three times a day) as an adjunct to intravenous epoprostenol in patients with PAH, the adverse reactions that were more frequent in the REVATIO + epoprostenol group than in the epoprostenol group (greater than 6% difference) are shown in Table 2.

Table 2: Adverse Reactions (%) in patients with PAH in Study 2 (incidence in REVATIO + Epoprostenol group at least 6% greater than Epoprostenol group)

	REVATIO + Epoprostenol (n=134)	Epoprostenol (n=131)	(REVATIO + Epoprostenol) minus Epoprostenol
Headache	57	34	23
Edema^	25	13	14
Dyspepsia	16	2	14
Pain in extremity	17	6	11
Diarrhea	25	18	7
Nausea	25	18	7
Nasal congestion	9	2	7

^includes peripheral edema

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

Adjunct Therapy

// continued from page 1

reviewed data from 15 randomized clinical trials including 7,122 patients aged 12 years and older.

Overall, patients who took a LAMA had a lower risk of asthma exacerbation requiring systemic corticosteroids and improved spirometry measures than did the patients who took a placebo or used another controller as an adjunct therapy.

In trials that compared LAMAs with placebo as an add-on to inhaled corticosteroids, LAMA patients experienced a significantly reduced risk of exacerbation requiring systemic corticosteroids (–1.8) and a significantly reduced risk of asthma worsening (–4.8). Another benefit seen in the patients who used a LAMA rather than those who used a placebo was improved spirometry measures, but the differences between these two patient groups' numbers did not reach statistical significance.

The analysis also included studies that compared "triple therapy" – defined as use of a LAMA as add-on therapy to inhaled corticosteroids and LABAs – with use of LABA plus inhaled corticosteroids.

Triple therapy was significantly associated with a lower risk of asthma worsening, compared with inhaled corticosteroids and LABAs, but not with a reduced risk of exacerbation. In addition, no significant differences appeared in Asthma Control Questionnaire-7 scores or overall Asthma Quality of Life Questionnaire scores between the two patient groups.

"Triple therapy was not significantly associated with improvements in rescue medication use vs. combined inhaled corticosteroids and LABA therapy," the researchers added.

The review of LAMAs used as add-on therapy was limited by several factors, including a primary focus on tiotropium, a lack of analysis of harms or the costs of the various therapies, the lack of data for children, and an inability to perform a subgroup analysis, the researchers said. Although LAMA use was associated with a lower risk of asthma exacerbation, compared with placebo use, the review could not adequately compare LAMA with controllers other than LABA, they added.

In the second analysis, which also was published in JAMA, the researchers evaluated the use of inhaled corticosteroids and LABAs as both a controller and quick-relief treatment, a strategy known as SMART, or Single Maintenance and Reliever Therapy. The SMART protocol, which is not approved in the United States, involved taking a combination of the corticosteroid budesonide and the LABA formoterol in a dry-powder inhaler in most of the studies reviewed.

An absolute risk difference of –2.8% for asthma exacerbations was seen in those who used the SMART protocol versus those who used a higher dose of inhaled corticosteroids and inhaled LABA as controller therapy.

Overall, in the analysis of 22,524 patients aged 12 years and older, an absolute risk difference of –2.8% for asthma exacerbations was seen in those who used the SMART protocol versus those who used a higher dose of inhaled corticosteroids and inhaled LABA as controller therapy.

In addition, data from 341 children aged 4-11 years showed a –12% absolute difference in risk of asthma exacerbation with the SMART protocol.

In trials that compared patients using the SMART protocol with those taking only the dose of inhaled corticosteroids called for by SMART, the protocol was associated with an improvement in forced expiratory volume in 1 second (FEV_1) and a reduction in the need for rescue medication.

The SMART protocol also demonstrated advantages over taking the same dose of inhaled corticosteroid called for by SMART plus a LABA controller therapy or a higher dose of inhaled corticosteroids with a LABA controller therapy. Specifically, SMART patients experienced a –6.4% risk of asthma exacerbations, versus the first comparator group; and a –2.7% risk of asthma, compared with the group who took a higher dose of inhaled corticoste-

Continued on following page

Triple therapy cuts COPD exacerbations

BY BIANCA NOGRADY
MDedge News

Triple therapy for chronic obstructive pulmonary disease (COPD) achieved reductions in moderate to severe exacerbations when compared with two kinds of dual therapy, in a study published online in the New England Journal of Medicine.

The trial compared the outcomes of COPD patients using an inhaled therapy comprising a corticosteroid, a long-acting muscarinic antagonist (LAMA), and a long-acting beta-agonist (LABA) with the outcomes of similar patients taking one of two other therapy combinations – a corticosteroid and a LAMA or a LABA and a LAMA. This trial – Informing the Pathway of COPD Treatment (IMPACT) – included 10,355 patients with symptomatic COPD in 37 countries, according to David A. Lipson, MD, and his colleagues.

IMPACT was the first study to compare a single inhaler triple therapy with two dual therapies, according to a statement made by Patrick Vallance, president of research and development at GlaxoSmithKline (GSK), when the Food and Drug Administration approved the triple therapy in September 2017.

The study randomized patients to 52 weeks of either triple inhaled therapy involving a once-daily combination of 100 mcg fluticasone furoate (a corticosteroid), 62.5 mcg of the LAMA umeclidinium and 25 mcg of the LABA 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.

Triple therapy was associated with a significantly longer time to first event and greater improvements in quality of life, compared with the dual therapies.

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).

When the analysis was limited to severe exacerbations alone, the difference was significant only between the triple therapy, which GSK is marketing as Trelegy Ellipta, and the vilanterol-umeclidinium dual therapy.

Dr. Lipson, of GSK and the University of Pennsylvania, and his coauthors noted that their finding of a greater benefit with the glucocorticoid-containing dual therapy, compared with the LABA-LAMA vilanterol-umeclidinium combination, contradicted the findings of the earlier FLAME trial. This was likely because of differences in patient populations and design, as all patients in the FLAME trial had a 1-month run-in treatment with the bronchodilator tiotropium, the researchers explained.

"Therefore any patients who would require an inhaled glucocorticoid may have had an increase in exacerbations and a decrease in lung function during the run-in period and would have been forced to leave the trial," they wrote.

Patients with higher eosinophil levels seemed to do even better with triple therapy. In those with eosinophil levels of 150 cells per microliter or above, the annual rate of moderate to severe exacerbations was 0.95 with triple therapy, 1.08 with fluticasone furoate–vilanterol, and 1.39 with vilanterol-umeclidinium.

Triple therapy also was associated with a significantly longer time to first event and greater improvements in quality of life, compared with the dual therapies.

Overall, the adverse event profile of triple therapy was similar to that of dual therapy. Contrasting that finding were differences in the incidences of physician-diagnosed pneumonia between the treatment groups. Physician-diagnosed pneumonia was 53% higher among patients who received fluticasone furoate – either in dual or triple therapy combinations. Eight percent of patients in the triple therapy group experienced pneumonia, compared with 7% of patients in the

Continued from previous page

roids with LABA controller therapy.

No significant associations appeared in any of the studies between the SMART protocol and outcomes that included all-cause mortality or changes in FEV_1, forced vital capacity, or the percentage of predicted FEV_1, when compared with those for patients who used a LABA controller therapy plus inhaled corticosteroids at either dose.

The SMART protocol review was limited by factors that included a lack of data on adverse events, a lack of subgroup analysis, and the potential for bias, because of the open-label nature of some of the studies, the researchers noted.

However, despite the limitations in both reviews, the results support the SMART strategy and LAMAs as alternatives for patients with persistent asthma, and highlight the need for further research, they noted.

The reviews were supported by the Agency for Healthcare Research and Quality. Dr. Sobieraj had no financial conflicts to disclose.

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SOURCE: Sobieraj DM et al. JAMA. 2018;319(14):1473-84. Sobieraj DM et al. JAMA. 2018;319(14):1485-96.

VIEW ON THE NEWS

New asthma guidelines needed

Asthma remains a major public health problem in the United States, but 11 years have passed since the last update to treatment guidelines, and an update to the current guidelines for asthma treatment is needed, wrote Jerry A. Krishnan, MD, FCCP, and David H. Au, MD, in an accompanying editorial (JAMA. 2018;319[14]:1441-3). "It is time to connect the efforts of the Food and Drug Administration, the evidence presented by Sobieraj et al., and the support from the National Asthma Education and Prevention Program to update the 2007 [Expert Panel Report 3] guidelines on asthma."

Both reviews showed effectiveness for the treatments being assessed, compared with placebo, but each had limitations, the editorialists noted.

The study findings in the report on the efficacy of inhaled long-acting muscarinic antagonists (LAMAs) in adolescents and adults with uncontrolled asthma were limited by several factors including a focus primarily on tiotropium, absence of data on potential harms and relative costs of treatment, and a lack of data on children younger than 12 years, they noted. The findings in the analysis of the strategy known as Single Maintenance and Reliever Therapy (SMART) containing formoterol, a long-acting beta-agonist (LABA), were similarly limited by a lack of assessment of potential harm and data on children within the same age group, they said.

However, the effectiveness of the treatments seen in both reviews suggest that the forthcoming revision of the Expert Panel Report 3 guidelines on asthma from the National Asthma Education and Prevention Program should include the option for inhaled tiotropium, a LAMA, and for the formoterol-based SMART protocol, the editorialists wrote.

"For patients and clinicians, the results from these meta-analyses suggest that dual therapy with scheduled doses of inhaled corticosteroids and LABA or inhaled corticosteroids and LAMA should help reduce the risk of future asthma exacerbations in patients with inadequate asthma control while using inhaled corticosteroids alone," they said. The new guidelines should include evidence for the SMART protocol as well, but "studies assessing the efficacy of SMART using combination formoterol and budesonide via a metered-dose inhaler are needed," they concluded.

Dr. Krishnan is affiliated with the division of pulmonary, critical care, sleep, and allergy at the University of Illinois, Chicago, and disclosed having received compensation from Sanofi for participation on an independent data-monitoring committee. Dr. Au is affiliated with the division of pulmonary, critical care, and sleep medicine at the University of Washington, Seattle, and disclosed having received compensation from Novartis for participation on a data-monitoring committee and for serving as a consultant to Gilead Sciences.

fluticasone furoate–vilanterol group and 5% in the vilanterol-umeclidinium group.

All-cause mortality was significantly lower in patients who received the inhaled glucocorticoid, although the authors said this finding was "fragile" and needed further investigation.

The rate of discontinuation or withdrawal from the trial was 6% for the triple-therapy group, 8% for the fluticasone furoate–vilanterol group, and 9% for the vilanterol-umeclidinium group. The rates of serious adverse events in each group were 22%, 21%, and 23%, respectively.

At trial entry, 38% of patients were already receiving triple therapy and 29% were taking an inhaled glucocorticoid. The authors noted that any patients taking an inhaled glucocorticoid who were randomized to the vilanterol-umeclidinium group would have had to abruptly stop taking their inhaled glucocorticoids.

"It is unknown whether the abrupt discontinuation of inhaled glucocorticoids would have contributed to our finding of a lower rate of exacerbations in the inhaled glucocorticoid groups than in the LAMA-LABA group," they wrote.

Fernando Martinez, MD, chief of the division of pulmonary and critical care medicine at New York–Presbyterian Hospital/Weill Cornell Medical Center, said the study advanced the understanding of COPD management by addressing some key evidence gaps, in a statement issued by GSK.

"By comparing various combinations of effective medications in the same device, the study clarifies which type of patient gains greatest benefit from each class of medicine," Dr. Martinez said in the statement. "As many patients experience frequent exacerbations or 'flare ups,' which can often result in hospitalization, these data will be highly relevant to patients and clinicians as they consider the optimal treatment."

The study was funded by GSK, which manufactures Trelegy Ellipta triple therapy for COPD. Eight authors were employees of GSK and two were on advisory boards for the company. Seven authors declared funding from a range of pharmaceutical companies including GSK. One author had no conflicts of interest to declare.

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SOURCE: Lipson DA et al. N Engl J Med. 2018 Apr 18. doi: 10.1056/NEJMoa1713901.

VIEW ON THE NEWS

More data on COPD triple therapy, but questions remain

The data from the IMPACT study fills a gap in the evidence supporting a step-up from dual to triple inhaled therapy for COPD, which so far has been recommended only for patients with severe loss of lung function and those with frequent exacerbations despite maximum bronchodilator treatment. The study has the strengths of comparing the step-up to triple therapy with the GOLD guideline–recommended dual therapies and using the same dosages in the triple therapy as in the dual therapy.

However, it is important to note that nearly 40% of patients enrolled in the trial were already being treated with triple therapy, 70% were receiving a glucocorticoid, and patients with a history of asthma were not excluded. This means patients assigned to the dual therapy without glucocorticoids would have had an abrupt cessation of their glucocorticoid therapy, which may explain a rapid surge in exacerbations in the first month and the lower rate of exacerbations in the dual-therapy group that did include glucocorticoids. The choice of patients for the study could potentially have artificially inflated the observed effectiveness of triple therapy over dual bronchodilator treatment.

As such, we suggest clinicians stick with the GOLD 2017 recommendations that escalation to triple therapy only occur after maximization of bronchodilator treatment.

Samy Suissa, PhD, is with the Center for Clinical Epidemiology at Lady Davis Institute–Jewish General Hospital, and the departments of epidemiology and biostatistics and medicine at McGill University, Montreal. Jeffrey M. Drazen, MD, is editor-in-chief of the New England Journal of Medicine. These comments are taken from an editorial (N Engl J Med. 2018 Apr 18. doi: 10.1056/NEJMe1716802). Dr. Suissa declared personal fees and grants from the pharmaceutical industry outside the submitted work.

Switch to mepolizumab safe in eosinophilic asthma

BY NICK ANDREWS
MDedge News

ORLANDO – Switching to mepolizumab resulted in a clinically significant benefit and a reduction in exacerbations for patients with severe eosinophilic asthma, according to late-breaking research presented at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization.


DR. ALBERS

Frank C. Albers, MD, PhD, of GlaxoSmithKline in Chapel Hill, N.C., and his colleagues examined safety and efficacy outcomes for 145 patients aged 12 years or older with severe eosinophilic asthma (SEA) that was not well controlled with omalizumab.

"You see similar research in oncology where, if a patient doesn't respond, you want to try a switch," Dr. Albers said in an interview. "The key is deciphering which patients would benefit from a switch."

The researchers discontinued omalizumab at baseline and treated patients with 100 mg of mepolizumab every 4 weeks for 28 weeks and observed patients for 4 more weeks following last treatment. They examined Asthma Control Questionnaire-5 and St. George's Respiratory Questionnaire results. In a secondary analysis, the researchers also compared their results with placebo-arm data from previously published research.

At 32 weeks, the least-squares mean ACQ-5 score changed by -1.45 (+/- 0.107) points and the SGRQ scores changed by –19.0 (+/– 1.64) points.

"The response appears to happen quickly," Dr. Albers said. "But you also see that the improvement seems steady."

At 4 weeks, 57% of patients experienced a minimum clinically important difference in ACQ-5 score and at 12 weeks, 69% of patients experienced a minimum

clinically important difference in SGRQ response. At 32 weeks, minimum clinically important difference ACQ-5 and SGRQ scores were reported for 77% and 79% of patients, respectively.

Dr. Albers and his colleagues also analyzed how these results might look in a randomized phase 3 setting by comparing their results to previously reported data from the MENSA (Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma) and DREAM (epolizumab for severe eosinophilic asthma) studies.

They reported that, compared with the previously reported placebo cohorts, patients who switched to mepolizumab experienced an ACQ-5 score improvement of –0.90 (*P* less than 0.001).

The researchers presented safety results in an accompanying poster and reported a 65% (*P* less than 0.001) reduction in the rate of clinically significant exacerbations for patients with SAE who switched to mepolizumab. They also reported a 69% (*P* less than 0.001) reduction in exacerbations that required ED visits and/or hospitalizations.

"This study provides practical reassurance to clinicians considering substituting one biologic for another in the treatment of patients with SEA," the researchers concluded.

This research was funded by GlaxoSmithKline, the makers of mepolizumab.

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App links symptoms to local airborne triggers

BY THOMAS R. COLLINS
MDedge News

ORLANDO – Use of an app combining patient-reported symptoms with local environmental triggers led patients to take action to improve their health, Penny Jones, PhD, reported at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization.

AirRater is a smartphone app and data collection network that includes information on air particulates, daily pollen and fungi counts, temperature, and planned burn locations. Patients enter their respiratory symptoms, which are correlated with local environmental conditions, according to Dr. Jones, a postdoctoral fellow at the University of Tasmania (Australia) in Hobart.

Most of the environmental data are gathered from government agencies; however, researchers collect pollen and fungi counts at their own stations.

Patients do not see the environmental data until they've logged in their symptoms so that their reports aren't biased by that information, Dr. Jones said, adding that the app also sends notifications when pollen and pollutant levels are high.


DR. JONES

"It's an environmental monitoring system coupled with a smartphone app designed to help people with allergies and asthma make better decisions around their health," Dr. Jones said.

The AirRater network and app are now operating in both Tasmania and Canberra, Australia.

There are more than 6,000 users, and data from surveys show that it is having an effect, Dr. Jones said. About 40% of users said they have changed their behavior in some way because of information provided by the app, including staying indoors, taking preventive medication, or speaking with their doctors."It does appear that people are generally finding it a useful tool," she said.

In a pilot study, researchers found that several environmental triggers were significantly correlated with exacerbation of patient symptoms, including maximum temperature (*P* less than .001), particulate pollution (*P* less than .001), relative humidity (*P* = .01), birch pollen (*P* = .006), and cypress pollen (*P* = .004).

Researchers plan to expand use of the network and app to other parts of Australia and are working to refine the understanding of aerobiological symptom drivers through DNA analysis of airborne particles. Their goal is to be able to identify personalized drivers of sensitivities, she said.

"We'll keep working on this," Dr. Jones said. "But we think that certainly has promise."

The investigators reported no financial conflicts of interest.

The study received no outside funding.

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Asthma flourishing among health care, social workers

BY RICHARD FRANKI
MDedge News

Workers in the health care and social assistance industry are more likely to have asthma than those in any other segment of the American economy, according to the Centers for Disease Control and Prevention.

Current asthma prevalence was 8.8% for adults aged 18 years and older who worked in health care and social assistance in 2011-2016, which put them above those in education services (8.2%); arts, entertainment, and recreation (8.1%); accommodation and food services (7.7%); and finance and insurance (7.5%). The overall rate for all working adults was 6.8%, Jacek M. Mazurek, MD, PhD, and Girija Syamlal, MBBS, reported in the Morbidity and Mortality Weekly Report.

"New-onset work-related asthma in [health care] workers has been associated with exposure to cleaning and disinfecting products, powdered latex gloves, and aerosolized medications."

"New-onset work-related asthma in [health care] workers has been associated with exposure to cleaning and disinfecting products, powdered latex gloves, and aerosolized medications," they wrote.

Among persons with asthma who were employed in health care and social assistance, 45.8% reported having at least one asthma attack in the previous year. Among the subgroups of the industry, those working in hospitals were highest with a 51.7% rate of past-year asthma attacks, followed by those working in nursing and residential care facilities at 45.2%, those working in ambulatory health care services at 43.2%, and those working in social assistance at 42.9%. The highest asthma attack rates among all industries were 57.3% for wood product manufacturing and 56.7% for plastics and rubber products manufacturing, the investigators said, based on data from the National Health Interview Survey.

Asthma-related visits to the emergency department in the past year were much less common for those in health care – 11.3% overall – and followed a pattern different from asthma attacks. Those working in nursing and residential care facilities were highest at 13.8%, with those in social assistance at 12.3%, those in ambulatory care at 10.5%, and those in hospitals the lowest at 10.1%. The highest ED-visit rate for any industry, 22.9%, was for workers in private households, said Dr. Mazurek and Dr. Syamlal, both of the respiratory health division at the CDC's National Institute for Occupational Safety and Health in Morgantown, W.Va.

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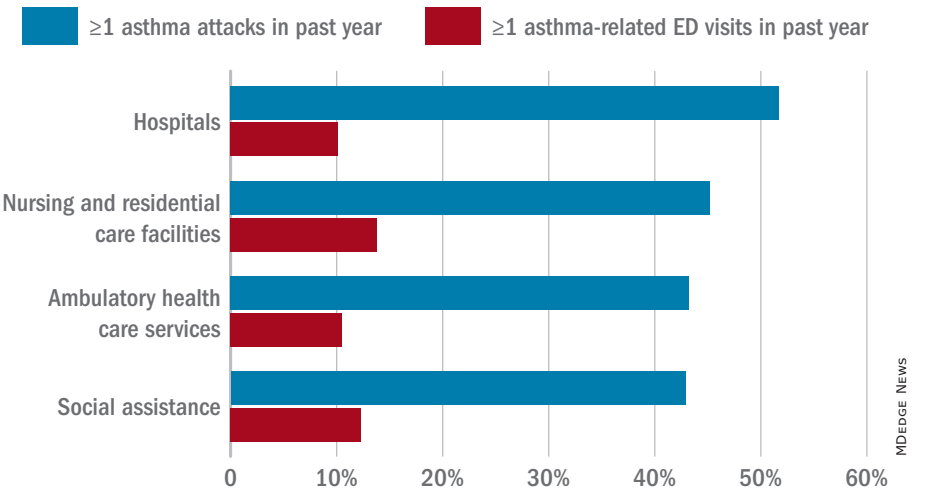
HEALTH CARE AND SOCIAL ASSISTANCE WORKERS

Adults with asthma who had a related attack or ED visit



Note: Based on data from the National Health Interview Survey, 2011-2016.
Source: MMWR. 2018 Apr 6;67(13):377-86

SOURCE: Mazurek JM, Syamlal G. MMWR. 2018 Apr 6;67(13):377-86.

Talc administration improves indwelling catheter outcomes

BY ANDREW D. BOWSER
MDedge News

Patients with malignant pleural effusion treated with an indwelling pleural catheter have an improved chance of a positive outcome when talc administration is part of their procedure, suggest the results of a randomized, placebo-controlled study.

Malignant pleural effusion, which is usually caused by the spread of metastatic cancer, is typically treated by inducement of pleurodesis. Talc is probably the most effective agent for achieving this result, but there are drawbacks to using talc to induce pleurodesis. Patients who receive this treatment often need to stay in the hospital for 4-7 days, according to Rahul Bhatnagar, PhD, and the coauthors of a study published in the New England Journal of Medicine. Indwelling pleural catheters provide an "amblatory alternative" for fluid management, they noted. In a noncomparative series of 22 patients, administering talc through such a catheter produced high rates of pleurodesis, they added.

In the new study, Dr. Bhatnagar of the Academic Respiratory Unit, University of Bristol (England) and his coauthors evaluated the use of an indwelling catheter, with or without talc, in patients with malignant pleural effusion recruited at 18 centers in the United Kingdom over 4 years.

"Our primary-outcome results, which were backed up by robust sensitivity analyses, strongly suggest that the administration of talc through an indwelling pleural catheter was significantly more efficacious than the use of an indwelling pleural catheter alone among patients without substantial lung entrapment," the authors wrote.

A total of 154 patients underwent randomization to the talc or placebo group, and 139 had sufficient data to evaluate the primary outcome of successful pleurodesis at 35 days after randomization. The researchers excluded patients with evidence of lung entrapment, or nonexpandable lung, according to the study report.

"Our primary-outcome results ... strongly suggest that the administration of talc through an indwelling pleural catheter was significantly more efficacious than the use of an indwelling pleural catheter alone among patients without substantial lung entrapment."

In the talc group, pleurodesis was successful at day 35 in 30 of 69 patients (43%) versus 16 of 70 patients (23%) in the placebo group ($P = .008$).

At day 70, the success rate was 51% for the talc group vs. 27% for the placebo group, respectively.

The rate of pleurodesis was significantly higher when talc was administered through an indwelling pleural catheter, Dr. Bhatnagar and his colleagues noted.

"Success rates at day 70 suggested that pleurodesis was maintained to a point that is clinically relevant for patients with short median survival," they added.

No excess of side effects or catheter blockages were associated with talc vs. placebo administration through a catheter. Additionally, no differences were seen between the talc and placebo groups in the number of adverse events, number of inpatient days, mortality, or other outcomes tracked by the researchers.

Dr. Bhatnagar reported he had no disclosures related to the study. Study coauthors reported disclosures related to Becton Dickinson – CareFusion, Rosetrees Trust, GE Medical, and Rocket Medical.

Becton Dickinson supported the trial with an unrestricted research grant and supplied catheters and drainage bottles for the study's participants.

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SOURCE: Bhatnagar R et al. N Engl J Med. 2018;378:1313-22.

NUCALA—Prescribe with confidence

The first anti-interleukin 5 (IL-5) for severe eosinophilic asthma

NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DiscoverNucalaHCP.com

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

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

*As of January 2018, more than 20,000 patients have received NUCALA**

*December 2015 to January 2018 data sourced from IQVIA and GSK. Claims data based on total number of unique patients who had at least 1 claim for NUCALA in the United States. Not all patients remain on therapy. Individual results may vary.[1]

In patients with blood eosinophil levels ≥150 cells/µL,

NUCALA provided a strong and consistent reduction in exacerbations[2,3†]

MENSA

53%

Reduction in exacerbation frequency at Week 32
(*P*<0.001)[2]

MUSCA

58%

Reduction in exacerbation frequency at Week 24
(Rate ratio: 0.42; 95% CI: 0.31, 0.56)[3]
Other endpoint; results are descriptive.
CI=confidence interval.

MENSA (Trial 2) Study Description[2]: 32-week study comparing treatment with NUCALA or placebo added to standard of care (SOC) in 576 patients with severe eosinophilic asthma. **Primary Endpoint:** Frequency of exacerbations.† **Results:** Exacerbations/year 0.83 for NUCALA vs 1.74 for placebo.

MUSCA Study Description[3]: 24-week study comparing treatment with NUCALA or placebo added to SOC in 551 patients with severe eosinophilic asthma. **Primary Endpoint:** Mean change from baseline in St George's Respiratory Questionnaire total score at Week 24. **Results:** –15.6 for NUCALA vs –7.9 for placebo; treatment difference of –7.7 (*P*<0.0001). The improvement in both treatment arms was clinically meaningful (defined as a reduction in score of ≥4 points). **Other endpoint:** Included frequency of exacerbations. **Results:** Exacerbations/year 0.51 for NUCALA vs 1.21 for placebo.

†Exacerbations were defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients on maintenance oral/systemic corticosteroids, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

SOC=regular treatment with high-dose inhaled corticosteroids and at least 1 other controller with or without oral corticosteroids

The approved dose of NUCALA for severe eosinophilic asthma is 100 mg administered every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

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

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

USE IN SPECIFIC POPULATIONS

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

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

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. **3.** Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390-400.

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

Printed in USA. 828398R0 March 2018

Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use

The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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

6.1 Clinical Trials Experience in Severe Asthma

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

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

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

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

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects receiving mepolizumab 75 mg IV compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.

Long-term Safety

Nine hundred ninety-eight subjects received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

6.3 Immunogenicity

In subjects with asthma receiving NUCALA 100 mg, 15/260 (6%) developed anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.4 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg SC *(see Data)*.

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

Clinical Considerations

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

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

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

(continued on next page)

8 USE IN SPECIFIC POPULATIONS (cont'd)

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the Phase 3 asthma studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.

The safety and efficacy in pediatric patients other than those with asthma have not been established.

8.5 Geriatric Use

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

10 OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

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

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Don't use cannabis to treat OSA, AASM recommends

BY KATIE WAGNER LENNON
MDedge News

The American Academy of Sleep Medicine (AASM) opposes the use of medical cannabis and its synthetic extracts for treating obstructive sleep apnea, according to a position statement published in the Journal of Clinical Sleep Medicine's April issue.

In the statement, the professional society recommends that state legislators, regulators, and health departments exclude obstructive sleep apnea (OSA) as an indication for medical cannabis programs.

The "unreliable delivery methods and insufficient evidence of treatment effectiveness, tolerability, and safety" of medical cannabis and its synthetic extracts are among the reasons the AASM gave for making its recommendations. "Further research is needed to better understand the mechanistic actions of medical cannabis and its synthetic extracts, the long-term role of these synthetic extracts on OSA treatment, and harms and benefits," the AASM concluded in its statement, authored by Kannan Ramar, MD, and other members of a panel of experts on sleep medicine.

Dronabinol is the only cannabis product that has been tested on patients with OSA for the treatment of this disorder. While some synthetic cannabis products are approved by the Food and Drug Administration for other medical indications, the synthetic-based cannabis product dronabinol has not received FDA approval for the treatment of OSA.

Researchers have examined dronabinol's use for treating OSA in small pilot and proof-of-concept studies and most patients in these studies reported experiencing treatment-related side effects, such as somnolence, wrote Dr. Ramar, of the division of pulmonary and critical care medicine at the Center for Sleep Medicine, Mayo Clinic, Rochester Minn., and his colleagues.

The "unreliable delivery methods and insufficient evidence of treatment effectiveness, tolerability, and safety" of medical cannabis and its synthetic extracts are among the reasons the AASM gave for making its recommendations. "Further research is needed to better understand the mechanistic actions of medical cannabis and its synthetic extracts, the long-term role of these synthetic extracts on OSA treatment, and harms and benefits," the AASM concluded in its statement.

These trials involved patients having taken dronabinol pills in strengths ranging from 2.5 mg to 10 mg. One such study (Front Psychiatry. 2013 Jan 22. doi: 10.3389/fpsyt.2013.00001), authored by Bharati Prasad of the University of Illinois, Chicago, and colleagues, showed a significant improvement in apnea-hypopnea index (AHI) of 32%, after 17 patients used dronabinol for 3 weeks, when compared with baseline AHIs (–14.1; $P = .007$).

A placebo-controlled randomized study of 73 adults with moderate or severe OSA similarly found a 33% decline in AHI in patients following 6 weeks of treatment with 10-mg doses of dronabinol (Sleep. 2018 Jan 1. doi: 10.1093/sleep/zsx184).

In the placebo-controlled study, 73 patients were randomized to receive 2.5 mg of dronabinol or 10 mg of dronabinol daily for up to 6 weeks, or placebo. At the end of treatment, researchers saw significant increases in the AHI among the patients on placebo, while those who received dronabinol showed decreases in the number of apnea and hypopnea events per hour. Patients given the 2.5-mg dose of dronabinol had a mean decrease of 10.7 events per hour, and those on the 10-mg dose had a mean decrease of 12.9 events per hour compared with placebo. The difference between the placebo and treatment arms was significant for both dosages, and the AHI decreases were similar between the two dosages of dronabinol.

These effects were largely due to reductions in apnea events; the largest reduction was seen in the REM apnea index in patients treated with the 10-mg dose of dronabinol. However, there were few effects on the expression of hypopneas, except in the higher-dose group.

After adjustment for age, race, ethnicity, and baseline AHI, the increases seen in the placebo group were no longer significant, but the decreases from baseline seen in the treatment arms were greater. Dronabinol treatment also was associated with significant decreases, compared with placebo, in non-REM AHI and REM AHI.

Overall, nearly 90% of patients in this trial reported at least one adverse event, with the rates having not differed significantly between the treatment and placebo arms. The most frequently reported adverse events were "sleepiness/drowsiness" (n = 25; 8% of total adverse events reported), headache (n = 24; 8%), "nausea/vomiting" (n = 23; 8%), and "dizziness/lightheadedness" (n = 12; 4%). In addition, one patient experienced diarrhea and vomiting that required admission to a hospital, which was judged as possibly related to the study medication. There were six other withdrawals due to adverse events, including dizziness and vision changes, vertigo, ECG arrhythmias, and headache with dizziness and vomiting.

"Synthetic medical cannabis may have differential side effects, with variable efficacy and side effects in the treatment of OSA. Therefore, it is the position of the American Academy of Sleep Medicine that medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA," Dr. Ramar and his associates wrote.

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SOURCE: Rainar K et al. J Clin Sleep Med. 2018 April;14(4):679-81.

Impact of sleep loss on metabolism is highly individualized

BY CHRISTOPHER PALMER
MDedge News

Shift work – and the various light exposures that go with it – can place some people at a greater risk of weight gain and obesity. But the impact of various light exposures inherent in shift work appear to affect the metabolism of each person differently, reported Edward L. Melanson, PhD, and his coinvestigators.

"Such individual differences were not explained by sex, age, weight, fat mass, or fat free mass," Dr. Melanson and his coinvestigators wrote. "Thus, understanding mechanisms underlying such individual differences in waking and sleep energy metabolism and how they may or may not contribute to health outcomes ... requires additional research."

The investigators' conclusions are based on the results of two studies. Both studies used whole-room, indirect calorimetry to measure energy expenditure. The participants, all of whom were free of medications and illicit drugs, maintained a consistent 8-hour sleep schedule before the study took place, and consumed a specified diet throughout the study. Meal tests were used to assess the participants' glucose metabolism responses, a protocol cited as one of the study's limitations.

"Individual differences were not explained by sex, age, weight, fat mass, or fat free mass," Dr. Melanson and his coinvestigators wrote.

The first study, comprising 15 healthy young adults, looked for changes in energy expenditure and glucose metabolism in response to different lighting conditions, such as full-spectrum bright light or blue-enriched bright light. In that study, no effects were found on patients' metabolism. The other study, comprising 14 healthy young adults, used a simulated shift-work protocol and found a decrease in 24-hour energy expenditure in certain individuals in response to circadian misalignment. "This finding may help identify individuals who may be at a higher risk of unwanted weight gain and obesity during shift work," the investigators wrote.

Read the full report in Neurobiology of Sleep and Circadian Rhythms.

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SOURCE: Melanson EL et al. Neurobiol Sleep Circadian Rhythms. 2017 Dec 29. doi: 10.1016/j.nbscr.2017.12.002.

Study: Caffeine shown safe in apnea of prematurity

BY AMY KARON
MDedge News


Herjua/Thinkstock

Caffeine for apnea of prematurity was neurobehaviorally safe and significantly improved fine motor coordination, visuomotor integration, visual perception, and visuospatial organization at 11-year follow-up, according to the results of a double-blind, randomized, controlled trial.

"There was little evidence for differences between the caffeine and placebo groups on tests of general intelligence, attention, executive function, and behavior. This highlights the long-term safety and efficacy of caffeine therapy for apnea of prematurity in very-low-birth-weight neonates," wrote Ines M. Mürner-Lavanchy, PhD, of Monash University, Clayton, Australia, and her associates. The Caffeine for Apnea of Prematurity (CAP) trial, the first to assess long-term neurobehavioral outcomes of neonatal caffeine therapy, was published online April 11 in Pediatrics.

Apnea of prematurity affects more than half of preterm neonates. Respiratory stimulation with caffeine therapy is standard care, having been shown to improve disability-free survival and gross motor skills. In this randomized, multicenter, double-blind trial, very-low-birth-weight infants (500-1,250 g) received either normal saline placebo or caffeine citrate (20-mg/kg loading dose, followed by 5-mg/kg daily maintenance dose; could be increased to up to 10 mg/kg for refractory apnea). Patients started treatment at a median of 3 days and were weaned off by postmenstrual age 35 weeks.

Neonatal caffeine therapy significantly lowered the risk of death before 18 months, cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness, as has been reported (N Engl J Med. 2007;357:1893-902). By 5 years, caffeine no longer showed significant benefits, apart from improved motor performance, Dr. Mürner-Lavanchy and her associates noted.

At 11 years, available data from 870 patients showed generally similar neurobehavioral outcomes between groups, although the caffeine group scored higher on most scales. The most apparent benefits included visuomotor integration (mean difference from placebo, 1.8; 95% confidence interval, 0.0-3.7; *P* less than .05), visual perception (2.0; 95% CI, 0.3-3.8; *P* = .02), fine motor coordination (2.9; 95% CI, 0.7-5.1; *P* = .01), and Rey Complex Figure copy accuracy, a measure of visuospatial organization (1.2; 95% CI, 0.4-2.0; *P* = .003).

Eleven-year follow-up data were missing for 22% of patients, but their birth characteristics and childhood outcomes resembled those of patients with available data, the investigators said. "Therefore, we are confident that the outcomes of the whole cohort are reflected in the present results with sufficient accuracy."

The Canadian Institutes of Health Research provided funding. The investigators reported having no relevant conflicts of interest.

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SOURCE: Mürner-Lavanchy IM et al. Pediatrics. 2018 Apr 11. doi: 10.1542/peds.2017-4047.

CPAP may help stroke patients with obstructive sleep apnea

BY ANDREW D. BOWSER
MDedge News


yelo34/Thinkstock

For stroke patients with obstructive sleep apnea using continuous positive airway pressure (CPAP) may improve stroke outcomes and reduce the recurrence of vascular events, the results of a randomized study suggest.

Obstructive sleep apnea is present in 50%-80% of patients with stroke, previous studies show, and its presence is associated with impaired function and cognition, delirium, and longer rehabilitation time, among other negative impacts, wrote Anupama Gupta, PhD, and her coauthors from the All India Institute of Medical Sciences, New Delhi, in the Journal of Clinical Sleep Medicine. Although multiple trials have shown a positive effect of CPAP on stroke recovery, relatively few investigations have looked specifically at whether the intervention prevents subsequent vascular events.

This study included 70 patients with first arterial stroke at least 6 weeks after the event and moderate to severe obstructive sleep apnea (OSA). These patients were randomized to be treated with CPAP or standard medical care. Initially, 34 patients were treated with CPAP and 36 were treated with standard care. Four of the patients receiving CPAP crossed over to the control group during the trial.

Patients' clinical stroke outcomes were categorized in accordance with the Modified Rankin Scale (mRS), which is most widely used to assess disability and dependence outcomes among patients with stroke.

Significantly more patients who were treated with CPAP experienced an improvement in their mRS score by at least 1 point, when assessed at both 6 and 12 months following entrance into the study. Specifically, 53% (16) of patients in the CPAP group had an improvement of at least 1 point in their mRS score at 12 months, compared with 27% (11) of patients who did not use CPAP (*P* = .03).

"These differences are statistically significant, as well as clinically meaningful and relevant," Dr. Gupta and her colleagues said in their report.

This finding was consistent with what researchers have seen in some earlier studies of stroke patients who used CPAP, the researchers wrote.

Additionally, CPAP-treated patients had fewer subsequent vascular events, compared with those who did not use CPAP, though the difference did not reach statistical significance. There was only one new vascular event (3.33%) in the CPAP group at 12-month follow-up, versus six events (15%) in the non-CPAP group (*P* = .23).

Nevertheless, the results provide more evidence for the potential benefit of CPAP in stroke patients with obstructive sleep apnea, the researchers noted.

"Our results indicate that new vascular events may be better prevented – and significantly more patients may make good stroke recovery – with CPAP treatment as compared to only best medical treatment," Dr. Gupta and her colleagues wrote.

Before the study started, investigators determined that they would have needed 80 patients per arm for a power of 80%. A total of 679 patients were screened, but only 116 reported for polysomnography testing, and of those, 83 had at least moderate obstructive sleep apnea.

Because of a lack of CPAP devices, only 70 of those 83 patients made it all the way to randomization, investigators reported.

Dr. Gupta and her coauthors reported no conflicts of interest related to the study.

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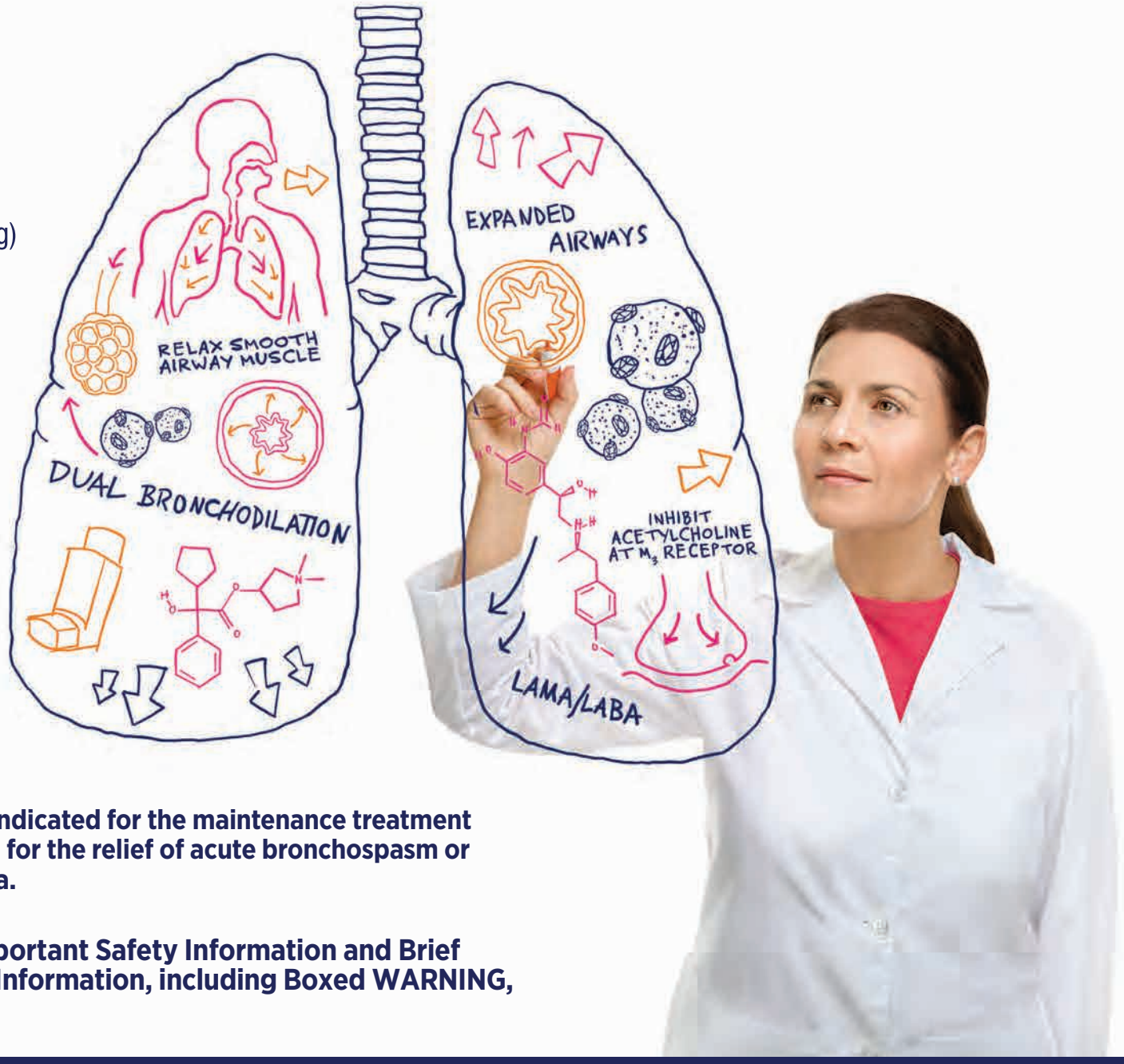
SOURCE: Gupta A et al. J Clin Sleep Med. 2018 Mar 30. doi: 10.5664/jcsm.7034.

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.

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‡**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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Smoking increases heart failure risk in black patients

BY ANDREW D. BOWSER
MDedge News

Cigarette smoking is an important risk factor for heart failure in blacks, according to results of an investigation of patients in the Jackson Heart Study.

Current smoking among blacks was associated with higher mean left ventricular (LV) mass and lower mean LV systolic function, even after adjustment for confounding factors, authors of the analysis reported in the journal Circulation.

beichh4046/Getty Images

Hospitalization for heart failure among blacks was associated not only with current smoking but also with smoking intensity, measured in cigarettes per day, and smoking burden, measured in pack-years, reported Daisuke Kamimura, MD, PhD, of the University of Mississippi Medical Center, Jackson, and associates.

While blacks are known to have a higher incidence of heart failure than do whites, Hispanics, and Asians, this is believed to be the first prospective study of a large black cohort demonstrating a dose-response relationship between smoking and incident heart failure.

"Smoking cessation may be a potential strategy to attenuate the higher rate of heart failure in blacks," wrote Dr. Kamimura and coauthors.

The published analysis included data on 4,129 participants in the Jackson Heart Study, a large, prospective, community-based observational study investigating cardiovascular risk factors in blacks.

That group, which was 63% female, included 503 current smokers, 742 former smokers, and 2,884 individuals who had never smoked.

At baseline, no patients had a history of heart failure or coronary heart disease, and over a median follow-up of 8.0 years, there were 147 hospitalizations for heart failure in the cohort, the investigators reported.

Current smoking, compared with never smoking, was significantly associated with incident heart failure hospitalization after adjusting for risk factors and coronary heart disease (hazard ratio, 2.82; 95% confidence interval, 1.71-4.64).

Likewise, smoking intensity of at least 20 cigarettes a day (HR, 3.48; 95% CI, 1.65-7.32) and smoking burden of at least 15 pack-years (HR, 2.06; 95% CI, 1.29-3.33) both were significantly associated with incident heart failure hospitalization.

Compared with never smoking,

current smoking was significantly associated with higher mean LV mass index and lower mean LV circumferential strain, even after adjusting for confounding variables (*P* less than 0.05 for both comparisons).

Smoking status also was associated with higher mean levels of brain natriuretic peptide, as were smoking intensity and burden (*P* less than 0.05 for all three comparisons), data show.

While cigarette smoking is a well-known risk factor for cardiovascular disease, the influences on cardiac structure and function may not be fully appreciated because of the strong association with coronary heart disease, a major cause of heart failure, the authors noted.

The Jackson Heart Study is supported by Jackson (Miss.) State University, Tougaloo College, and the University of Mississippi Medical Center, all in Jackson, contracts from the National Heart, Lung, and Blood Institute and the National Institute for Minority Health and Health Disparities. This study was supported by the NHLBI. One author has also received support from the National Institute of Diabetes and Digestive and Kidney Diseases and The National Institute of General Medical Sciences.

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SOURCE: Kamimura D et al. Circulation. 2018. doi: 10.1161/CIRCULATIONAHA.117.031912.

Trial redefines secondary cardiovascular prevention

BY BRUCE JANCIN
MDedge News

ORLANDO – In what was hailed as a major advance in preventive cardiology, the ODYSSEY Outcomes trial has shown that adding the PCSK9 inhibitor alirocumab on top of intensive statin therapy reduced major adverse cardiovascular events and all-cause mortality significantly more than placebo plus intensive statin therapy in patients with a recent acute coronary syndrome and an elevated on-statin LDL cholesterol level.

The study findings suggest the key to improving outcomes in ACS patients is to drive their LDL cholesterol level below 50 mg/dL, P. Gabriel Steg, MD, said in presenting the results at the annual meeting of the American College of Cardiology.

ODYSSEY Outcomes was a double-blind trial in which 18,924 pa-

tients at 1,315 sites in 57 countries were randomized to alirocumab (Praluent) or placebo plus background high-intensity statin therapy starting a median of 2.5 months after an acute coronary syndrome. All participants had to have a baseline LDL cholesterol level of 70 mg/dL or higher despite intensive statin therapy. Alirocumab was titrated to maintain a target LDL of 25-50 mg/dL. An LDL of 15-25 mg/dL was deemed acceptable, but if the level dropped below 15 mg/dL on two consecutive measurements the patient was blindly switched to placebo, as occurred in 7.7% of the alirocumab group.

Bruce Jancin/MDedge News

Dr. P. Gabriel Steg

The primary study endpoint was a composite outcome comprising CHD (coronary heart disease) death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization. During a median 2.8 years of follow-up, this outcome occurred in 9.5% of the overall population randomized to alirocumab and 11.1% of those on placebo, for a statistically significant and clinically meaningful 15% reduction in relative risk. The CHD death rates in the two study arms were similar; however, the other three components of the primary endpoint occurred significantly less often in the alirocumab group: The risk of nonfatal MI was 14% less (6.6% vs. 7.6%), ischemic stroke was 27% less (1.2 vs. 1.6%), and unstable angina was 39% less (0.4% vs. 0.6%).

All-cause mortality occurred in 3.5% of patients receiving alirocumab and 4.1% on placebo, once again for a statistically significant 15% reduction in risk. This was a major achievement, since even statins haven't shown a mortality benefit in the post-ACS setting, observed Dr. Steg, cochair of the study.

The greatest benefits were seen in the 5,629 participants with a baseline LDL of 100 mg/dL or more on high-intensity statin therapy. In this large subgroup at highest baseline risk, alirocumab resulted in an absolute 3.4% risk reduction and a 24% reduction in relative risk of major adverse cardiac events (MACE). All-cause mortality decreased by an absolute 1.7%, translating to a 29% relative risk reduction. The number-needed-to-treat (NNT) for the duration of the study in order to prevent one additional MACE event in this group was 29, with an NNT to prevent one additional death of 60, added Dr. Steg, professor of cardiology at the University of Paris and chief of cardiology at Bichat Hospital.

"The risk/benefit for alirocumab is extraordinarily favorable. There was almost no risk over the course of the trial. There was no increase in neurocognitive disorders, new-onset or worsening diabetes, cataracts, or hemorrhagic stroke," the cardiologist said.

Indeed, the sole adverse event that occurred more frequently in the alirocumab group was mild lo-

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cal injection site reactions, which occurred in 3.8% of the alirocumab group and 2.1% of controls.

There was a tendency for LDL to creep upward in both the alirocumab and placebo arms over the course of follow-up. Dr. Steg attributed this to downtitration or cessation of alirocumab as per protocol along with the inability of a substantial proportion of patients to tolerate intensive statin therapy. Most study participants had never been on a statin until their ACS.

A year ago at ACC 2017, other investigators presented the results of FOURIER, a large clinical outcomes trial of evolocumab (Repatha), another PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor. FOURIER also showed a 15% relative risk reduction in major adverse cardiovascular events, but unlike in ODYSSEY Outcomes, there was no significant impact upon mortality. Dr. Steg attributed this to several key differences between the two trials. The post-ACS population of ODYSSEY Outcomes was on average higher-risk than FOURIER participants, who had stable atherosclerotic cardiovascular disease. The background statin therapy was more intensive in ODYSSEY, and the average follow-up was close to 8 months longer, too.

Session cochair Valentin Fuster, MD, declared, "I believe this trial is going to change practice. It's a hypothesis that has been fulfilled."

The study population is representative of an enormous number of patients seen in clinical practice, added Dr. Fuster, professor of medicine and physician-in-chief at Mount Sinai Hospital in New York. He estimated that one-third of patients who experience ACS can't subsequently get their LDL down to the 70-mg/dL range on statin therapy, generally because of drug intolerance.

He voiced a concern: "Up until now, the feasibility and affordability of using this type of drug has been extremely difficult. I hope this particular study is a trigger – a catalyzer – for making this drug much more available to people who need it."

The study met with an enthusiastic audience reception. Prior to presentation of the results at the meeting's opening session, 79% of the audience of more than 4,000 in the main arena indicated they either don't prescribe PCSK9 inhibitors or do so only a handful of times per year. Immediately after seeing the data, 62% of the audience said their practice will change as a result of the study findings.

ODYSSEY Outcomes was funded by Sanofi and Regeneron Pharmaceuticals. Dr. Steg reported serving as a consultant to and receiving research grants from those pharmaceutical companies and numerous others.

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Bruce Jancin/MDedge News

Dr. Valentin Fuster

Wearable defibrillator cuts post-MI mortality

BY MITCHEL L. ZOLER
MDedge News

ORLANDO – Wearable cardioverter defibrillator vests failed to significantly cut the rate of arrhythmic death in at-risk post-MI patients but succeeded in significantly dropping total mortality during a median of 84 days of use in the first randomized trial of nonimplanted defibrillators in such patients.

Post-MI patients with a left ventricular ejection fraction of 35% or less at baseline who wore the wearable cardioverter defibrillator (WCD) had a statistically significant 36% relative risk reduction in total mortality and an absolute total death reduction of 1.7%, compared with controls, in the first randomized trial to test the efficacy of a WCD, Jeffrey Olgin, MD said at the

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annual meeting of the American College of Cardiology.

Despite this overall mortality benefit, the 1,524 patients randomized to the WCD group failed to show a significant improvement in the rate of sudden and ventricular tachycardia death, the primary endpoint for the study, said Dr. Olgin, chief of cardiology at the University of California, San Francisco. Total mortality was a secondary endpoint in the study. Based on the total mortality benefit observed and the "totality of evidence" from prior, uncontrolled observational studies, Dr. Olgin concluded that it is now "reasonable" to protect post-MI patients with ejection fractions of 35%

Dr. Jeffrey Olgin

Dr. David J. Wilber

Photos Mitchel L. Zoler/MDedge News

or less during the first 40-90 days following an MI when patients can then be assessed for receiving an implantable cardioverter defibrillator.

That would be an upgrade from the current American College of Cardiology/American Heart Association guidelines on managing ventricular arrhythmias and preventing sudden cardiac death, issued in 2017, that classified WCDs as a class IIb recommendations – "may be reasonable" – for post-MI patients with a reduced left ventricular ejection fraction (Circulation. 2017 Oct 30;doi:10.1161/CIR.0000000000000549).

WCDs are currently approved for routine prescribing by U.S. physicians, but their use is very variable in post-MI patients. Just before Dr. Olgin delivered his report at the meeting, a poll of the several thousand meeting attendees who heard his talk showed that roughly a third reported routinely prescribing WCDs, with the other two-thirds saying they did not.

Several electrophysiologists who heard the report agreed that further research needs to better tease out which post-MI patients get the most benefit from this treatment.

With a cost for a WCD of about $10,000 for about 3 months of treatment it would be better to target a "subgroup at higher risk," commented David J. Wilber, MD, professor of medicine and director of the Cardiovascular Institute at Loyola University Medical Center in Maywood, Ill.

The patients enrolled in the study "were not a sick population; they had a low event rate," commented

Dr. Sana M. Al-Khatib

Photos Mitchel L. Zoler/MDedge News

Dr. Dhanunjaya Lakkireddy

Sana M. Al-Khatib, MD, professor of medicine at Duke University in Durham, N.C. and chair of the panel that wrote the 2017 ventricular arrhythmia guidelines. She suggested testing the efficacy of WCDs in post-MI patients with lower ejection fractions or those with a greater history of heart disease prior to their index MI. Nearly half of the patients enrolled in the study had New York Heart Association class I symptoms, indicating that they had mild heart disease, she noted in an interview. Another issue left unresolved by the results Dr. Olgin reported was how much of the mortality benefit was attributable to the shocks delivered by the tested WCDs and how much derived from the arrhythmia monitoring that the WCDs provided. Dr. Al-Khatib suggested a new study to compare the efficacy of WCDs against management directed by use of an implantable loop recorder.

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Smoking cessation therapy did not up CV events risk

BY AMY KARON
MDedge News

Smoking cessation therapy with transdermal nicotine replacement therapy (NRT), bupropion hydrochloride, or varenicline did not increase the risk of cardiovascular events among stable adult smokers with up to 1 year of follow-up.

"In what we believe to be the largest smoking cessation clinical trial and the only trial comparing NRT, bupropion, and varenicline [with] placebo, we found no signal that smoking cessation pharmacotherapy increases the risk of serious cardiovascular disease or cardiovascular adverse events in a general population of smokers," concluded Neal L. Benowitz, MD, of the University of California, San Francisco, and his associates. "While the number of events was small, the incidence of serious cardiovascular events was low, suggesting that any absolute increase in risk that we might have missed would be low and not clinically meaningful." The findings were reported online April 9 in JAMA Internal Medicine.

In this double-blind, multicenter, triple-dummy trial (EAGLES), Dr. Benowitz and his associates randomly assigned 8,058 adult smokers, who did not have acute or unstable cardiovascular disease, to receive bupropion (150 mg twice daily), varenicline (1 mg twice daily), NRT (21-mg/day patch with tapering), or placebo for 12 weeks, followed by 12 weeks of follow-up. A total of 4,595 patients agreed to be followed for another 28 weeks during an extension phase of the trial. More than half of the patients were women and the average age of a participant was 47 years. The primary endpoint was time to major adverse cardiovascular event (MACE), including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The researchers selected time to MACE as their primary endpoint to better detect differences among groups. One of the secondary end points was the occurrence of MACEs over the same three time intervals. Additionally, cardiovascular deaths, nonfatal MI, and nonfatal stroke (the components of MACE) were evaluated individually, as were hospitalizations for congestive heart failure and serious arrhythmias.

Differences in time to onset of MACE between all four patient groups were not significant. The overall incidence of MACEs was less than 0.5% during all observation periods. There were also no significant differences in rates of the individual types of MACE, coronary revascularization, hospitalization for unstable angina, or new or worsening peripheral vascular disease requiring treatment among groups. Changes in body weight, blood pressure, and heart rate also were similar across patients.

There were five cardiovascular deaths, including one in the varenicline group, two in the bupropion group and two in the placebo group, according to the researchers. Overall the trial results "are consistent with and support previously published findings from meta-analyses and small clinical trials in smokers with known [cardiovascular disease]," they wrote.

GlaxoSmithKline and Pfizer, who make and market smoking cessation therapies, sponsored the study. Dr. Benowitz disclosed a consulting relationship with Pfizer and other pharmaceutical companies. He also has been a paid expert witness in litigation against tobacco companies. Eight coinvestigators disclosed ties to Pfizer, GlaxoSmithKline, and other companies.

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SOURCE: Benowitz NL et al. JAMA Intern Med. 2018 Apr 9. doi: 10.1001/jamainternmed.2018.0397).

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Another way to better target WCDs to post-MI patients who could derive the most benefit might be to focus on patients with frequent premature ventricular contractions and nonsustained ventricular tachycardia, suggested Dhanunjaya Lakkireddy, MD, professor of medicine and director of the Center for Excellence in AF and Complex Arrhythmias at the University of Kansas Medical Center in Kansas City. But Dr. Lakkireddy acknowledged that currently left ventricular ejection fraction is the primary surrogate marker cardiologists rely on to identify post-MI patients who are at increased risk for ventricular arrhythmia.

Dr. Olgin countered that the total mortality rate seen among the control, usual-care patients in his study, 4.9% during the median 84-day follow-up, closely matched the 5% rate reported in prior trials of at-risk patients who received implantable cardioverter defibrillators.

The Vest Prevention of Early Sudden Death Trial (VEST) randomized patients within the first 7 days following an acute MI who met the reduced left ventricular ejection fraction criterion. The study ran at 108 sites in the United States and three European countries during 2008-2017. During follow-up, total mortality occurred in 3.1% of the patients randomized to WCD use and 4.9% among the control patients.

The results also showed that 19% of the patients randomized to the WCD arm failed to ever use the device, and that over the course of follow-up the usage rate fell below 50%.

VEST was sponsored by Zoll, the company that markets the tested device. Dr. Olgin has no personal disclosures. Dr. Al-Khatib and Dr. Lakkireddy had no disclosures. Dr. Wilber is a consultant to Biosense Webster and Medtronic.

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Consider spironolactone in treatment-resistant hypertension

BY BRUCE JANCIN
MDedge News

ORLANDO – More than one-third of patients with treatment-resistant hypertension in U.S. cardiology practices are eligible for preferential consideration of spironolactone as their fourth-line agent in accord with the practice-changing findings of the PATHWAY-2 trial, Lauren Thompson, MD, said at the annual meeting of the American College of Cardiology.

She presented a study that harnessed the ACC's National Cardiovascular Data Registry PINNACLE Registry – the largest observational outpatient cardiovascular registry in the world – to assess the potential impact of PATHWAY-2 on the management of treatment-resistant hypertension (TRH) in U.S. cardiology practices. And as she discovered, the potential implications for daily practice are huge.

PATHWAY-2 was a randomized, double-blind, crossover trial involving 314 U.K. patients with TRH despite treatment with maximally tolerated doses of three drugs: a diuretic, an ACE inhibitor or angiotensin receptor blocker, and a calcium channel blocker. Patients were randomized to rotate through 12 weeks of once-daily add-on therapy with spironolactone at 25-50 mg, bisoprolol at 5-10 mg, modified-release doxazosin at 4-8 mg, and placebo. All of the add-ons were similarly well tolerated, but spironolactone proved to be easily the most effective fourth drug for TRH (Lancet. 2015 Nov 21;386[10008]:2059-68).

BRUCE JANCIN/MDEDGE NEWS

Dr. Lauren Thompson

Dr. Thompson, a cardiology fellow at the University of Colorado, Denver, identified 19,044 patients in the PINNACLE registry for 2013-2014 with TRH, defined as uncontrolled blood pressure despite use of drugs from three antihypertensive classes. Of these patients, 37% met the PATHWAY-2 enrollment criteria by virtue of already being on an ACE inhibitor or angiotensin receptor blocker, a calcium channel blocker, and a thiazide diuretic, but not spironolactone. This is the large subgroup which, on the basis of PATHWAY-2, should receive serious consideration of spironolactone as the fourth drug.

The most widely prescribed antihypertensive agents in PINNACLE registry patients with TRH were beta-blockers, in 87%; ACE inhibitors, in 72%; calcium channel blockers, in 71%; and thiazide diuretics, in 69%. Of note, 27% of patients

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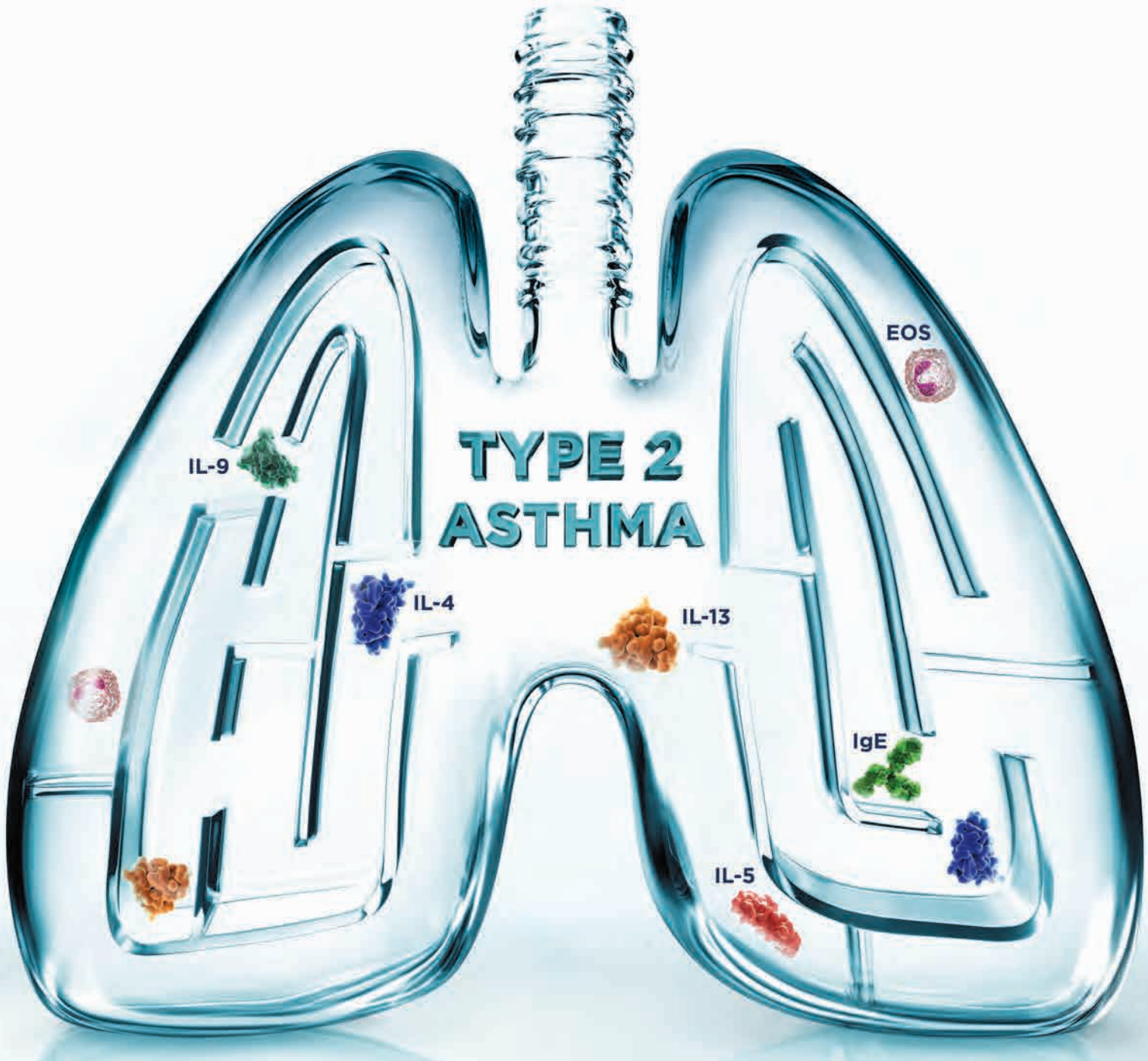

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Triple-antihypertensive pill is effective early therapy

BY MITCHEL L. ZOLER
MDedge News

ORLANDO – Hypertensive adults started on a triple-drug, single daily pill regimen as either initial or early treatment had a sharply better rate of reaching their goal blood pressure after 6 months, compared with usual-care controls, in a multicenter, randomized trial with 700 patients.

"Early use of a low-dose, three-in-one blood pressure – lowering pill is safe and provides faster and better control of blood pressure compared with usual care," Ruth Webster, PhD, said at the annual meeting of the American College of Cardiology.

The tested polypill contained half the standard doses of the angiotensin receptor blocker telmisartan (20 mg), the calcium channel blocker amlodipine (2.5 mg), and the diuretic chlorthalidone (12.5 mg). After 6 months on this regimen, 70% of patients were at their goal blood pressure, compared with 55% of the control patients, and patients on the polypill had on average a 10/5–mm Hg greater reduction in their blood pressure than did patients on usual care, reported Dr. Webster, head of research programs at the George Institute for Global Health in Sydney. Rates of total and serious adverse events and withdrawals because of adverse events

"Early use of a low-dose, three-in-one blood pressure–lowering pill is safe and provides faster and better control of blood pressure."

were similar in the two study arms, and both arms also had nearly identical levels of treatment adherence, about 95%.

"No prior trial has evaluated a triple, low-dose pill for initial or early treatment," she noted.

"This is a home run," said Karol E. Watson, MD, professor of medicine and director of the Women's Cardiovascular Health Center at the University of California, Los Angeles. "In the past, clinicians were told to pick one drug and push it as hard as you could and then maybe think about adding a second drug. Experience has shown that this does not increase efficacy, but it does increase adverse events, so current guidelines say start with two drugs. Now they are showing for the first time that you should start with three drugs. That goes with what we know."

"Triple-drug therapy for the masses makes complete sense," especially now that the blood pressure goal for most patients is less than 130/80 mm Hg, said William B. White, MD, professor of medicine and chief of hypertension and clinical pharmacology at the University of Connecticut in Farmington. Plus, "compliance is vastly improved when you use a combination-drug pill," he noted.

The blood pressure targets that Dr. Webster and her associates used were less than 140/90 mm Hg except in patients with diabetes or chronic kidney disease, who had a target of less than 130/80 mm Hg. At the time researchers designed the trial the generally accepted blood pressure target for antihypertensive treatment was less than 140/90 mm Hg, Dr. Webster noted.

She also stressed that she did not believe the three specific drugs selected for the polypill made a difference. "The specific drugs we used were not that important. We would probably get the same result with different drugs. It's about the strategy of using triple, low-dose therapy," Dr. Webster suggested. Dr. Watson agreed.

The TRIUMPH (Triple Pill vs. Usual Care Management for Patients with Mild to Moderate Hypertension) study enrolled patients at 11 hospital outpatient clinics in Sri Lanka. The average age of the patients was 56 years. The average blood pressure was 154/90 mm Hg. About 59% of patients were not on any antihypertensive drug at baseline, with the rest on a single drug. The study protocol excluded patients on two or more drugs at entry. Roughly 30% of enrolled patients had diabetes, and 1%-2% had chronic kidney disease. Their target blood pressure on treatment during the study was less than 130/80 mm Hg.

The study's primary endpoint was the percentage of patients at their goal blood pressure after 6 months. Patients in the triple-drug polypill group achieved their goal blood pressure 23% more often relative to the control, usual-care patients, a statistically significant difference. The between-group difference in achievement of goal blood pressure was apparent by the end of the first 6 weeks in the study. Patients in the control arm generally received either one or two drugs during the study, but often at full dose rather than the half doses used in the triple-drug patients. The study's design specified that patients in the triple-drug arm who were not at their target blood pressure after 6 weeks could, at the discretion of their treating physician, switch to a second formulation that doubled the dosage of each of the three drugs. Patients in the usual-care arm could have their treatment adjusted after 6 or 12 weeks as long as they continued to receive either one or two drugs. After 6 weeks, 68% of patients in the triple-drug arm and 44% receiving usual care were at their blood pressure goal. After 12 weeks, the percentages at goal were 73% of patients on the triple-drug pill and 47% on usual care.

Dr. Webster hypothesized that the triple-drug, low-dose strategy for initial or early treatment would surpass usual care not only in low- and middle-income countries, like Sri Lanka, but also in high-income, industrialized countries such as the United States.

TRIUMPH received no commercial funding. Dr. Webster had no disclosures. Dr. Watson has been a consultant to Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, and GlaxoSmithKline. Dr. White has been a consultant to Novartis.

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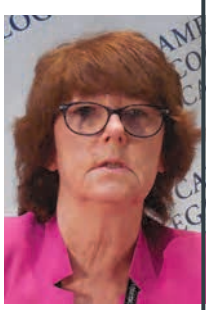
VIEW ON THE NEWS

Triple-drug pill boosts compliance, cuts adverse effects



The TRIUMPH results showed the feasibility and efficacy of achieving good blood pressure control with a single pill containing low doses of three different antihypertensive drugs that are well tolerated and have different mechanisms of action. This strategy avoids the adverse effects from drugs used at their maximum dose.

An attraction of this strategy is how seamless it is for patients. They take a single pill with three drugs, which can enhance compliance and in routine practice can reduce their copay. It's much easier for patients to take a single pill.

Eileen M. Handberg, PhD, is a research professor of medicine and director of the Clinical Trials Program at the University of Florida in Gainesville. She had no relevant disclosures. She made these comments in an interview.

Continued from page 38

with TRH were already on spironolactone.

Audience discussion centered around the uncertainties regarding treatment adherence in patients labeled as having TRH.

"I think sometimes clinicians are afraid to prescribe spironolactone in patients that they think might be nonadherent," one cardiologist observed.

Dr. Thompson noted that it's not possible to look at prescription-filling rates in the PINNACLE registry.

"Unfortunately, we can't exclude white coat hypertension or nonadherence as reasons why patients in PINNACLE end up on multiple antihypertensive medication classes. We can see that a prescription was written, but we have no way to know if it was actually filled or not," she observed.

Also, since patients in cardiology clinics typically have multiple cardiovascular comorbidities, it's quite possible that patients with TRH who are on a beta-blocker, for example, might not have received that drug for blood pressure control.

Dr. Thompson's study was supported by the ACC's National Cardiovascular Disease Registry. She reported having no financial conflicts of interest.

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Long-term statin use may prevent death in sepsis

BY MICHELE G. SULLIVAN
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Long-term statin use appears to decrease sepsis mortality by up to 28%, a large health care database review has determined.

Among almost 53,000 sepsis patients, those who had been taking simvastatin were 28% less likely to die within 30 days of a sepsis admission than were patients not taking a statin. Atorvastatin conferred a similar significant survival benefit, reducing the risk of death by 22%, Chien-Chang Lee, MD and his colleagues wrote in the April issue of the journal CHEST®.

ANDREWSOUNDARAJAN/THINKSTOCK

"Of note, simvastatin was shown by several reports to have the most potent antibacterial activity," targeting both methicillin-resistant and -sensitive Staphylococcus aureus*, as well as gram-negative and -positive bacteria.*

Although the physiological link isn't completely clear, animal studies suggest the survival benefit may be linked to statins' ability to improve cardiac function, reduce inflammatory cytokines, and slow down neutrophil infiltration into the lung, wrote Dr. Lee of the National Taiwan University Hospital, Taipei, and colleagues.

The drugs also exert a direct antimicrobial effect, he asserted.

"Of note, simvastatin was shown by several reports to have the most potent antibacterial activity," targeting both methicillin-resistant and -sensitive *Staphylococcus aureus*, as well as gram-negative and -positive bacteria.

Dr. Lee and his colleagues extracted mortality and statin prescription data from the Taiwan National Health Insurance Database from 2000 to 2011. They looked at 30- and 90-day mortality in 52,737 patients who developed sepsis; the statins of interest were atorvastatin, simvastatin, and rosuvastatin. Patients had to have been taking the medication for at least 30 days before sepsis onset to be included, and patients taking more than one statin were excluded from the analysis.

Patients were a mean of 69 years old. About half had a lower respiratory infection. The remainder had infections within the abdomen, the biliary or urinary tract, skin, or orthopedic infections. There were no significant differences in comorbidities or in other medications taken among the three

Continued on following page

Few acutely ill hospitalized patients receive VTE prophylaxis

BY DOUG BRUNK
MDedge News

SAN DIEGO – Among patients hospitalized for acute medical illnesses, the risk of venous thromboembolism (VTE) remained elevated 30-40 days after discharge, results from a large analysis of national data showed.

Moreover, only 7% of at-risk patients received VTE prophylaxis in both the inpatient and outpatient setting.


DR. AMIN

"The results of this real-world study imply that there is a significantly unmet medical need for effective VTE prophylaxis in both the inpatient and outpatient continuum of care among patients hospitalized for acute medical illnesses," researchers led by Alpesh Amin, MD, wrote in a poster presented at the biennial summit of the Thrombosis & Hemostasis Societies of North America.

According to Dr. Amin, who chairs the department of medicine at the University of California, Irvine, hospitalized patients with acute medical illnesses face an increased risk for VTE during hospital discharge, mainly within 40 days following hospital admission. However, the treatment patterns of VTE prophylaxis in this patient population have not been well studied in the "real-world" setting. In an effort to improve this area of clinical practice, the researchers used the Marketscan database between Jan. 1, 2012, and June 30, 2015, to identify acutely ill hospitalized patients, such as those with heart failure, respiratory diseases, ischemic stroke, cancer, infectious diseases, and rheumatic diseases. The key outcomes of interest were the proportion of patients receiving inpatient and outpatient VTE prophylaxis and the proportion of patients with VTE events during and after the index hospitalization. They used Kaplan-Meier analysis to examine the risk for VTE events after the index inpatient admission.

The mean age of the 17,895 patients was 58 years, 55% were female, and most (77%) were from the Southern area of the United States. Their mean Charlson Comborbidity Index score prior to hospitalization was 2.2. Nearly all hospitals (87%) were urban based, nonteaching (95%), and large, with 68% having at least 300 beds. Nearly three-quarters of patients (72%) were hospitalized for infectious and respiratory diseases, and the mean length of stay was 5 days.

Dr. Amin and his associates found that 59% of hospitalized patients did not receive any VTE prophylaxis, while only 7% received prophylaxis in both the inpatient and outpatient continuum of care. At the same time, cumulative VTE rates within 40 days of index admission were highest among patients hospitalized for infectious diseases and cancer (3.4% each), followed by those with heart failure (3.1%), respiratory diseases (2%), ischemic stroke (1.5%), and rheumatic diseases (1.3%). The cumulative VTE event rate for the overall study population within 40 days from index hospitalization was nearly 3%, with 60% of VTE events having occurred within 40 days.

The study was funded by Portola Pharmaceuticals. Dr. Amin reported having no financial disclosures.

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statin groups or the nonusers.

Of the entire cohort, 17% died by 30 days and nearly 23% by 90 days. Compared with those who had never received a statin, the statin users were 12% less likely to die by 30 days (hazard ratio, 0.88). Mortality at 90 days was also decreased, when compared with nonusers (HR, 0.93).

Simvastatin demonstrated the greatest benefit, with a 28% decreased risk of 30-day mortality (HR, 0.72). Atorvastatin followed, with a 22% risk reduction (HR, 0.78). Rosuvastatin exerted a nonsignificant 13% benefit.

The authors then examined 90-day mortality risks for the patients with a propensity matching score using a subgroup comprising 536 simvastatin users, 536 atorvastatin users, and 536 rosuvastatin users. Simvastatin was associated with a 23% reduction in 30-day mortality risk (HR, 0.77) and atorvastatin with a 21% reduction (HR, 0.79), when compared with rosuvastatin.

Statins' antimicrobial properties are probably partially caused by their inactivation of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase pathway, Dr. Lee and his colleagues noted. In addition to being vital for cholesterol synthesis, this pathway "also contributes to the production of isoprenoids and lipid compounds that are essential for cell signaling and structure in the pathogen. Secondly, the chemical property of different types of statins may affect their targeting to bacteria. The lipophilic properties of simvastatin or atorvastatin may allow better binding to bacteria cell walls than the hydrophilic properties of rosuvastatin."

The study was funded by the Taiwan National Science Foundation and Taiwan National Ministry of Science and Technology. Dr. Lee had no financial conflicts.

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SOURCE: Lee C-C et al. CHEST 2018. Apr;153(4):769-70.

VIEW ON THE NEWS

The Taiwan connection – as good as it gets

The statin-sepsis mortality link will probably never be definitively proven, but the study by Lee and colleagues gives us the best data so far on this intriguing connection, Steven Q. Simpson, MD and Joel D. Mermis, MD wrote in an accompanying editorial.

"It is unlikely that prospective randomized trials of statins for prevention of sepsis mortality will ever be undertaken, owing to the sheer number of patients that would require randomization in order to have adequate numbers who actually develop sepsis," the colleagues wrote. "We believe that the next best thing to randomization and a prospective trial is exactly what the authors have done – identify a cohort, track them through time, even if nonconcurrently, and match cases to controls by propensity matching on important clinical characteristics."

Nevertheless, the two said, "This brings us to one aspect of the study that leaves open a window for some doubt."

Lee et al. extracted their data from a large national insurance claims database. These systems "are commonly believed to overestimate sepsis incidence," Dr. Simpson and Dr. Mermis wrote. A 2009 U.S. study bore this out, they said. "That study showed that in the U.S in 2014, there were approximately 1.7 million cases of sepsis in a population of 330 million, for an annual incidence rate of five sepsis cases per 1,000 patient-years."

However, a "quick calculation" of the Taiwan data suggests that the annual sepsis caseload is about 5,200 per year in a population of 23 million at risk – an annual incidence of only 0.2 cases per 1,000 patient-years.

"This represents an order of magnitude difference in sepsis incidence between the U.S. and Taiwan, providing some issues to ponder. Does Taiwan indeed have a lower incidence of sepsis by that much? If so, is the lower incidence related to genetics, environment, health care access, or other factors?

"Although Lee et al. have provided us with data of the highest quality that we can likely hope for, the book may not be quite closed, yet."

Dr. Mermis and Dr. Simpson are pulmonologists at the University of Kansas, Kansas City. They made their comments in an editorial published in the April issue of CHEST® *(Mermis JD and Simpson SQ. CHEST. 2018 April. doi: 10.1016/j.chest.2017.12.004.)*

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WARNING: ASTHMA-RELATED DEATH

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

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

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

gsk | INNOVIVA

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

Patients experienced greater lung function with TRELEGY vs patients taking fluticasone furoate/vilanterol (FF/VI)

Primary endpoint: Change from baseline in trough FEV_1 at Day 85[1,2]
In patients with COPD run-in on FF/VI 100/25, TRELEGY provided

124 mL ADDITIONAL LUNG FUNCTION IMPROVEMENT

vs FF/VI
($P < 0.001$)

Similar results were demonstrated in a replicate study.

STUDY DESCRIPTION[1,2]

Design: 12-week, randomized, double-blind, parallel-group study. Following a 4-week run-in period on FF/VI 100/25, patients were randomized to treatment with umeclidinium (n=206) or placebo (n=206) added to FF/VI 100/25 (each administered once daily in the morning by the ELLIPTA inhaler). Treatment with TRELEGY refers to patients who received UMEC added to FF/VI 100/25.

Patients: COPD patients (mean age: 64 years). At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 46%, a mean postbronchodilator FEV_1/FVC ratio: 0.48, and a mean mMRC score of 2.5.

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; UMEC=umeclidinium; VI=vilanterol.

IMPORTANT SAFETY INFORMATION (cont'd)

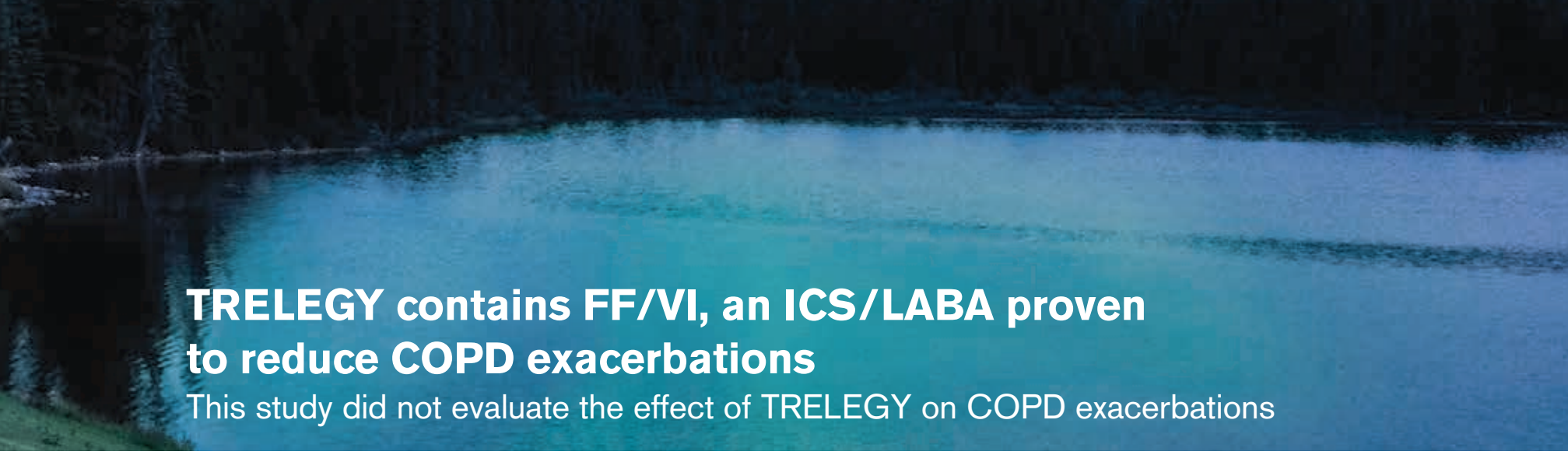
CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of inhaled corticosteroids, like fluticasone furoate.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.

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



TRELEGY contains FF/VI, an ICS/LABA proven to reduce COPD exacerbations

This study did not evaluate the effect of TRELEGY on COPD exacerbations

Primary endpoint: Annual rate of moderate/severe exacerbations[1,3]

In patients with a history of COPD exacerbations, FF/VI 100/25 provided

21% EXACERBATION REDUCTION

in annual rate vs vilanterol

0.90 vs 1.14 for FF/VI 100/25 and VI, respectively; $P=0.024$

Similar results were demonstrated in a replicate study.

STUDY DESCRIPTION[1,3]

Design: 12-month, randomized, double-blind, parallel-group study that evaluated the effect of FF/VI 100/25 mcg (n=403) and VI 25 mcg* (n=409) (each administered once daily by the ELLIPTA inhaler) on the rate of moderate/severe exacerbations. Patients with a history of ≥1 moderate or severe exacerbation in the previous year were randomized to treatment following a 4-week run-in period on fluticasone propionate/salmeterol 250/50 mcg twice daily.

Patients: COPD patients (mean age: 64 years). At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 46% and a mean postbronchodilator FEV_1/FVC ratio: 0.46.

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

* Vilanterol is not approved as monotherapy.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

To learn more, go to TrelegyMD.com

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

100% of eligible commercially insured patients will pay no more than $10 a month* for TRELEGY with savings offer

*Subject to eligibility. Restrictions apply. Offer is good for up to 12 uses. Patients in government programs, including Medicare, are not eligible for savings offers. Please see the savings offer for complete rules and eligibility.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of inhaled corticosteroids or inhaled anticholinergics; therefore, monitoring is warranted.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develops.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develops.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in two 12-week clinical trials with umeclidinium + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

References: 1. Data on file, GSK. **2.** Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. *Respir Med*. 2015;109(9):1155-1163. **3**. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1(3):210-223.

To learn more, go to TrelegyMD.com

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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

BRIEF SUMMARY

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

TRELEGY is indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.

Important Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25,15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in TRELEGY.

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

5.2 Deterioration of Disease and Acute Episodes

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

TRELEGY should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. TRELEGY has not been studied in the relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms.

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

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

TRELEGY should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

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

5.5 Pneumonia

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

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was less than 1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.
In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (less than 0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression

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

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [FEV$_1$]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Continued on next page

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

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

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

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

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

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY *[see Contraindications (4)]*.

5.12 Cardiovascular Effects

Vilanterol, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

TRELEGY, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

5.13 Reduction in Bone Mineral Density

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

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (eg, eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and/or cataracts.

5.15 Worsening of Urinary Retention

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

5.16 Coexisting Conditions

TRELEGY, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

The safety of TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol, and on the long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy. *[see Description (11), Clinical Pharmacology (12.3), and Clinical Studies (14.1) of full prescribing information]*.

Confirmatory Trials

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14.1) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based upon the two 12-week trials.

Continued on next page

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

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

Supporting Long-Term Safety Data

The long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy are similar to that reported in the 12-week clinical trials described in Table 1. *[See full prescribing information for BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder), and INCRUSE ELLIPTA (umeclidinium inhalation powder).]*

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

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

8.2 Lactation

Risk Summary

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

8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

Fluticasone Furoate/Vilanterol

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

Umeclidinium

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

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

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

10.1 Fluticasone Furoate

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

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

10.2 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.3 Vilanterol

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

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death

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

Not for Acute Symptoms

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

Continued on next page

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

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

Tell patients they should not stop therapy with TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.

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

Instruct patients not to use other LABA.

Local Effects

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

Pneumonia

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

Immunosuppression

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

Hypercorticism and Adrenal Suppression

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

Paradoxical Bronchospasm

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

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY.

Reduction in Bone Mineral Density

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

Ocular Effects

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

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

Worsening of Urinary Retention

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

Risks Associated With Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 09/2017 TRL:1BRS

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

Sepsis versus SIRS blood test shows high sensitivity

BY RANDY DOTINGA
MDedge News

A molecular host response assay, called SeptiCyte Lab, holds promise as a tool to distinguish between sepsis and noninfectious systemic inflammation (SIRS), reported researchers in an industry-funded study.

Sepsis is a complex and hard-to-diagnose condition, noted two members of the editorial advisory board of *CHEST® Physician* in interviews. To make things more complicated, there's not even a standard definition of sepsis, explained board member Nirmal S. Sharma, MD, of the University of South Florida, Tampa.


DR. SHARMA

"Although newer sepsis definitions have been proposed, all of them have pitfalls and are not used universally. Additionally, the presence of inflammatory response leading to suspicion of sepsis can be due to a new infection or underlying disease processes, thus making it difficult to identify the possible cause," said Dr. Sharma. "Culture-negative cases due to the use of antibiotics prior to suspicion/onset of sepsis can further muddle the picture. Finally, in certain subsets of patients, such as the immunocompromised and elderly, the signs of sepsis may be delayed due to inadequate/dampened immune response, thus making early diagnosis difficult."

Blood testing can provide information about germs that are causing an infection, but "they often take several days, and we need to start the antibiotics before we have those results," added Daniel Ouellette, MD, FCCP, the other board member interviewed.

The SeptiCyte Lab assay, which was approved by the Food and Drug Administration for use in diagnosing sepsis in 2017, was developed to help physicians distinguish sepsis from SIRS in patients during their first day of ICU treatment, noted the authors of the new study in the American Journal of Respiratory and Critical Care Medicine.

This new tool seems to overcome some of the obstacles encountered when other diagnostic methods are used to determine if a patient has sepsis.

Russell R. Miller III, MD, FCCM, and his colleagues performed their SeptiCyte Lab assay on patients' blood samples; this involved real-time, reverse-transcription, quantitative polymerase chain reaction screening designed to analyze the relative expression levels of four genes. The testing procedure took approximately 6 hours from the draw of the blood sample, according to the study, which was recently published online,

The predictive sensitivity of the test was 0.97 in patients unanimously considered to have sepsis

Continued on following page

Peanut was the biggest culprit in anaphylaxis PICU admissions

BY THOMAS R. COLLINS
MDedge News

ORLANDO – Food was found to be the most commonly identified trigger, with peanuts the most prevalent food cause, in what researchers say is the largest comprehensive review of anaphylaxis episodes in North America that led to pediatric intensive care unit stays.

MATES/FOTOLIA

Researchers examined the Virtual Pediatrics Systems database, an international database of pediatric intensive care unit (PICU) information, said Carla M. Davis, MD, a pediatrician at Baylor College of Medicine, Houston. During 2010-2015, there were 1,989 pediatric anaphylaxis admissions to these units in North America, she reported at the joint congress of the American Academy of Allergy, Asthma and Immunology and the World Asthma Organization.

Dr. Davis said the study is intended to give a much-needed broad look at what is causing the most severe cases of child anaphylaxis.

"Because anaphylaxis is one of the most severe consequences of allergic disease, we decided that this study needed to be done to see really what the landscape was in the most critically ill children," she said.

Peanuts accounted for 45% of the food triggers, followed by tree nuts and seeds at 19%, and milk at 10%.

Common causes aside from food included drug, blood products, and venom, Dr. Davis said.

Anaphylaxis accounted for 0.3% of all PICU admissions over the 5-year period, researchers found. Dr. Davis said this was "higher than what we anticipated."

The overall mortality rate was 1%, and researchers found that peanuts and dairy were main causes of death of all the food-induced cases.

THOMAS R. COLLINS/MDEDGE NEWS

Dr. Carla M Davis: "Because anaphylaxis is one of the most severe consequences of allergic disease, we decided that this study needed to be done."

Anaphylaxis occurred more often in children ages 6-18 years than in kids of other ages and was least common among those aged 2-5 years. Asian children were disproportionately represented among the PICU anaphylaxis patients, but the mortality rate didn't vary by any demographic factors.

Admissions were most likely to happen in the fall and were more common in the Northeast and Western regions of the United States, Dr. Davis reported.

She said the deep look at the causes of these severe cases should help drive home the importance of counseling patients and families about prevention.

"For patients that have had a history of an allergic reaction to food or medication, but specifically food, I think really stressing avoidance measures will be something that will be very helpful, as well as counseling about epinephrine injectors and carrying them is going to help," she said. "I think having a little more knowledge, pediatricians should be able to counsel and refer to allergists when they don't feel they have all the necessary skills."

Dr. Davis reported having financial relationships with the companies Aimmune Therapeutics and DBV Technologies.

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Continued from previous page

by expert panels comprising three members. Negative predictive values were at least 0.89, according to the researchers.

Overall, the findings show "good reliability," wrote Dr. Miller of the Intermountain Medical Center in Murray, Utah, and the University of Utah, Salt Lake City, and his colleagues.

The test produced scores in four bands, with scores at or above 3.1 considered to be evidence of infection. Lower levels were considered to be evidence of noninfection.

Dr. Miller and his coauthors reported that 86% of patients unanimously considered to have sepsis had scores above 3.1, In contrast, only 30% of those considered to have SIRS had such high scores.

In addition, the study authors determined that the test was more reliable than were the clinical signs and laboratory variables that are commonly used to diagnose sepsis within 24 hours of arrival at the ICU.

Reaching a definitive sepsis diagnosis is challenging based on clinical signs alone, since various conditions mimic the signs of sepsis, noted Dr. Ouellette of Henry Ford Hospital and Wayne State University School of Medicine in Detroit.

In some cases, physicians simply assume that a patient has sepsis and begin antibiotics, he said, "but that's not a free ride. Each [antibiotic] may produce side effects with consequences for patients. The other problem is that overuse of antibiotics leads to resistance."

The study by Dr. Miller and his colleagues combined the results of three trials conducted from during 2011-2016 in the United States and the Netherlands in 447 subjects.

One trial analyzed the experiences of 198 consecutive subjects, all critically ill, who met various criteria. (They were part of a consortium trial of 7,500 patients.) The second trial had 129 participants, and the third had 120. Of the total participants, 71% were white and 20% were black.

Inclusion of procalcitonin levels in the laboratory variables didn't appear to make a significant difference. The study authors wrote that the test "differs from, and is complementary to that of procalcitonin. The latter test is cleared for predicting progression from severe sepsis to septic shock, for predicting 28-day mortality, and for managing antibiotic de-escalation."

DR. OUELLETTE

According to the researchers, differences in age, sex, and race/ethnicity did not significantly affect the test.

The study concludes by noting that "future studies are warranted to determine how host gene expression could most effectively be integrated into clinical decision making to ensure susceptible patients are accurately managed early in the course of disease."

The test is "promising new technology, but I don't think you could say it's definitive," noted Dr. Ouellette. "Like any test, it's not perfect," he explained. "That's important because physicians wouldn't want to guess wrong. We might err on the side of choosing to treat with antibiotics even in the face of a test that suggested they might not have infection."

Immunexpress and the Australian Government funded the study. Fourteen authors disclosed being current or former employees of Immunexpress and/or shareholders; others reported receiving funding from the company via their institutions. Four authors declared having filed patent applications related to the study or to the diagnosis of community-acquired pneumonia upon ICU admission. Some authors reported various other disclosures.

Dr. Ouellette and Dr. Sharma said they did not have any disclosures.

SOURCE: Miller RR et al. Am J Respir Crit Care Med. 2018 Apr 6. doi: 10.1164/rccm.201712-2472OC.

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

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

AstraZeneca

MedPAC urges CMS to curb low-value care

BY GREGORY TWACHTMAN
MDedge News

WASHINGTON – Prior authorization, clinical decision support, provider education, altered cost sharing, and evidence review can and should be employed to reduce the volume of low-value services paid for by Medicare, according to a staff presentation at a meeting of the Medicare Payment Advisory Commission.

MedPAC found that about 20% of Virginians, across all payers, received a low-value service in 2014, while 15% of Medicaid patients and 11% of commercially insured patients in Oregon received a low-value service in 2013.

At the commission's April meeting, MedPAC staff presented data from various literature searches, noting a "substantial use of low-value services in Medicare." For example, they found that about 20% of Virginians, across all payers, received a low-value service in 2014, while 15% of Medicaid patients and 11% of commercially insured patients in Oregon received a low-value service in 2013.

Similarly, 23%-37% of Medicare beneficiaries received at least one low-value service in 2014, based on analysis of claims data, for an expenditure of $2.4 billion to $6.5 billion, although MedPAC staff said that was probably an underestimate.

"It is very hard to know at the beginning of coverage that something is going to be low value," MedPAC commission member Kathy Buto, former vice president of global health policy at Johnson & Johnson, noted. "It may be covered for something narrow for which it is high value and then spreads. It's important to have those kinds of tools once technologies and procedures are covered to be able to actually monitor what is going on and assess."

But, she added, the Centers for Medicare & Medicaid Services needs to do more to routinely reexamine its coverage decisions.

"Part of the conversation needs to be about revisiting the coverage after a certain amount of time,"

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Photos Gregory Twachtman/MDedge News

"It is very hard to know at the beginning of coverage that something is going to be low value," noted MedPAC commission member Kathy Buto.

Even with tools to cut coverage, CMS's hands may be tied by outside forces, noted commissioner Dr. Rita Redberg.

Patients more likley to hide from care than seek care

BY RICHARD FRANKI
MDedge News

Some people are more likely to seek medical care, and some people are less likely, but which type is more common? The results of a survey of over 14,000 Medicare beneficiaries suggest that the avoid-care type may be a bit more prevalent.

In the survey, 40% of respondents said that they were more likely to keep it to themselves when they got sick, but 36% visit a physician as soon as they feel bad. Almost 29% reported that they avoid going to a physician, but 25% worry about their own health more than others, the Centers for Medicare & Medicaid Services reported based on the results of the 2015 Medicare Current Beneficiary Survey.

The last two questions on propensity to seek care put the avoid-care type in the minority, albeit a somewhat disturbing one: 11% of Medicare patients responding to a survey said that they had a problem and did not seek a physician and 7% had a prescription they did not fill, the CMS noted.

Race and ethnicity made a big difference for some questions: 59% of Hispanics said that they visit a doctor as soon as they feel bad, compared with 44% of non-Hispanic blacks and 31% of non-Hispanic whites. That same order was seen for "worry about your health more than others" – 54% Hispanic, 38% black, and 19% white – and for "avoid going to the doctor" – 44% Hispanic, 34% black, and 26% white, the CMS reported.

The three groups, which were the only race/ethnicities included in the report, were all around 40% for "when sick, keep it to yourself," while two of the three were the same for "had a problem and did not seek a doctor" (blacks and Hispanics at 14% and whites at 10%) and for "ever had a prescription you did not fill" (whites and Hispanics at 7% and blacks at 10%), the report said.

The estimates on propensity to seek care did not include Medicare recipients who lived part or all of the year in a long-term care facility, which was about 4% of the Medicare population in 2015. The survey included a total of 14,068 respondents.

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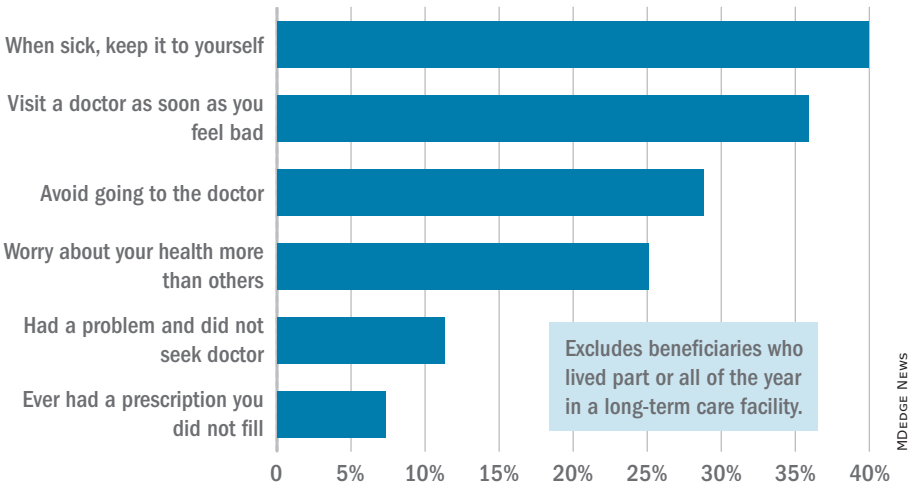
Self-reported indicators of propensity to seek care, 2015



Note: Based on data from the 2015 Medicare Current Beneficiary Survey.
Source: Centers for Medicare & Medicaid Services

ILLUMINATEOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

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

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

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

References: 1. Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med.* 2005;172:149-160. **2.** Trivedi SG, Lloyd CM. Eosinophils in the pathogenesis of allergic airways disease. *Cell Mol Life Sci.* 2007;64(10):1269-1289. **3.** de Groot JC, Ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res.* 2015;1:1-11. **4.** de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res.* 2016;2(2):1-8. **5.** Zeiger RS, Schatz M, Li Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract*. 2014;2:741-750. **6.** Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol.* 2015;136(6):1488-1495.

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she said. "I think that will prompt additional evidence development. Whether it is done at the beginning where the agency says, 'We are not going to cover this unless you give us more evidence,' or whether it is done on an ongoing basis ... there will be greater evidence development. That is part of what's missing."

Ms. Buto noted that noncoverage decisions are rarely issued and suggested that "there is an opportunity for us to take a look at whether we would advise CMS to take a look at using more of those tools more aggressively."

The Centers for Medicare & Medicaid Services needs to do more to routinely reexamine its coverage decisions, noted MedPAC commission member Kathy Buto.

Paul Ginsburg, PhD, commissioner and senior fellow in economic studies at the Brookings Institution, Washington, suggested that, for any new procedure or drug, initial coverage is always provisional for a certain length of time, which would force CMS to revisit coverage decisions.

"If there is no evidence, the coverage ends," Dr Ginsburg said. "If there is positive evidence, the coverage proceeds."

However, as commissioner Rita Redberg, MD, of the University of California, San Francisco, said of CMS, even with tools to cut coverage, its hands may be tied by outside forces. "CMS needs a lot more political cover."

She recalled a December 2007 CMS proposal to cut back reimbursement for cardiac CT scans to symptomatic patients and to only within the context of an approved clinical trial. Three months later, the agency withdrew the proposed national coverage decision and left it to local carriers to determine whether the procedure would be covered.

Dr. Redberg noted that there was extensive lobbying of local carriers, and within 6 months, despite the lack of evidence, everyone was covering cardiac CT.

"A few years later, CMS tried to walk back the coverage because it was just hemorrhaging money for cardiac CT, but there was no chance because it was a capital investment," she added. "Even when there are restrictions on coverage, CMS doesn't enforce them."

Ms. Buto also raised the issue of how much influence CMS has over Medicare Part D prescription drug plan sponsors' coverage decision policies, but suggested CMS could play a larger role in that.

Commissioner Amy Bricker, vice

president of supply chain strategy at Express Scripts, St. Louis, suggested that, "We need to do more from a Part D perspective to allow plans to manage drug coverage more aggressively and in line with the commercial space. CMS has handcuffed them," noting that FDA approval, regardless of value, generally means Medicare coverage.

Commissioner Jack Hoadley, PhD, of Georgetown University in Washington, cautioned that any discussion on these or possibly other tools needs to take into account the needs of those who will legitimately benefit from some of the low-value services so they do not inadvertently prevent access for those patients.

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Gregory Twachtman/MDedge News

"We need to do more from a Part D perspective," said Amy Bricker.

Doctors call for a pause to rethink MIPS measures

BY GREGORY TWACHTMAN
MDedge News

A "time-out" is needed to re-evaluate how quality measures are used as part of Medicare's Merit-Based Incentive Payment System (MIPS), according to officials at the American College of Physicians.

The call comes in the wake of an analysis of MIPS quality measures that found a majority are not valid for ambulatory care internal medicine, according to ACP criteria.

Of the 86 MIPS quality measures considered relevant to ambulatory general interest medicine, 37% (32) were rated as valid, 35% (30) were rated as invalid, and 28% (24) were rated as of uncertain validity, Catherine H. MacLean, MD, and her colleagues on the ACP Performance Measurement Committee wrote in a perspective published April 18 in the New England Journal of Medicine.

The quality measures were assessed regarding importance, appropriate care, clinical evidence base, measure specifications, and measure feasibility and applicability.

"We also determined that the proportion of the measures that had been developed by the National Committee for Quality Assurance [NCQA] or endorsed by the National Quality Forum [NQF] that were rated as valid by our method," Dr. MacLean and colleagues wrote. "As compared with measures that were not endorsed by these organizations, greater percentages of NCQA-developed and NQF-endorsed measures were deemed valid [59% and 48%, respectively, vs. 27% for nonendorsed measures], and smaller percentages were deemed not valid [7% and 22% vs. 49% for nonendorsed measures]."


DR. ENDE

The lack of measures that were found to be valid for primary care is frustrating for doctors and could cause harm to patients, according to the authors. "We need a time-out during which to assess and revise our approach to physician performance measurement."

The ACP recommends that "physicians with expertise in clinical medicine and research develop measures using clinically relevant methodology," President Jack Ende, MD, said in a statement. "Performance measures should be fully integrated into care delivery so they can help address the most pressing performance gaps and direct quality improvement."

The time-out call comes amidst differing opinions on how to proceed with the MIPS track. The Medicare Payment Advisory Commission has recommended to Congress that MIPS be repealed and replaced, while health care experts and physician associations believe the program should stay the course.

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SOURCE: MacLean CH et al. New Engl J Med. 2018 Apr 18. doi: 10.1056/NEJMp1802595.

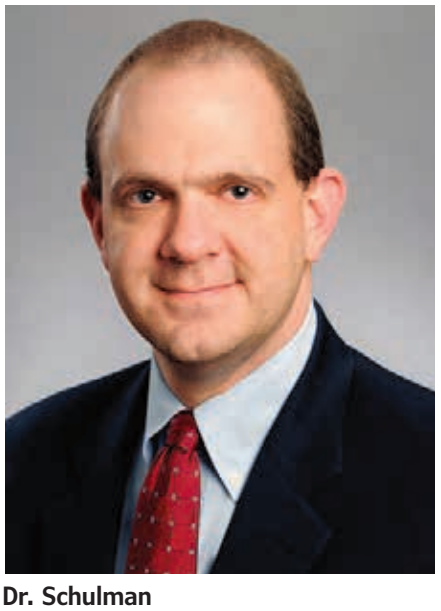
News From the Board – April 2018

BY DAVID SCHULMAN, MD, FCCP
Editor in Chief, CHEST® Physician

As Editor-in-Chief of *CHEST® Physician*, one of my missions is to better utilize this publication to facilitate communications between CHEST membership and CHEST leadership. This will be the first of a new quarterly column intended to keep our members apprised of Board activities that are of key organizational importance or may simply be of interest.

In 2017, CHEST President John Studdard commissioned a task force to look at the process by which College and Foundation leadership are selected, developed, and assessed. This was partly spurred on by a desire to ensure that we were engaged in best practices, but also an effort to improve the diversity of our leadership profile. After meeting several times through the fall and winter, and looking at practices of both our sister societies and medical societies in other specialties, the task force presented their plan for the creation of a new Governance Committee to both the Board of Regents and the Board of Trustees at the February board meetings.

This committee will be chaired by the Past Presidents of the Board of Regents and the Board of Trustees, and composed of an additional five individuals selected from current members of the Boards. First and foremost, the duty of this new body will be to ensure the overall health and performance of our Boards, by providing ongoing assessment of and feedback about members of our leadership. In addition, the Governance Committee will identify potential gaps in the make-up of our leadership, with a focus on diversity and inclusiveness, and will use those findings in interviewing and selecting both future Board members and new Presidents. Lastly, the committee will regularly review organizational bylaws and committee structures and will propose any recommended changes to the Board of Regents for review and formal vote.



Dr. Schulman

The presentation of this proposal was met with one of the most robust discussions that this writer has seen in his 4 years on the Board of Regents. This would represent a significant change in how CHEST selects its leadership; it would result in a sunsetting of the Nominating Committees of both boards, which had previously taken lead on the selection of Board members and Presidents. This is an important difference, as the College Nominating committee had included representation from both the Council of NetWorks and the Council of Global Governors, which ensured that a broad swath of our membership had a voice in selecting its leaders.

That noted, many current Board members previously served on these Councils, and so judicious selection of Governance Committee members could continue to ensure broad representation in the selection of our leaders. Another important point is that the process by which members are nominated for leadership positions would not change with this proposal, we would simply have a new body of voters that would select from this group of nominees.

At the end of the discussion, the Board voted to move forward with the formation of the Governance Committee, with an additional commitment to track its success in achieving its goals of improving the function and diversity of CHEST leadership on a regular basis.

Expanding CHEST's 'Women in Pulmonary' Program

The gender gap exists for women in pulmonary medicine. According to the Medscape Pulmonologist Compensation Report 2017, women pulmonologists earned 23% less than their male counterparts even though:

- 2% of women pulmonologists work part time vs 8% of men;
- more women (66%) than men (48%) reported seeking promotion. (Grisham, 2017)

If we take a look at a recent report done by Doximity that analyzed responses on more than 65,000 licensed US doctors across the country, the report reveals that the gap between female and male physicians across the nation, women on average make about $91,000 less annually (Doximity, 2018).

Despite ever-growing enrollment rates for women in medical schools, female physicians are often underrepresented in academic and research settings. According to a study published in the *Journal of National Medical Association*, "between 80 and 90 percent of leadership roles in medicine, like medical school deans, are filled by men." (Morton & Sonnad, 2007)

These astounding gaps do not stop at the clinician's door. This gender inequality is evident in the women who are receiving medical treatment, as well. There are two major issues that exist for women seeking treatment:

1. Not being taken as seriously as male patients:

- Women are more likely to be prescribed sedatives for their pain, and men are more likely to be prescribed pain medication. (L. Calderone, 1990)
- Women are more likely to be treated less aggressively in their initial encounters with the health-care system until they prove that they are as sick as male patients with similar symptoms. (Hoffmann & Tarzian, 2001)
- Nationwide, men wait an average of 49 minutes before receiving an analgesic for acute abdominal pain. Women wait an average of 65 minutes for the same thing. (Chen, et al., 2008)
- Multiple studies have shown that female patients' symptoms are less likely to be taken seriously by doctors, and women are more likely to be misdiagnosed, have their symptoms go unrecognized, or be told what they're experiencing is psychosomatic. (Hoffmann & Tarzian, 2001) (Carnlöf, Iwarzon, Jensen-Urstad, Gadler, & Insulander, 2017)

2. Being diagnosed and treated the same as male patients

- Up until 1993 when the National Institutes of Health Revitalization Act mandated that all women and minorities be included in clinical trials funded by the NIH, the guidelines and diagnosis for treatment have historically been based off the archetypal patient: a 154-pound white male. Because of this, women are often misdiagnosed or receive treatments that are ineffective or potentially harmful to their health. Even still, researchers frequently do not enroll an adequate number of women or fail to analyze or report data separately by sex. (MHC Center, 2014)
- Women and men metabolize drugs differently, yet dosages are rarely broken down by sex. Women also experience different side effects and derive different benefits from the same treatments. (Soldin & Mattison, 2009)
- Female patients have a 1.5 to 1.7 times higher chance of having an adverse drug reaction. (Rademaker, 2001)
- There are many diseases and conditions that are alarmingly more prevalent among women. Nonsmoking women are three times more likely to get lung cancer than nonsmoking men, according to a comprehensive 2014 report by Brigham and Women's Hospital in Boston, called "Women's Health Can't Wait." (MHC Center, 2014)

"While the number of women participating in lung cancer clinical trials has risen, women—particularly those from racial and ethnic minorities—are still less likely to enroll in these trials than men. Even when studies include women, researchers often fail to analyze data by sex or include hormone status or other gender-specific factors, making it difficult to uncover differences in incidence, prevalence, and survivability between men and women and to replicate the studies." (MHC Center, 2014)

In the pulmonary space, there is growing evidence that a number of pulmonary diseases affect women differently and with a greater degree of severity than men. Respiratory conditions that impact women nearly exclusively include pulmonary hypertension, catamenial diseases, and pregnancy-associated asthma exacerbation. (Pinkerton, et al., 2015) According to the CDC, cancer is the number one cause of death for women ages 35-64, and the number one cancer killer in women is lung cancer. Women have been taught to care and take notice of the symptoms of breast cancer, HPV, ovarian cancer, and other "women's diseases," and, yet, more women die every day from lung cancer than from breast, ovarian, and uterine cancers combined.

Why CHEST?

Now, why does this matter to us at CHEST? What can we do about it? How do we begin to tackle such a large issue that permeates nearly every facet of society?

CHEST is in a unique position to not only address the professional development needs of our female membership, but with the help and leadership of the CHEST Foundation and a new partnership with HealthyWomen, we are poised to address the gaps in education for our clinicians, patients, and the public.

To address these needs, the *Women in Pulmonary* program was created. *Women in Pulmonary* started as a yearly luncheon and has expanded into a yearlong program that will work to fill these gaps by not only elevating the wants and needs of women in pulmonary medicine, but also by bringing awareness to clinicians, patients, and the public on diseases that are not typically considered "women's issues."

CHEST and HealthyWomen are working to provide education, in the form of free webinars, multimedia resources, and live events to achieve the following outcomes:

Women in Pulmonary Medicine: CHEST and HealthyWomen aim to create the tools and educational opportunities that will empower our female clinicians to elevate their voices and become advocates for their career advancement, as well as improved diagnosis and treatment of women with pulmonary diseases.

Patients, Caregivers, and the Public: With this initiative, CHEST and HealthyWomen strive to empower women with the knowledge they need to become champions of their lung health. We will provide them with talking points, questions and awareness of symptoms of pulmonary conditions and diseases, such as: lung cancer, ILD/IPF, COPD, pulmonary hypertension, and asthma so that they are better able to go to their doctor appointments ready to advocate for the care they need.

Clinicians: CHEST and HealthyWomen will aim to equip all clinicians, not just women, with exposure and education that address gender differences in treatment and diagnosis of diseases like lung cancer, asthma, COPD, PH, and ILD/IPF.

Women in Pulmonary aims to provide essential education to every clinician treating women, promote awareness among patients and the public on key information to improve conversations with their health-care providers, and create opportunities for women in chest medicine to advance their careers through professional development, engagement, networking, and mentorship connections. This program will be one step in the direction of changing how women are viewed in medicine and how diseases are perceived across genders.

Bibliography

Calderone K. The influence of gender on the frequency of pain and sedative medication administered to postoperative patients. *Sex Roles.* 1990;23(11-12): 713-725.

Carnlöf C, et al. Women with PSVY are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J.* 2017; 51(6): 299-307.

Chen EH, et al. Gender disparity in analgesic treatment of emergency departmetn patietns with acute abdominal pain. *Acad Emerg Med.* 2008;15(5):414-418.

Doximity. 2018 *Physician Compensation Report.* Doximity.

Grisham S. *Medscape Pulmonologist Compensation Report 2017*. https://www.medscape.com/slideshow/compensation-2017-pulmonary-medicine-6008586. Accessed Jan 16, 2018.

Hoffmann DE, Tarzian AJ. The girl who cried pain: a bias against women in the treatment of pain. *J Law Med Ethics.* 2001;29(1):13-27.

MHC Center. *Sex-Specific Medical Research: Why Women's Health Can't Wait.* Brigham and Women's Hospital, Mary Horrigan Connors Center for Women's Health & Gender Biology. Brigham and Women's Hospital;2014.

Morton MJ, Sonnad SS. Women on professional society and journal editorial boards. *J National Med Assoc.* 2007;99(7):764-771.

Pinkerton K, et al. Women and lung disease. sex differences and global health disparities. *Am J Respir Crit Care Med.* 2015;192(1):11-16.

Rademaker M. (2001). Do women have more adverse drug reactions? *Am J Clin Dermatol.* 2001;2(6): 349-351.

Soldin O, Mattison M. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinetics.* 2009;48(3):143-157.

Get social, stay connected with CHEST Twitter chats

BY TAYLOR PECKO-REED
CHEST New Media Specialist

One of the best ways to stay connected with CHEST and up-to-date on the latest news and research is through our social channels. Twitter is a social platform that is constantly growing for the organization. Since 2009, we've had the opportunity to connect with over 20,000 individuals and impact millions with just a simple tweet or sharing of information. As a means to inform our highly active audience and bring the conversation to a social space, we've utilized the platform to help drive the conversation on various topics. CHEST moderates a public conversation via Twitter (@accpchest) around topics in pulmonary, critical care, and sleep medicine every few weeks.

Twitter chats are conversations that are held on the social platform and linked together by a distinct hashtag.

So, what exactly is a Twitter chat? Twitter chats are conversations that are held on the social platform and linked together by a distinct hashtag. We typically use the hashtag #pulmCC (which stands for pulmonary, critical care) and allow individuals from all across the globe to join in on the conversation and share their input. In addition to being a great networking opportunity, our chat recently began offering MOC points to CHEST members who attend Twitter chats and are eligible to receive participation points. We recently began offering CME credit for some of our chats, as well.

Over the last 6 years, we've hosted a wide range of Twitter chat topics, ranging from asthma to lung cancer. Some of those chats focused on the following topics:

- The Best of 2017: Highlights, Advancements, New Science
- Improving Lung Health Through Pulmonary Rehabilitation
- Caring for the Caregiver: Vulnerability and Burnout
- What Trainees Need to Know About Pulmonary, Critical Care & Sleep
- #VTEonSoMe Twitter Chat—Let's Talk Blood Clots! Surgeries, Birth Control, and 40

This past March, we held our Twitter chat Sepsis: Revisions, Advancements, New Therapies, led by Drs. Chris Carroll, Alex Niven, and Steven Q. Simpson. We had over 4.2 million impressions!

Every Twitter chat serves a different purpose, typically based on the topic and the individuals we believe would be most interested in the topic. These chats help us spark conversations on the latest research, advancements, and potential opportunities within the pulmonary/critical care field. They also provide physicians with a great opportunity to network and get acquainted with the #pulmCC community.

DR. McNICHOLAS

SLEEP STRATEGIES

COPD-OSA overlap syndrome

BY WALTER T. MCNICHOLAS, MD, FCCP

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) each affect at least 10% of the general adult population and, thus, both disorders together, commonly referred to as the overlap syndrome, could be expected in at least 1% of adults by chance alone. However, there is evidence of important interactions between

the disorders that influence the prevalence of the overlap, which have implications for the development of comorbidities,and also for management (McNicholas WT. *Chest.* 2017; 152[6]:1318). Furthermore, sleep quality is typically poor in COPD, which has been linked to worse pulmonary function and lung hyperinflation and may contribute to daytime fatigue.

Interactions between COPD and OSA that may influence the prevalence of overlap

Previous reports have presented conflicting results regarding the likely association between COPD and OSA, which may partly reflect different definitions of OSA, patient populations, and methodologies of investigation. However, COPD represents a spectrum of clinical phenotypes ranging from the hyperinflated patient with low BMI (predominant emphysema phenotype) to the patient with higher BMI and tendency to right-sided heart failure (predominant chronic bronchitis phenotype). The predominant emphysema phenotype may predispose to a lower likelihood of OSA, and there is recent evidence that lung hyperinflation is protective against the development of OSA by lowering the critical closing pressure of the upper airway during sleep. Furthermore, the degree of emphysema and gas trapping on CT scan of the thorax correlates inversely with apnea-hypopnia index in patients with severe COPD (Krachman SL et al. *Ann Am Thorac Soc.* 2016;13[7]:1129).

In contrast, the predominant chronic bronchitis phenotype predisposes to a higher likelihood of OSA because of higher BMI and likelihood of right-sided heart failure. Peripheral fluid retention in such patients predisposes to OSA because of the rostral fluid shift that occurs during sleep in the supine position, predisposing to upper airway obstruction by airway narrowing. The COPDGene study reports that the chronic bronchitis phenotype has a higher prevalence of OSA even in the absence of differences in BMI and lung function (Kim V et al. *Chest.* 2011;140[3]:626). Upper airway inflammation associated with cigarette smoking may also contribute to the development of OSA, and corticosteroid therapy may adversely affect upper airway muscle function. OSA also appears to exacerbate lower airway inflammation in COPD. In practice, most patients with COPD have a mixture of emphysema and chronic bronchitis, and the probability of OSA will represent the balance of these protective and promoting factors in individual patients (Fig 1).

While there is evidence of increased mortality in patients with COPD and OSA alone, a recent report based on the Sleep Heart Health Study somewhat surprisingly found that the incremental contribution of declining lung function to mortality diminished with increasing severity of SDB measured by AHI (Putcha N et al. *Am J Respir Crit Care Med.* 2016;194[8]:1007). Thus, the epidemiologic relationship of COPD and OSA and related clinical outcomes remains an important research topic comparing different clinical phenotypes.

Mechanisms of interaction in the overlap syndrome and implications for comorbidity

COPD and OSA are associated with

Continued on following page

Update: FDA workshop on medical devices for SDB

Drs. Neil Freedman and Barbara Phillips represented CHEST at an FDA workshop on April 16 on "Study Design Considerations for Devices Including Digital Health Technologies for Sleep Disordered Breathing (SDB) in Adults. The other organizational participants were The American Academy of Dental Sleep Medicine; The American Academy of Neurology; the American Academy of Otolaryngology, Head and Neck Surgery; The American Academy of Sleep Medicine; and The American Sleep Apnea Association. Here are the questions that the FDA asked the panelists:

1. FDA is seeking to promote innovation and expedite the clinical development of devices intended for the diagnosis and treatment of sleep disordered breathing (SDB). How should the following conditions (including their severity, eg, mild, moderate, severe, if appropriate) be defined for the purpose of creating appropriate inclusion/exclusion criteria for a clinical study for SDB devices?

- **a.** Apnea
- **b.** Hypopnea
- **c.** Sleep-Disordered Breathing (SDB)
- **d.** Obstructive Sleep Apnea Syndrome (OSAS)
- **e.** Central Sleep Apnea Syndrome (CSAS)
- **f.** Primary Snoring

2. Polysomnography (PSG) has been widely accepted as the "gold standard" test for the diagnosis of OSA and primary snoring. However, home sleep apnea testing (HSAT) has emerged in recent years as an alternative or complementary diagnostic tool for SDB.

- **a.** Can HSAT be used for establishing a baseline diagnosis and for the collection of clinical performance data for device trials for OSA, CSA, or primary snoring? If so, what are the recommended parameters that should be collected by an HSAT (eg, nasal pressure, oximetry, chest and abdominal respiratory inductance plethysmography)?
- **b.** What constitutes a technically adequate test (either PSG or HSAT, if appropriate) for establishing a baseline diagnosis of SDB for device studies (eg, number of hours, number of nights)?

3. FDA has received an increasing number of premarket applications for devices intended to treat SDB. How should studies for the various technologies (eg, intra-oral appliances, externally worn devices, electrosurgical devices for tissue reduction, and passive or active implantable devices of the upper airway) be designed with respect to the following factors (please consider whether your recommendations would vary if the device was an implant vs an externally worn device):

- **a.** What is the most appropriate control group (eg, comparison to baseline measures, randomization to a concurrent control group)?
- **b.** What is the minimum duration of the study? For implants and surgical procedures, how long after the intervention should the effectiveness endpoint be assessed?
- **c.** What objective parameter or combination of parameters should be used for the primary effectiveness endpoints (eg, AHI, ODI, T90, or other non-PSG/HSAT parameters)?
- **d.** What would be a clinically meaningful difference for the above primary effectiveness endpoint(s) between/among study arms or within a study arm?
- **e.** What patient-reported outcomes (PROs) are appropriate in the evaluation of SDB devices?

4. What are the safety and effectiveness concerns when a digital health device provides a diagnosis and monitoring of SDB?

- **a.** What factors are important in developing a reference database (eg, demographics, validation)?
- **b.** What are the important safety and effectiveness concerns for SDB digital health devices used in the following settings:
  - **i.** A physician office or sleep center environment?
  - **ii.** A nonclinical environment?
  - **iii.** Prescription vs OTC use?

There was significant discussion and quite a bit of controversy. Among the recommendations to the FDA were that home testing is adequate and acceptable for clinical trials, that the ODI4 is more predictive and reliable than the AHI, and that the syndrome of OSAHS includes symptoms, one of the most important of which is sleepiness. It was acknowledged that digital health devices have the potential to greatly increase access to diagnosis, but access to treatment will need to be addressed, as well. I think this was a very important meeting, and the outcome will likely impact our members. The ultimate goal is to publish a paper about recommended techniques, outcomes, and inclusion characteristics/definitions to be used in clinical trials for new devices to diagnose or treat sleep apnea.

Continued from previous page

several overlapping physiological and biological disturbances, including hypoxia and inflammation, which may contribute to cardiovascular and other comorbidities. Thus, the probability should be high that the overlap syndrome will be associated with a greater risk of comorbidity than with either disease alone. Patients with the overlap syndrome demonstrate greater degrees of oxygen desaturation predisposing to pulmonary hypertension, which is especially common in these patients.

COPD and OSA are each associated with systemic inflammation and oxidative stress, and C-reactive protein (CRP) has been identified as a measure of systemic inflammation that is commonly elevated in both disorders, although in OSA, concurrent obesity is an important confounding factor. Systemic inflammation contributes to the development of cardiovascular disease, which is a common complication of both COPD and OSA. Thus, one could expect that cardiovascular disease is particularly prevalent in patients with overlap syndrome, but there are limited data on this relationship, which represents an important research topic.

Clinical assessment

Patients with the overlap syndrome present with typical clinical features of each disorder and additional features that reflect the higher prevalence of hypoxemia, hypercapnia, and pulmonary hypertension. Thus, morning headaches reflecting hypercapnia and peripheral edema reflecting right-sided heart failure may be especially common. Screening questionnaires may be helpful in the initial evaluation of likely OSA in patients with COPD, and objective clinical data, including anthropometrics such as age, sex, and BMI, and medical history such as cardiovascular comorbidity, are especially useful in clinical prediction (McNicholas WT. *Lancet Respir Med.* 2016;4[9]:683). Thus, screening for OSA in patients with COPD should not be complicated, and the widespread failure to do so may reflect a lack of awareness of the possible association by the clinician involved.

The specific diagnosis of OSA in COPD requires some form of overnight sleep study, and there is a growing move toward ambulatory studies that focus on cardiorespiratory variables. Overnight monitoring of oxygen saturation is especially useful, particularly if linked to special analysis software, and may be sufficient in many cases. Full polysomnography can be reserved for select cases where the diagnosis remains in doubt.

Management and outcomes

Nocturnal hypoxemia in patients with COPD benefits from inhaled, long-acting beta-agonist and anticholinergic therapy, and mean nocturnal oxygen saturation is 2% to 3% higher on each medication compared with placebo. Supplemental oxygen may be indicated when nocturnal oxygen desaturation persists despite optimum pharmacotherapy and does not appear to be associated with significant additional risk of hypercapnia.

However, in patients with COPD-OSA overlap, nonnvasive pressure support is the most appropriate management option. In patients with predominant OSA, continuous positive airway pressure therapy (CPAP) is the preferred option, but where COPD is the dominant component, noninvasive ventilation (NIV) in the form of bi-level positive airway pressure (BIPAP) may be more appropriate. Recent reports in severe COPD indicate that NIV targeted to markedly reduce hypercapnia is associated with improved quality of life and prolonged survival (Köhnlein T et al. *Lancet Respir Med.* 2014;2[9]:698), and patients with COPD with persistent hypercapnia following hospitalization with an acute exacerbation show improved clinical outcomes and survival with continuing home NIV (Murphy PB et al. *JAMA.* 2017;317[21]:2177).

The recognition of co-existing OSA in patients with COPD has important clinical relevance as the management of patients with overlap syndrome is different from COPD alone, and the long-term survival of patients with overlap syndrome not treated with nocturnal positive airway pressure is significantly inferior to those patients with overlap syndrome appropriately treated (Marin JM et al. *Am J Respir Crit Care Med.* 2010;182[3]:325).

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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.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

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CHEST®

2018 Education Calendar

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Difficult Airway Management
June 8-10 | September 7-9

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July 13-15

Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows
July 20

Mechanical Ventilation: Advanced Critical Care Management
July 26-28

Cardiopulmonary Exercise Testing (CPET)
August 10-12

Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers
August 24-26

Ultrasonography: Essentials in Critical Care
September 13-15
November 29-December 1

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 20-22

Comprehensive Pleural Procedures
November 3-4

Critical Care Ultrasound: Integration Into Clinical Practice
November 9-11

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

Advanced Critical Care Board Review Exam Course
December 7-9

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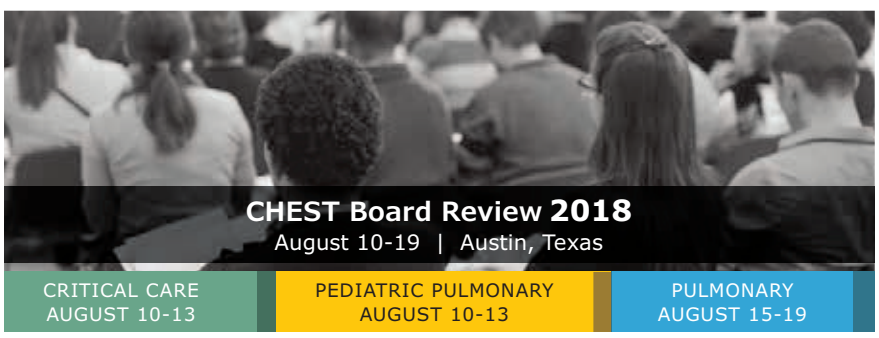

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Impacting careers, impacting patient care

Thank you for all you do to champion lung health. Your donation supports projects, such as grant funding, which are boosting patient outcomes, improving community health, and advancing the research that continues to enhance the journey for those facing pulmonary illnesses. Each year, your generosity funds more than $550,000 in clinical research and community service grants, allowing CHEST members to develop and implement their ideas through securing preliminary data support, distinguishing themselves among their colleagues, and advancing chest medicine toward medical breakthroughs.

CHEST® FOUNDATION

One such story of the advancements being made in communities around the world begins in New York City.

Kids in urban settings are disproportionately affected by asthma. Although we know that being active is good for respiratory health, in an urban setting, children may be breathing in more pollutants. In inner city neighborhoods playgrounds are often next to major highways or industrial areas. These recreational areas may be increasing the risk of developing pulmonary diseases. This is a prime example of why researchers like Dr. Stephanie Lovinsky-Desir are working to find a solution to champion lunch health.

Dr. Lovinsky-Desir is a pediatric pulmonologist based at Columbia University and the recipient of the CHEST Diversity and Young Investigator Award in 2014 for her project on Urban Tree Canopy Exposure, DNA Methylation, and Allergies in Pediatric Asthma. The grant helped launch her into the research that she is most passionate about – asthma and health disparities in urban populations.

As Stephanie can attest, junior faculty often struggle to find funding for their research, especially when focusing on disparities, diversity, and socioeconomic factors that affect public health. **"A lot of people can't take the risk to pursue higher-risk careers like research, because they don't have seed funding that allows them to dive into bigger awards or research grants."**

She made it her mission to find funding at the beginning of her research, so she could establish her reputation as a researcher and continue to receive further funding. Her plan began to fall into place when she applied for, and won, the CHEST Diversity and Young Investigator Award. Dr. Lovinsky believes the CHEST Foundation grant is what launched her research. **"Much of my success in getting grant funding is because I was awarded grants in the past! Once you start getting them and conducting research that produces meaningful results, you keep getting more, and it really starts to snowball. The CHEST Foundation award was the first award I as a Principal Investigator —my idea, my metrics. I feel so proud to have accomplished this."**

The findings she concluded from her CHEST diversity grant research allowed her to modify her study and receive the following awards: an award through her institution, the National Institute of Health KL2 award, and multiple awards including an NIH K01, a children's scholar award, and the Harold Amos Medical Faculty Development Award. Stephanie is excited for her future research after recently receiving a very competitive score from her NIHK. She believes the CHEST Foundation award jump started her research career, and these other successes have resulted from it. **"It's more than a research project. We are building a research program."** Her current research involves exploring epigenetic mechanisms, particularly DNA methylation, in pediatric and adult allergic asthmatics, as well as understanding the effects of environmental pollutants on asthma, activity, and obesity.

Though Dr. Lovinsky's career as a researcher grew from the foundation grant, she says, **"The benefit of this award specifically was the gateway to the CHEST Foundation and all of the other opportunities within CHEST."** She is actively involved in the Diversity and Inclusion Task Force and brings many ideas to the table for the future of the CHEST Foundation. **"I am committed to being involved with CHEST because of how much the organization has impacted my career. I enjoy giving back by participating in the task force."** Her clinical research and involvement in CHEST demonstrates the direct impact your generous

Continued on following page

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support has on physicians, patients, and lung health.

Thank you for making important research like this possible. Your generosity is the catalyst for change in a world where lung diseases are ranking as one of the top causes of death for men and women everywhere. You're improving patient outcomes every day, and we thank you from the bottom of our hearts.

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Again, thank you for all you do to improve patient outcomes. You are the lung health champions that patients and families count on to positively impact lung health.

Lisa K. Moores, MD, FCCP
President & Trustee

Mike E. Nelson, MD, FCCP
Immediate Past President & Trustee

AACN Update

AACN releases expert consensus statement on teleICU nursing practice

To remain at the forefront of expanding evidence-based practices in all aspects of critical care, facilities must include teleICUs.

In 2013, the American Association of Critical-Care Nurses (AACN) first defined standards for the emerging telenursing practice in the ICU and has recently published an update, AACN TeleICU Nursing Practice: An Expert Consensus Statement Supporting High Acuity, Progressive and Critical Care.[1]

The new consensus statement, which creates a framework for implementing, evaluating, and improving teleICU nursing practice, addresses the new findings in this fast-growing area of health care. It also establishes a model for achieving excellence and optimal patient care outcomes through the following:

- Shared knowledge and goals
- Mutual respect
- Skilled communication
- True collaboration
- Authentic leadership
- Optimized technology
- Practice excellence

A 12-person task force, including teleICU nurse leaders, contributed to the statement and brought a fresh perspective to this area of practice.

Task force co-chair Pat Herr, clinical integration director of eCARE ICU at Avera Health, says it was important to harness the energy and lessons learned from experienced teleICU leaders.

"TeleICUs continue to evolve to meet the needs of patients and health systems," Herr adds. "New technology options and new partnership models are available, and nurse leaders play an important part in using these tools to improve patient care."

The earliest teleICU design concepts employed a physician-only model of care, but it quickly became clear that critical-care nursing was a necessary component. Today, the most effective teleICU models implement collaborative care that includes physicians, nurses, information technology, and administrative support personnel.

Opportunities in teleICU are one way to retain knowledgeable nurses, who can bridge clinical expertise gaps and provide an additional layer of skilled critical care. TeleICU care ensures delivery of both optimal patient outcomes and timely knowledge to support physicians, nurses, and the entire bedside care team.

Task force member Lisa-Mae Williams, operations director of telehealth and eICU at Baptist

Continued on following page

San Antonio hotels for CHEST 2018

Are you ready for CHEST Annual Meeting 2018? Get ready with exclusive hotel deals for your trip to San Antonio from onPeak, the official hotel provider for CHEST 2018. Through onPeak, we are able to bring you the lowest rates, best hotels, and great amenities for your trip all along the beautiful San Antonio River Walk. onPeak also provides flexible booking policies, great group tools, and a full team of wonderful customer service agents to ensure you have a smooth booking process.

CHEST® Annual Meeting 2018

Marriott Rivercenter – HQ Hotel

The San Antonio Marriott Rivercenter, a magnificent 38-story hotel, is just steps away from premier shopping, dining, and entertainment destinations. Guests will enjoy supreme comfort conveniently located near many hot attractions, including Six Flags Fiesta Texas and the San Antonio Zoo. The Alamo, one of the nation's most storied and revered landmarks, is within easy walking distance from the hotel.

Grand Hyatt San Antonio

Discover the distinctly diverse personality of the Alamo City in grand style. Also along the spectacular River Walk, Grand Hyatt San Antonio is steps from trendy downtown bars, Zagat-rated restaurants, and all the sites and attractions that make San Antonio one of the most culturally rich cities in the country.

Hilton Palacio Del Rio

Located in beautiful downtown San Antonio, the Hilton Palacio del Rio hotel is surrounded by Texas culture and attractions, including the Alamo, just two blocks away. The Hilton Palacio del Rio offers superior service, extensive guest amenities, and is the only hotel in downtown San Antonio that features a private balcony in every room. Tex's Riverwalk Sports Bar & Grill, Durty Nelley's Irish Pub, Ibiza Riverwalk Patio Restaurant & Bar, and the Rincon Allegre Lobby Bar await to satisfy individual tastes.

Hotel Contessa

Step into the marble lobby accented with glass sconces and towering palm trees and you'll know you've made the right choice on where to stay. The ambiance of this 265 all-suite property with heated rooftop pool, full-service spa, gourmet restaurant, and modern meeting space is unmatched by any other downtown hotel. Our dedicated service team is devoted to making any stay – leisure or business – a memorable experience. The Hotel Contessa extends to her guests a relaxing respite in an urban setting coupled with all the amenities of a large resort.

Hyatt Regency San Antonio

Experience the heart of the River Walk at Hyatt Regency San Antonio. This is the only hotel on the River Walk directly overlooking the historic Alamo, connecting two of San Antonio's top destinations through the 16-story atrium lobby. This four-diamond hotel includes contemporary guest rooms, a rooftop pool, Stay-Fit gym, and a relaxing spa. The experienced staff adds a genuine touch to world-class amenities.

Marriott Riverwalk

The San Antonio Marriott Riverwalk hotel charmingly captures the vibrant culture and style of this romantic city, welcoming you and ensuring an enchanting stay. This hotel is located in the heart of downtown San Antonio, offering sweeping balcony views of the fabulous River Walk district. The 30-story hotel invites guests into a contemporary lobby with Texas flair: chili-red walls, dark-wood trim, and wrought-iron accents. Explore the history, culture, and culinary delights along the River Walk.

Sean Pavone/Getty Images

Westin Riverwalk Hotel

The Westin Riverwalk Hotel boasts 473 rooms and luxury suites with Texan hospitality and warm residential style. This riverfront hotel is the perfect location to relax and recharge. Expect a warm welcome when you visit the best of San Antonio River Walk hotels. Enjoy delicious dark chocolates imported from Venezuela when you check in and amenities such as The Westin Heavenly Bed® and Heavenly Bath® products that will leave you feeling refreshed and rejuvenated. The hotel rooms also include sparkling city or river views and elegant, oversized marble bathrooms with pampering bath amenities.

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Hotel information provided by onPeak.

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Health South Florida, says telemedicine doesn't mean fewer jobs for bedside nurses; it's an extra set of eyes to surveil vitals and support a clinical workforce that may be stretched thin.

"At the bedside, when teleICU came to my unit, I was very skeptical," Williams recalls. "But after seeing for myself what those extra nurses brought to the table – the available technology and time they had to assess trends and really delve into what's going on – it turned out to be the best tool to care for our patients."

In addition to knowledge gaps, nurse turnover is on the rise, according to the "2017 Survey of Registered Nurses: Viewpoints on Leadership, Nursing, Shortages and Their Profession" from AMN Healthcare, San Diego.[2] The survey also finds that more than one in four nurses plan to retire within a year, and 73% of baby boomers expect to retire in 3 years or less.

The shortfall is already more pronounced in rural hospitals facing staffing challenges and in specialty areas where additional education, training, and experience are critical to improve patient safety and outcomes.

The expertise and dynamic, front-line viewpoint of teleICU experts has resulted in a comprehensive, patient-centric update. Their experience delivering both bedside and remote care was instrumental in developing valuable clinical scenarios. The scenarios in the statement are genuine examples of how each key recommendation is implemented by physicians and bedside and teleICU nurses to provide continuity of care; identify high-risk patients; and decrease mortality rates by filling gaps in monitoring and staff expertise.

As a leader in the delivery of evidence-based practices, AACN offers CCRN-E specialty certification[3] for nurses who primarily provide acute or critical care for adult patients in a teleICU setting, which is connected to the bedside via audiovisual communication and computer systems. Visit www.aacn.org > Certification > Get Certified > CCRN-E Adult to learn more.

The expert consensus statement is available for AACN members to download or to purchase a hard copy.[4]

References

1. https://www.aacn.org/nursing-excellence/standards/aacn-teleicu-nursing-consensus-statement

2. https://www.amnhealthcare.com/uploadedFiles/MainSite/Content/Campaigns/AMN%20Healthcare%202017%20RN%20Survey%20-%20Full%20Report.pdf

3. https://www.aacn.org/certification/get-certified/ccrn-e-adult

4. https://www.aacn.org/nursing-excellence/standards/aacn-teleicu-nursing-consensus-statement

Yale University
School of Medicine

THE SECTION OF PULMONARY, CRITICAL CARE & SLEEP MEDICINE IS SEEKING OUTSTANDING INDIVIDUALS

Yale School of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, is seeking candidates to be members of our Pulmonary Vascular Disease (PVD) Center. This academic position will be filled at a rank of: Instructor, Assistant Professor, Associate Professor with qualifications. Experienced candidates who have a specific career interest in advancing PVD research and clinical programs are encouraged to apply. 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 in clinical & translational research. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. The PVD Center at Yale is rapidly expanding clinically, is accredited by the Pulmonary Hypertension Association as a Comprehensive Care Center, and is involved in basic science, translational, and clinical research. The candidates are expected to evaluate and manage all groups of pulmonary hypertension, and should have experience in all forms of PAH management, including oral, inhaled, and infused therapies. Research experience and proven productivity are an advantage. Minimum requirements include: board certification in pulmonary diseases and critical care medicine. All application materials should be submitted electronically to: **http://apply.interfolio.com/46514**

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

Yale University is an affirmative action/equal opportunity employer and welcomes applications from women, persons with disabilities, protected veterans and members of minority groups.

Yale SCHOOL OF MEDICINE

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:
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For more information on Yale PCCSM
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Facebook **https://www.facebook.com/yalepccsm/**
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YouTube **https://www.youtube.com/channel/UC12y2CWB9774zxNZwy1TmbA/videos**

Yale SCHOOL OF MEDICINE

THE SECTION OF PULMONARY, CRITICAL CARE & SLEEP MEDICINE, 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

For more information on Yale PCCSM
Website **https://medicine.yale.edu/intmed/pulmonary/**
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CHEST NETWORKS

Talc pleurodesis, ICS, cardiopulmonary exercise testing

Interventional Chest/ Diagnostic Procedures

Review of The AMPLE Trial: is talc making a comeback?

A proposed advantage of indwelling pleural catheters (IPC) is their purported ability to reduce hospitalization time when compared with the more traditional talc pleurodesis procedure. The recently published AMPLE trial was a multicenter randomized trial comparing the impact of IPCs vs talc pleurodesis on hospitalization days in patients with malignant pleural effusions. One-hundred forty-six patients were randomized for pleurodesis to either IPC vs pleurodesis via talc slurry in nine centers in Australia, New Zealand, Singapore, and Hong Kong. Patients were followed for up to 12 months. Secondary outcomes included need for further pleural intervention, breathlessness, quality of life, and adverse events.

DR. ARGENTO

DR. MALDONADO

Patients randomized to IPC spent on average 2 days less in the hospital (10 vs 12 days), a difference that was statistically significant, though of questionable clinical relevance, and somewhat disappointing in light of a prior prospective study from the same group suggesting a benefit of 6 to 7 days (Fysh. Chest. 2012;142[2]:394. As in previous studies, additional pleural procedures were more common in the talc group, adverse events occurred more frequently with IPC, but breathlessness and quality of life were identical in both groups.

This study raises interesting questions. Clearly, IPCs have been favored over talc pleurodesis in the US in the last decade, primarily because of a perceived benefit in terms of hospitalization time. In the absence of clear advantage of IPC on time spent in the hospital, impact on breathlessness and quality of life, and considering the inconvenience of frequent drainage, co-pay incurred by patients, and increased adverse events with IPC, the pendulum may swing again toward talc pleurodesis.

Christine Argento, MD, FCCP
Fabien Maldonado, MD, FCCP
Steering Committee Members

Pediatric Chest Medicine

Early escalation of inhaled corticosteroids: does it help prevent asthma exacerbations?

Asthma is one of the most common chronic conditions in children. The importance of effective control of asthma to prevent exacerbations is well accepted. Inhaled corticosteroids (ICS) are a preferred component of treatment to improve asthma control in children with persistent asthma; however, exacerbations can still occur and result in significant morbidity. Most patients receive systemic corticosteroids during acute asthma exacerbations. The most recent Global Initiative for Asthma (GINA) guidelines recommend increasing ICS at the first signs of an asthma exacerbation in an effort to lessen the need for systemic corticosteroids (GINA. Global strategy for asthma management and prevention. 2017. http://www.ginasthma.org/).

In a recent issue of the New England Journal of Medicine, Jackson and colleagues at the National Heart, Lung, and Blood Institute AsthmaNet published the results of a randomized, double-blind 48-week trial, which included 254 children between ages 5 and 11 years with mild-moderate asthma. Their objectives were to compare exacerbation rates, time to first exacerbation, acute care visits, and bronchodilator use in children randomized to treatment with either high (5 x baseline ICS dose x 7 days) or low dose inhaled corticosteroids early in a drop to the "yellow zone" (Jackson, et al. N Engl J Med. 2018;378[10]:891).

Time to asthma exacerbations and exacerbations that required treatment with corticosteroids did not significantly differ between the low dose and high dose groups. Unexpectedly, the rate of exacerbations was higher with the high dose compared with the low dose group (0.48 vs 0.37). The children who were in the high dose group received 16% more ICS compared with the low dose group. Although not significant, there was a lower linear growth rate, ~0.23 cm per year seen in this high-dose group than in the low-dose group. Additionally, the use of bronchodilator, symptoms, and the rates of evaluation by a physician (ie, emergency department or urgent care visits) did not significantly differ between the two groups.

DR. BISHARA

This study was specific to school-age children with mild-moderate persistent asthma treated with low dose ICS with a history of good adherence. Overall, this well-designed study helps address a question that many clinicians have regarding escalating ICS in the "yellow zone." Escalating ICS did not reduce exacerbations at the cost of a lower linear growth rate. When it comes to escalating ICS for asthma exacerbation, more is not better.

In conclusion, in children with mild-to-moderate persistent asthma treated with daily inhaled

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

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glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth. (Funded by the National Heart, Lung, and Blood Institute; STICS ClinicalTrials.gov number, NCT02066129).

John Bishara, DO
Fellow-in-Training Member

Pulmonary Physiology, Function, and Rehabilitation

Understanding cardiopulmonary exercise testing

The cardiopulmonary exercise test (CPET) is an underutilized tool for evaluating patients with dyspnea of uncertain etiology. This is often due to the daunting task of trying to make sense of seemingly large amounts of interacting data, along with clinicians not having been taught a systematic approach for interpreting the results. Unlike other typical tests we order that point to a specific laboratory or anatomic radiographic abnormality, narrowing our differential to a few possibilities, one needs a different mindset when interpreting a CPET. This is a study to demonstrate the body's normal or abnormal physiologic responses to increasing levels of physical stress. Because different conditions can give similar findings, the physiologic abnormalities must be interpreted in the context of the clinical presentation. If the results do not entirely fit the suspected diagnosis, they should be reported in a manner that may help guide the ordering physician down an alternate pathway. This CHEST NetWork has sought ways to reach out to members to promote a better understanding of the utilization of the basics of pulmonary physiology in the management of patients. We created an online two-part video demonstrating a basic systematic approach toward understanding the combinations of findings one often sees when performing a CPET. A comprehensive understanding cannot be shown in a 40-minute video series, but, hopefully, this will give a starting point to make this task easier and more enjoyable.

DR. MORRIS

Zachary Morris, MD, FCCP
Steering Committee Member

Pulmonary Vascular Disease

BMPR2 mutation regulates singular millimetric fibrovascular lesions in bronchial circulation in PAH

Patients with PAH with BMPR2 mutation are younger with worse hemodynamics, ie, higher mean PAP with higher PVR and a lower cardiac index in comparison to the noncarriers. A systematic analysis of pulmonary imaging using CT angiography or magnetic resonance imaging in patients with PAH demonstrated increased bronchial arterial hypertrophy in BMPR2 mutation carriers compared with those without the mutation. Moreover, hemoptysis is more frequently encountered in patients with PAH with BMPR2 mutation and presumably related to bronchial artery remodeling and angiogenesis. French investigators described, in histopathology findings of explanted lungs of 44 patients with PAH (23 carriers of BMPR2 and 21 noncarriers), unusual singular millimetric fibrovascular lesions (SiMFi) in patients with BMPR2 mutations. The SiMFi is a structure of millimetric dimension with fibrovascular characteristics that are extremely rich in collagen and displayed more than one vascular channel. SiMFi did not show a classic glomeruloid pattern with predominant endothelial cell proliferation as seen in plexiform lesions but rather a large conglomerate of hypertrophic vessels. Performing an ink injection experiment in a freshly explanted lung highlighted a patent connection between bronchial/systemic vessels and pulmonary septal veins. SiMFis had an increased amount of bronchial microvessels and showed increased hypertrophy of larger bronchial arteries. SiMFi is directly related to hypertrophy and/or angiogenesis of vasa vasorum/bronchial arteries in the vicinity of the diseased artery. In patients with PAH with BMPR2 mutations, bronchial angiogenesis is more prevalent compared with patients with PAH lacking these mutations. This highlights the role of bronchial arteries in the spectrum of PAH.

DR. CAJIGAS

DR. SAHAY

Hector Cajigas, MD, FCCP
Sandeep Sahay, MD, FCCP
Steering Committee Members

References

1.Ghigna MR, et al. BMPR2 mutation status influences bronchial vascular changes in pulmonary arterial hypertension. *Eur Respir J.* 2016;48[6]:1668. Epub 2016 Nov 3.

2. Tio D, et al. Risk factors for hemoptysis in idiopathic and hereditary pulmonary arterial hypertension. *PLoS One.* 2013;8:e78132.

3. Elliott CG, et al. Relationship of BMPR2 mutations to vasoreactivity in pulmonary arterial hypertension. *Circulation.* 2006;113[21]:2509.

Thoracic Oncology

We have a lung cancer screening test but we could use it better

The American Lung Association recently demonstrated the majority of current and former smokers don't know about lung cancer screening (LCS) with low-dose CT scanning.[1] Researchers estimate less than 5% of eligible persons received LCS.[2] Awareness campaigns targeting patients and health care providers at the local level can improve LCS uptake.[3,4] While any new clinical practice has an expected implementation delay, LCS has another implementation barrier: complex eligibility criteria (age 55 – 80 years PLUS 30+ pack-year smoking history PLUS quit time less than 15 years). Electronic health record (EHR) tools might accelerate the adoption curve to identify eligible persons.[5] Moreover, assessing and recording a qualitative smoking history is challenging, at best. One center showed 96.2% discordance between EHR smoking history and that obtained during shared decision-making visit for LCS.[6] Mostly, the EHR underreported quantitative pack-year history; meaning LCS-eligible patients might fail to be identified by EHR review alone. Another small pilot showed that some patients age 55 – 79 years will update their EHR smoking history using patient portal, but this will not be effective for all patients.[7] For current smokers, age alone may be an effective identification strategy, given the average start time for most smokers.[8]

DR. BEGNAUD

Even though current LCS guidelines leave out some individuals at high risk for lung cancer, we must continue efforts to offer this potentially life-saving service to patients now eligible. Using EHR tools may help proactively identify those who are eligible for lung cancer screening.

Abbie Begnaud, MD
NetWork Member

References

1. New Study from American Lung Association's LUNG FORCE Reveals Low Awareness of Lifesaving Lung Cancer Screening Among Those at Greatest Risk. (2017). http://www.lung.org/about-us/media/press-releases/new-study-lung-cancer-screening.html. Accessed April 19, 2018.

2. Soneji S, et al. Underuse of Chest Radiography Versus Computed Tomography for Lung Cancer Screening. *Am J Public Health.* 2017;107(8):1248.

3. Cardarelli R, et al. Terminate lung cancer (TLC) study-A mixed-methods population approach to increase lung cancer screening awareness and low-dose computed tomography in Eastern Kentucky. *Cancer Epidemiol.* 2017;46:1.

4. Jessup, DL, et al. Implementation of digital awareness strategies to engage patients and providers in a lung cancer screening program: retrospective study. *J Med Internet Res.* 2018;20(2):e52.

5. Comparison of the Electronic Medical Record versus a Shared Decision Making Conversation. *Ann Am Thorac Soc.* 2018. In press.

6. Modin HE, et al. Pack-year cigarette smoking history for determination of lung cancer screening eligibility. *Ann Am Thorac Soc.* 2017 Aug;14(8):1320-1325.

7. Begnaud AL, et al. Randomized electronic promotion of lung cancer screening: a pilot. *JCO Clinical Cancer Informatics*(1), 1-6. doi:10.1200/cci.17.00033

8. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* (2014). Atlanta, GA.

In Memoriam

CHEST has been informed of the following members' deaths. We extend our sincere condolences to friends and family.

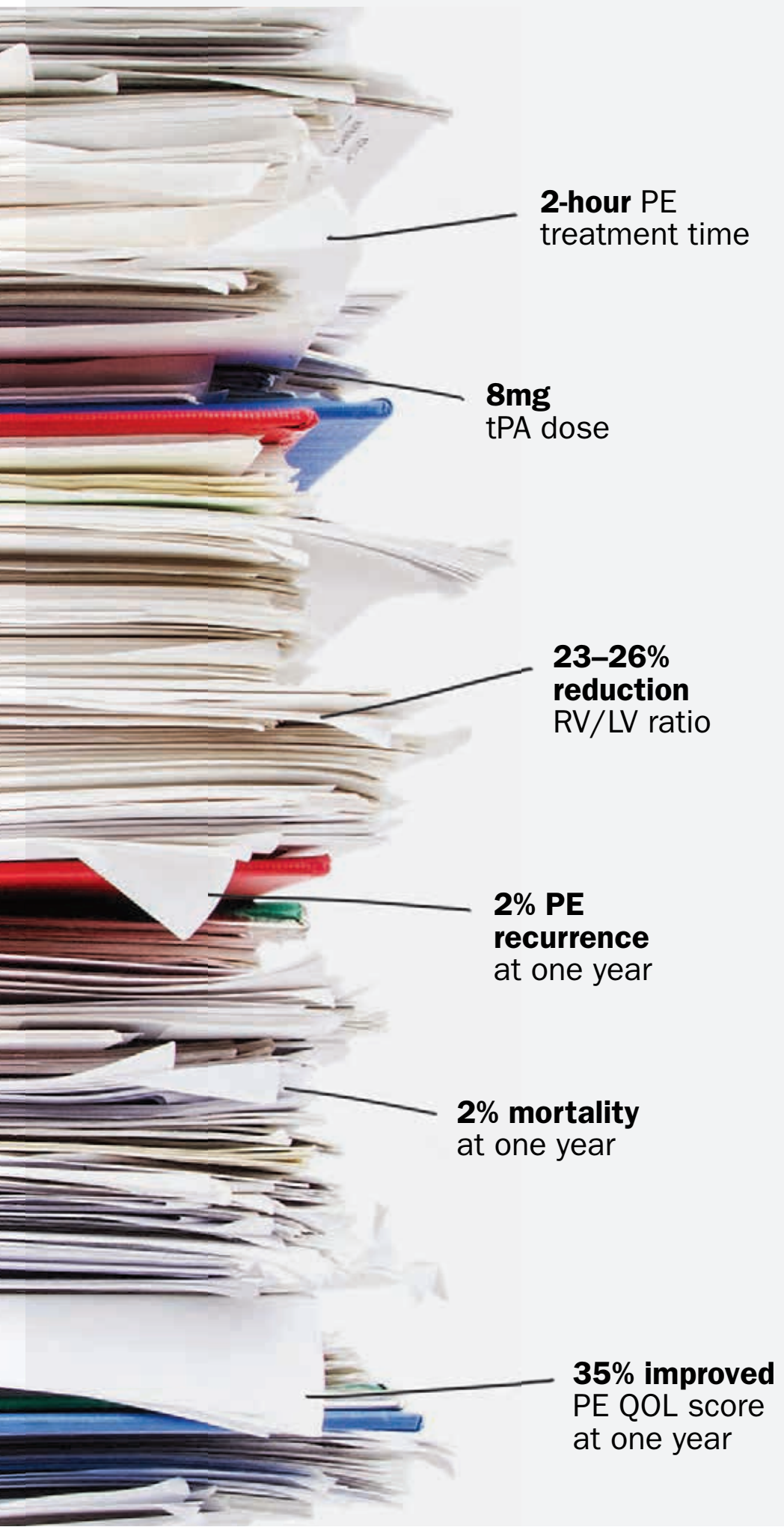
Nagesh V Salian, MD, FCCP (2016)

Ted A Calinog, MD, FCCP (2017)

Azam Ansari, MD (2017)

Arthur E. Schmidt, MD, FCCP (2017)

W. Gerald Rainer, MD, FCCP (2017)



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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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